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The 19th century gave Serbian medicine and literature a few outstanding persons. Those were: Dr. Mihailo Radmio Lazarević (center), Dr. Vladan Hipokrat Đorđević (up left), Dr. Jovan Jovanović Zmaj (up right), Dr. Jovan Stejić (down left), and Laza K. Lazarević (down right) (See pages 730–4).

ORIGINAL ARTICLES

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Troškovi lečenja infekcija urinarnog trakta kod primene pojedinih farmakoterapijskih smernica u Klinici za infektivne bolesti Kliničkog centra Vojvodine

The costs of urinary tract infection therapy with implementation of pharmacoeconomic guidelines at the Clinic for Infectious Diseases of the Clinical Center of Vojvodina

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Apstrakt

Uvod/Cilj. U našoj zemlji nema striktnih smernica za lečenje bakterijskih infekcija. Odabir antibakterijskih lekova je empirijski, što se ne slaže uvek sa preporučenom terapijom bakterijskih infekcija iz zemalja sa razvijenom farmakoterapijskom praksom. Želeli smo da sagledamo razlike između svakodnevne terapije i terapije po smernicama sa aspekta kliničke efikasnosti antibakterijskih lekova koji se primenjuju u terapiji infekcija urinarnog trakta, kao i farmakoekonomsku opravdanost njihove primene. **Metode.** U Klinici za infektivne bolesti Kliničkog centra Vojvodine rađeno je istraživanje kojim je bilo obuhvaćeno 100 bolesnika sa infekcijom urinarnog trakta, podeljenih u dve grupe. U prvoj grupi bili su bolesnici lečeni uobičajenim odabirom antibiotika po ličnom izboru ordinirajućeg lekara, a u drugoj grupi oboleli lečeni antibiotikom preporučenim prema farmakoterapijskim smernicama (*British National Formulary* – BNF, i Senford *Guide*). Poređene su dužine hospitalizacije, korišćeni antibiotici, promene u kliničkoj slici, rezultati laboratorijskih analiza i cene lečenja između ove dve grupe bolesnika. **Rezultati.** Nije bilo značajnih razlika u poboljšanju kliničke slike, kao ni u dužini hospitalizacije između grupa. Poređenje ukupnih troškova lečenja između grupa, pokazalo je uštedu od 34,48% u grupi lečenoj prema smernicama. **Zaključak.** Efikasnost standardnog načina lečenja bolesnika sa infekcijom urinarnog trakta ista je kao i efikasnost lečenja prema farmakoterapijskim smernicama, ali troškovi lečenja su niži u grupi bolesnika u kojoj su primenjivene smernice iz razvijenih zemalja.

Ključne reči:
urinarni trakt, infekcije; antibiotici; lečenje kombinovanjem lekova; farmakoekonomika; vodiči.

Abstract

Beckground/Aim. The Serbian health system does not have strict guidelines for the treatment of bacterial infections. The choice of treatment is empirical which is not necessarily the same compared to the treatment guidelines from countries with a developed pharmacotherapeutic practice. In this study we compared the difference between the current treatment and the treatment taking into account the latest pharmacotherapeutic and pharmacoeconomic guidelines in order to estimate clinical efficiency of antibacterial drugs that were given as a therapy of urinary tract infections and to evaluate pharmacoeconomic aspect of this therapy as well. **Methods.** Our study included 100 patients that were randomly chosen and divided into 2 groups. The first group was treated in an ordinary way, while the second one was treated strictly in accordance with the guidelines (British National Formulary – BNF, and Senford Guide). In both groups of the patients we compared length of hospitalization, combination of the used antibiotics, progress as a whole in clinical picture, laboratory analyses and the price of the whole treatment. **Results.** Analyzing these values independently and according to statistical tests we proved that there were no significant differences between two groups with regard to the progress in a clinical picture as a whole and the length of hospitalization. According to this analysis, however suggested treatment based on guidelines showed a saving of 34.48% in comparison with the usual system of therapy. **Conclusion.** Efficacy of current treatment of urinary tract infection and the treatment according to foreign guidelines is the same, but the costs of the treatment are lower if the guidelines of developed health care systems are applied.

Key words:
urinary tract infections; antibacterial agents; drug therapy, combination; economics, pharmaceutical; guidelines as topic.

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Uvod

Farmakoekonomija je disciplina zdravstvene ekonomije koja identifikuje, meri i upoređuje efekte terapije, troškove korišćenja farmaceutskih proizvoda, odnosno zdravstvenih intervencija. Cilj farmakoekonomije je da uskladi i nađe najbolji mogući lek, koji će dati optimalne efekte uz najniže troškove lečenja. Pristup u farmakoekonomiji je interdisciplinaran i uključuje znanja iz medicine, ekonomije, fermakoepidemiologije, prava, teorije odlučivanja, biostatistike, bioetike, farmacije i epidemiologije u širem smislu. Takvim multidisciplinarnim pristupom moguće je doći do rešenja do kojih se pojedinačnim pristupom ne bi moglo doći [1–3].

Farmakoekonomija usvaja i primenjuje principe i metodologiju zdravstvene ekonomije u farmakoterapiji. Farmakoekonomskim istraživanjima porede se efekti terapije i cene dve ili više različitih alternativa lečenja uz poštovanje principa „*primum non nocere*" (prevashodno ne naškoditi). Farmakoekonomski koncept se koristi da bi se postigao određeni optimalni cilj u lečenju za nižu cenu ili obrnuto, da se korišćenje datih, ograničenih resursa usmeri na način na koji se ostvaruje najbolji mogući odnos terapijske i ekonomske koristi (benefit) [4]. Za postizanje ovog cilja koriste se metode ekonomske analize (procene) za odabiranje najefikasnije opcije kako bi se pružanje zdravstvene usluge širokoj populaciji podiglo na najviši mogući nivo [5].

Kada se definiše aspekt farmakoekonomske analize, tada se meri količina sredstava potrošenih za određeno lečenje bolesti. Parametri koji utiču na potrošnju sredstava su vreme i znanje medicinskih radnika potrebno za pripremu i primenu terapije, utrošak lekova, broj bolesničkih dana i materijalnih sredstava. U širem smislu, u ekonomski aspekt spada i praćenje kvaliteta života i zdravstveni troškovi tokom lečenja i rekonvalescencije, kao i praćenje efekta i cene koštanja eventualnih invaliditeta, patologije izazvanih pri primeni jednih ili drugih terapijskih pristupa. Ukoliko se ekonomska analiza obavlja paralelno sa kliničkim ispitivanjem dolazi se direktno do ovih podataka. U drugom slučaju podaci se skupljaju retrospektivno ili prospektivno iz medicinske dokumentacije ili bolničkih kartona. Procena troškova završava se množenjem izmerenih utrošenih sredstava sa cenama (jediničnim troškovima). Ove vrednosti mogu se dobiti iz zvaničnih cenovnika finansijske službe određene institucije [6–8].

Preporuka za određenu terapiju zavisi od kliničke koristi od terapije, njene isplativosti i finansijskog opterećenja nacionalnog budžeta za zdravstvo. Značajno je da zdravstveni stručnjaci primenjuju tehnike ekonomskih analiza, posebno oni koji učestvuju u procesu izrade nacionalnih vodiča za lečenje određenih bolesti ili npr. polise korišćenja antibiotika [4].

Da bi se povećala efikasnost zdravstvene zaštite i usluga, dugoročno rešenje je procena svih postojećih tehnologija i terapija, uz identifikovanje onih koje su u širokoj primeni, a nisu isplative. Na taj način mogu se dobiti sredstva koja bi se mogla usmeriti na rentabilnije načine lečenja.

Farmaceutske kompanije su se donedavno koncentrisale na sprovođenje kliničkih ispitivanja kojima će prikupiti dokaze koje traže regulatorni organi za izdavanje dozvola za stavljanje lekova u promet (registraciju lekova). Uporedo sa informacijama o kliničkim efektima terapija, sve veći broj zemalja traži prikupljanje i ekonomskih podataka i pokazatelja [9].

Sve veći broj zdravstvenih stručnjaka poznavanjem tehnika ekonomskih analiza, može da utiče na podizanje kvaliteta industrijskih i akademskih analiza [9, 10].

Na uspeh farmakoterapije infekcija urinarnog trakta može uticati lokalizacija infekcije. Kod akutnog cistitisa najčešći uročnik je *E. coli*. Efikasna je trodnevna terapija kotrimoksazolom ili hinolonima [11, 12], ali se ona ne preporučuje kod bolesnica sa simptomima pijelonefritisa, kalkuloze ili ako je prethodno postojala infekcija uzrokovana rezistentnim bakterijama. Muškarci sa urinarnom infekcijom često imaju urološke abnormalnosti ili hipertrofiju prostate, tako da nisu pogodni za trodnevnu terapiju, već se preporučuje primena antibiotika 7–14 dana [11]. Preporuka Britanskog nacionalnog formulara (*British National Formulary* – BNF) [13] za lečenje infekcija gornjih partija urinarnog trakta je empirijska primena kotrimoksazola ili cefradina, dok je alternativa terapija amoksicilinom, amoksicilinom sa klavulanskom kiselinom, nitrofurantoinom ili ciprofloksacinom. Trajanje terapije kod žena je preporučeno 3–5 dana, a kod muškaraca 7–10 dana. Prema preporukama američkog vodiča za antimikrobnu terapiju (Senford) [14] preporučuje se primena hinolonskih antibiotika sedam dana, dok je alterantiva terapija amoksiclinom sa klavulanskom kiselinom ili kotrimoksazolom 14 dana.

Terapija izbora kod žena sa akutnim uretritisom zavisi od uzročnika. Kada je hlamidija uzročnik, preporučuje se doksiciklin u trajanju od sedam dana. Kod žena sa akutnim nekomplikovanim pijelonefritisom, s najčešćim uzročnikom *E. coli*, u terapiji se preporučuje lečenje kotrimoksazolom u trajanju od 14 dana ili hinolonima, aminoglikozidima ili cefalosporinima III generacije [11]. Prema Nacionalnom vodiču za lekare [12] lečenje započinje ceftriaksonom parenteralnim putem 1–2 dana, uz nastavak terapije ciprofloksacinom ukupno 14 dana ili gentamicinom prva 24 h, uz nastavak terapije ciprofloksacinom do 14 dana. Preporuka BNF-a [13] za lečenje pijelonefritisa je ciprofloksacin intravenski ili gentamicin. Prvih nekoliko dana preporučuje se primena antibiotika intravenski, a ako su simtomi blagi, lečenje se može sprovoditi peroralnim putem dve nedelje. Kod bolesnika koji ne reaguju na terapiju u roku od 72 h, ili kod kojih dođe do recidiva posle ukidanja terapije, potrebno je tražiti fokuse, kalkulozu ili urološke abnormalnosti. Prema preporukama američkog vodiča za antimikrobnu terapiju Senford [14], lek izbora je ciprofloksacin, ili ampicilin sa gentamicinom ili cefalosporini III generacije, dok je alternativa terapija piperacilin/tazobaktam ili ampicilin/sulbaktam u trajanju od 14 dana.

Komplikovane urinarne infekcije (zbog kateterizacije, manipulacija, uroloških abnormalnosti, kalkuloze, opstrukcije, imunosupresije, bubrežnih bolesti ili dijabetesa) obično su intrahospitalne, uzrokovane multirezistentnim sojevima. Prema preporukama indikovana je empirijska antibiotska terapija antibioticima širokog spektra [11]. Kod bolesnika sa blagim simptomima preporučuju se hinoloni peroralno, do dobijanja urinokulture i antibiograma.

Kod bolesnika sa težom kliničkom slikom (pijelonefritis i urosepsa), preporučuje se hospitalizacija i parenteralna terapija. Empirijska terapija u ovim slučajevima podrazumeva imipenem ili cefalosporine IV generacije (cefepim, cefpirom) kao monoterapiju ili peniciline širokog spektra, ili cefalosporine uz aminoglikozide, ili ceftazidim. Po dobijanju antibiograma potrebno je primeniti ciljanu terapiju. Preporučeno lečenje je 7–21 dan u zavisnosti od težine kliničke slike [11]. Urinokulture treba ponoviti posle 2–4 nedelje od završetka lečenja, da bi se potvrdilo izlečenje. Prema preporukama američkog vodiča za antimikrobnu terapiju Senford [14], lečenje komplikovane urinarne infekcije započinje se kombinacijom ampicilina sa gentamicinom ili piperacilin/tazobaktam ili imipenem ili meropenem u trajanju 2–3 nedelje. Alternativna terapija je hinolonskim preparatima intravenski, zatim prelazak na peroralne preparate u trajanju od tri nedelje.

Cilj ovog istraživanja bio je poređenje terapijskih efekata pojedinih antibiotskih tretmana za lečenje infekcija urinarnog trakta i ocena farmakoterapijske opravdanosti primenjenih terapijskih tretmana. Formirani su principi lečenja infekcija urinarnog trakta i upoređena je efikasnost i cena uobičajenog lečenja i lečenja prema aktuelnim smernicama.

Metode

Istraživanje cene lečenja infekcija urinarnog trakta kod primene pojedinačnih farmakoterapijskih smernica obavljeno je na Klinici za infektivne bolesti Kliničkog centra Vojvodine (KC Vojvodine). Istraživanje je bilo prospektivno, u trajanju od dve godine. Sastojalo iz tri dela. Prvi deo odnosio se na sagledavanje celokupnog dosadašnjeg načina lečenja hospitalizovanih bolesnika sa infekcijom urinarnog trakta (n = 50), koji su formirali kontrolnu grupu. Praćen je tok bolesti i efikasnost primenjene terapije. Izračunata je cena ukupnog lečenja.

U drugom delu formirane su smernice za lečenje infekcija urinarnog trakta, pošto u našoj zemlji ne postoje smernice (polisa) za korišćenje antibiotika, iz postojećih podataka iz literature (američkog vodiča za antimikrobnu terapiju Senford i britanskog BNF), te prema polisi korišćenja antibiotika. Smernice su primenjene kod 50 bolesnika, koji su činili ispitivanu grupu. Praćen je tok bolesti i efikasnost primenjene terapije.

Za navedenu dijagnozu primenjeno je više odgovarajućih, preporučenih antibiotika sa različitom cenom utrošenih lekova. U dogovoru sa lekarima specijalistima koji rade na Klinici za infektivne bolesti KC Vojvodine, primenjene su aktuelne preporuke za primeni određenih antibakterijskih lekova za infekcije urinarnog trakta, gde je poštovana najniža cena utrošenih lekova i formirane su smernice lečenja. Zatim je izračunata cena primenjene antibakterijske terapije po aktuelnim svetskim stavovima o lečenju.

U trećem delu poređena je efikasnost i cena lečenja nakon primene smernica iz zemalja sa razvijenom farmakoterapijom i dosadašnjeg načina lečenja u Klinici za infektivne bolesti. Upoređivanjem dobijenih rezultata, omogućeno je određivanje optimalnog načina lečenja kod nas.

Lečenje je bilo započeto na osnovu kliničke dijagnoze infekcije urinarnog trakta koja je potvrđena mikroskopskim pregledom urina, a u nekim slučajevima i izolacijom bakterija – urinokulturom. Kriterijumi za uključivanje bolesnika u studiju bili su klinička slika infekcije urinarnog trakta, koja je u najvećem broju slučajeva potvrđena povišenim brojem leukocita i/ili sedimentacijom i/ili fibrinogenom. U istraživanju su praćeni subjektivni i objektivni parametri, analizirane i poređene kliničke slike, laboratorijski nalazi, primenjena antibiotska terapija i neželjeni efekti terapije kod svih bolesnika.

Na osnovu cene bolesničko-opskrbnog dana, cene utrošenih antibakterijskih lekova, cene utrošenog sanitetskog i medicinskog materijala i cene stacionarnih usluga, te izračunavanja ukupne cene lečenja, sagledani su medicinski troškovi lečenja. Cene bolesničko-opskrbnog dana (BOD) dobijene su iz „Cenovnika zdravstvenih usluga u Republici Srbiji“ [15] iz 2008. godine, koji se i danas primenjuje. Cene lekova, sanitetskog i medicinskog materijala dobijene su iz centralne apoteke KC Vojvodine. Cene usluga medicinkog osoblja (stacionarne usluge) dobijene su iz Sektora zajedničkih službi, Fakturnog odeljenja KC Vojvodine.

Sagledavanjem mogućnosti primene smernica o lečenju bakterijskih infekcija sa farmakoekonomskog aspekta lečenja, ocenjivali smo: koliko je moguće u našim uslovima pridržavati se savremenih svetskih stavova o lečenju antibakterijskim lekovima, da li su preporuke univerzalno primenljive, da li je bolje da se pridržavamo svojih stavova i napravimo sopstvene smernice za lečenje bakterijskih infekcija. U poređenju sa aktuelnim tretmanom, sagledano je šta je farmakoekonomski isplativije.

U analizi su korišćene standardne metode statističkih istraživanja (deskriptivna statistika i distribucija frekvencija). Numerički podaci prikazani su putem srednjih aritmetičkih vrednosti i standardne devijacije, a komparacije su vršene *t*-testom. Za testiranje hipoteza razlike učestalosti (distribucija) posmatranih parametara korišćen je χ^2-test i McNemar test. Rezultati su prikazani tabelarno i grafički uz tekstualni komentar.

Rezultati

Rezultati istraživanja pokazali su da se po demografskim osobinama bolesnici ne razlikuju između grupa. Od ukupnog broja bolesnika u kontrolnoj grupi bilo je 20 (40,0%) muškog pola, a 30 (60,0%) ženskog. U ispitivanoj grupi 15 (30,0%) bilo je muškog, a 35 (70,0%) ženskog pola.

Prosečna starost bolesnika u kontrolnoj grupi bila je 49,64 ± 21,51 godina. Najmlađi bolesnik imao je pet a najstariji 86 godina. U ispitivanoj grupi prosečna starost bila je 56,68 ± 19,56 godina. Najmlađi bolesnik imao je 12, a najstariji 86 godina. Nije bilo statistički značajne razlike između kontrolne i ispitivane grupe u odnosu na polnu i starosnu strukturu bolesnika.

Kod 11 (22,0%) bolesnika kontrolne grupe i 12 (24,0%) ispitivne grupe, antibiotska terapija bila je ordinirana od strane lekara opšte prakse pre hospitalnog lečenja.

U obe grupe ispitivanih bolesnika prva dva mesta ambulantno ordiniranih antibiotika zauzimali su isti lekovi. Kod obe grupe bolesnika najviše je bila primenjena terapija gentamicinom, cefaleksinom i ampicilinom. Nije bilo istovremenog primenjivanja dva ili više antibiotika (tabela 1).

Pri prijemu na bolničko lečenje, svim bolesnicima uziman je urin za urinokulturu i svi uzorci poslati su na mikrobiološku analizu.

U kontrolnoj grupi bolesnika sa infekcijom urinarnog trakta, kod svih 50 bolesnika uzeta je urinokultura pri prijemu. Kod 28 (56%) bolesnika nalaz urinokulture bio je negativan. Kod 22 (44%) bolesnika u urinokulturi izolovane su bakterije: *E. coli* kod 12 (54,0%), *Klebsiella pneumoniae* kod 4 (18,0%) i *Pseudomonas aeruginosa* kod 3 (13,6%) bolesnika.

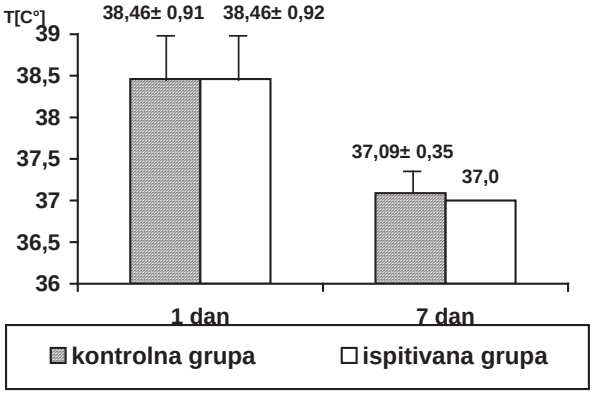
U ispitivanoj grupi, takođe, kod svih 50 bolesnika uzeta je urinokultura pri prijemu. Kod 27 (54%) bolesnika nalaz urinokulture bio je negativan. Kod 22 (44%) bolesnika u urinokulturi izolovane su bakterije: *E. coli* kod 15 (65,2%), *Enterococcus spp.* kod 4 (17,4%) i *Pseudomonas aeruginosa* kod 2 (8,7%) bolesnika (tabela 2).

Efikasnost terapije praćena je određivanjem telesne temperature i praćenjem tegoba: prisutnosti dizuričnih tegoba, bola u lumbalnoj regiji, kao i biohemijskim parametrima.

Kod obe grupe bolesnika sedmog dana lečenja došlo je do značajnog sniženja telesne temperature ($p < 0,001$, McNemar test) (slika 1).

Nije nađena statistički značajna razlika u visini povišene telesne temperature pri prijemu i sedmog dana lečenja između obe grupe bolesnika.

Kod svih bolesnika dizurične tegobe i bol u lumbalnoj regiji, bile su značajno manje izražene nakon sedmog dana lečenja nego pri prijemu ($p < 0,001$) (tabela 3).



Sl. 1 – Visina telesne temperature pri prijemu i sedmog dana bolničkog lečenja kod bolesnika sa infekcijom urinarnog trakta

Nije postojala statistički značajna razlika u prisutnosti dizuričnih tegoba i bola u lumbalnoj regiji prvog i sedmog dana lečenja između bolesnika obe grupe.

Prosečna vrednost leukocita pri prijemu u kontrolnoj grupi bila je $10,34 \pm 3,8\ 10^9$/L (min 4,3, maks $19,9\ 10^9$/L), a u ispitivanoj grupi bila je $8,80 \pm 4,54\ 10^9$/L (min 3,6, maks $33,2\ 10^9$/L).

Prosečna vrednost leukocita sedmog dana lečenja u kontrolnoj grupi je bila $10,18 \pm 4,4\ 10^9$/L 6 (min 4,0, maks $23,7\ 10^9$/L), a u ispitivanoj grupi $7,82 \pm 2,60\ 10^9$/L (min 4,5, maks $19,0\ 10^9$/L).

Broj bolesnika sa povišenim vrednostima ukupnog broja leukocita nakon sedmog dana lečenja bio je značajno manji nego pri prijemu unutar obe grupe (p k1/k7, $p < 0,001$, McNemar test, p i1/i7, $p < 0,001$, McNemar test).

Tabela 1

Frekvencija ambulantno primenjenih antibiotika pre prijema bolesnika sa infekcijom urinarnog trakta na bolničko lečenje

Antibiotik	Kontrolna grupa		Ispitivana grupa	
	n	%	n	%
Gentamicin	5	45,5	3	25,0
Cefaleksin	3	27,3	2	16,7
Ampicilin	1	9,1	2	16,7
Ceftriakson	1	9,1	1	8,3
Ciprofloksacin	1	9,1	1	8,3
Amoksicilin sa klavulanskom kiselinom	–	–	1	8,3
Cefaklor	–	–	1	8,3
Kotrimoksazol	–	–	1	8,3
Ukupno	11	100	12	100

Tabela 2

Struktura pozitivnih izolata urinokulture kod bolesnika uzetih pri prijemu na lečenje

Izolovano iz urinokulture	Kontrolna grupa		Ispitivana grupa	
	n	%	n	%
E. coli	12	54,0	15	65,2
Enterococcus spp	2	9,0	4	17,4
Klebsiella pneumoniae	4	18,0	1	4,35
Pseudomonas aeruginosa	3	13,6	2	8,7
Acinetobaster spp	1	4,5	1	4,35
Ukupno	22	100	23	100

Tabela 3

Prisutnost dizuričnih tegoba i bola u lumbalnoj regiji, pri prijemu i sedmog dana bolničkog lečenja kod bolesnika sa infekcijom urinarnog trakta

Grupe bolesnika	Prisutnost dizuričnih tegoba tokom bolničkog lečenja															
	1 dan								7 dan							
	da						ne		da						ne	
	blage		srednje izražene		veoma izražene				blage		srednje izražene		veoma izražene			
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Kontrolna (k)	10	20	13	26	16	32	11	22	17	34	12	24	1	2	20	40
Ispitivana (i)	13	26	17	34	13	26	7	14	11	22	14	28	2	4	23	46
	Prisutnost bola u lumbalnoj regiji tokom bolničkog lečenja															
	1 dan								7 dan							
	da						ne		da						ne	
	blag		srednje izražen		veoma izražen				blag		srednje izražen		veoma izražen			
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Kontrolna (k)	10	20	20	40	14	28	6	12	21	42	12	24	1	2	16	32
Ispitivana (i)	7	14	19	38	17	34	7	14	16	32	7	14	–	–	27	54

k1/k7, $p < 0,001$ (χ^2 test); i1/i7, $p < 0,001$ (χ^2 test); 1/7, $p > 0,05$ (χ^2 test)

Nije postojala statistički značajna razlika u broju bolesnika sa povišenim vrednostima ukupnog broja leukocita pri prijemu i sedmog dana od prijema između grupa (p 1/7, $p > 0,05$ χ^2 test) (tabela 4).

Prosečna vrednost sedimentacije eritrocita (prvi sat) pri prijemu u kontrolnoj grupi bila je 66,40 ± 35,57 mm/h (min 15,0, maks 142,0 mm/h), a u ispitivanoj grupi 61,36 ± 35,21 mm/h (min 10,0, maks 150,0 mm/h).

Prosečna vrednost sedimentacije eritrocita (prvi sat) sedmog dana lečenja u kontrolnoj grupi bila je 48,70 ± 26,90 mm/h (min. 12,0, maks. 110,0 mm/h), a u ispitivanoj grupi 48,22 ± 29,22 mm/h (min. 10,0, maks. 131,0 mm/h).

Nije postojala statistički značajna razlika u broju bolesnika sa povišenom vrednošću sedimentacije eritrocita (prvi sat) pri prijemu i sedmog dana lečenja u kontrolnoj i ispitivanoj grupi bolesnika, niti poredeći grupe pri prijemu i sedmog dana lečenja (p k1/k7, $p > 0,05$, p i1/i7, $p > 0,05$ McNemar test, p 1/7, $p > 0,05$ χ^2 test) (tabela 4).

Prosečna vrednost fibrinogena pri prijemu u kontrolnoj grupi bila je 6,66 ± 1,35 g/L (min. 4,5, maks. 9,39 g/L), a u ispitivanoj grupi 6,71 ± 1,49 g/L (min. 4,7, maks. 10,25 g/L).

Prosečna vrednost fibrinogena sedmog dana lečenja u kontrolnoj grupi bila je 5,05 ± 0,87 g/L (min. 4,5, maks. 7,50 g/L), a u ispitivanoj grupi 5,35 ± 1,0 g/L (min. 4,5, maks. 7,25 g/L).

Postojala je statistički značajna razlika u broju bolesnika sa povišenim vrednostima fibrinogena pri prijemu i sedmog dana lečenja unutar kontrolne i unutar ispitivane grupe bolesnika (p k1/k7, $p < 0,05$, McNemar test, p i1/i7, $p < 0,05$, McNemar test).

Nije postojala statistički značajna razlika u broju bolesnika sa povišenim vrednostima fibrinogena pri prijemu i sedmog dana lečenja unutar grupa bolesnika (p 1/7, $p > 0,05$–χ^2 test) (tabela 4).

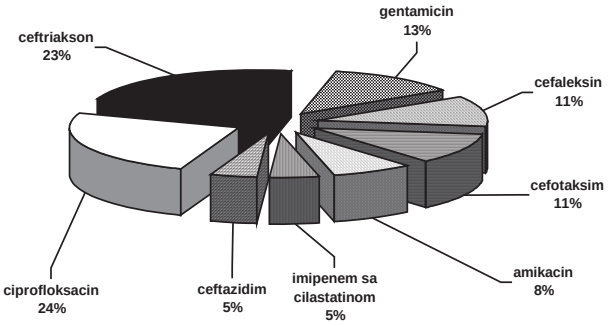
Tabela 4

Broj bolesnika sa infekcijom urinarnog trakta sa povišenom vrednošću ukupnog broja leukocita, sedimentacije eritrocita (prvi sat) i fibrinogena pri prijemu i sedmog dana bolničkog lečenja

Grupe bolesnika	Broj leukocita ($\times 10^9$)*							
	1 dan				7 dan			
	povišen		normalan		povišen		normalan	
	n	%	n	%	n	%	n	%
Kontrolna (k)	46	92,0	4	8,0	9	18,0	41	82,0
Ispitivana (i)	44	88,0	6	12,0	3	6,0	47	94,0
	Sedimentacija eritrocita (prvi sat) (mmHg)**							
	1 dan				7 dan			
	povišena		normalna		povišena		normalna	
	n	%	n	%	n	%	n	%
Kontrolna (k)	42	84,0	8	16	48	96,0	2	4,0
Ispitivana (i)	42	84,0	8	16	47	94,0	3	6,0
	Fibrinogen (g/L)***							
	1 dan				7 dan			
	povišen		normalan		povišen		normalan	
	n	%	n	%	n	%	n	%
Kontrolna (k)	47	94,0	3	6,0	37	74,0	13	26,0
Ispitivana (i)	46	92,0	4	8,0	33	66,0	17	34,0

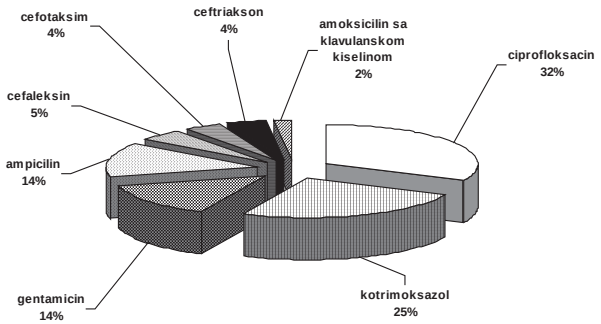
*** k1/k7 i p i1/i7, $p < 0,001$ (McNemar test); **1/7, $p > 0,05$ (χ^2 test); ***k1/k7 i i1/i7, $p < 0,05$ (McNemar test)**

U grupi bolesnika koji su dobijali antibiotsku terapiju prema ličnom izboru lekara, kao lek izbora bio je najviše korišćen ciprofloksacin (24%), na drugom mestu bio je ceftriakson (23%), a na trećem gentamicin sa 13% (slika 2).



Sl. 2 – Ordinirani antibiotici kod bolesnika koji su dobijali antibiotsku terapiju prema ličnom izboru lekara (kontrolna grupa)

U grupi bolesnika koji su dobijali antibiotsku terapiju po smernicama farmakoterapije, lek prvog izbora bio je ciprofloksacin, (32%), na drugom mestu je kotrimoksazol, (25%), a na trećem gentamicin, (14%) i ampicilin (14%) (slika 3).



Sl. 3 – Ordinirani antibiotici kod bolesnika koji su dobijali antibiotsku terapiju po farmakoterapijskim smernicama (ispitivana grupa)

Od 50 posmatranih bolesnika, kod 21 (42%) tokom celokupnog bolničkog lečenja nije bilo promene započete pojedinačne antibiotske terapije. Kod 31 (62,0%) bolesnika prvoizabrani antibiotik zamenjen je drugim (i dalje pojedinačnim antibiotikom), a promena antibiotske terapije sledila je nakon dva do tri dana primene prvog antibiotika. Kod tri (6%) bolesnika antibiotska terapija je i posle drugog izabranog antibiotika ponovo promenjena i primenjen je treći pojedinačni antibiotik. Promena antibiotske terapije kao posledice mikrobiološkog nalaza urinokulture bila je kod dva bolesnika. Na slici 2 svi primenjeni antibiotici su prikazani zbirno.

Istovremeno davanje dva antibiotika, kao početak bolničkog lečenja, ordinirano je kod 14 (28,0%) bolesnika. Najčešće kombinacije bile su cefotaksim sa ciprofloksacinom, ceftriakson sa amikacinom i gentamicin sa cefaleksinom.

U ovoj grupi bolesnika najčešći nastavak antibiotske tarapije posle primene ceftriaksona, bio je peroralni oblik ciprofloksacina kod 8 (16%) bolesnika i posle primene gentamicina cefaleksin kod 5 (10%) bolesnika.

Broj dana antibiotske terapije prosečno se kretao 11,78 ± 5,78 (min 5, maks 24).

Od 50 posmatranih bolesnika, kod 30 (70%) primenjen je samo jedan antibiotik, kod 20 (40%) ordiniran je drugi antibiotik posle primene prvog kao prelazak parenteralne na peroralnu terapiju.

Istovremeno davanje dva antibiotika bilo je kod sedam (14%) bolesnika, gde je davan istovremeno gentamicin parenteralno i ampicilin peroralno.

Ukupan broj dana antibiotske terapije iznosio je 10,38 ± 3,75 (min 5, maks 17).

Troškovi lečenja kod obe grupe bolesnika pokazuje velike raspone između maksimalnih i minimalnih troškova po računatim bolesničko-opskrbnim danima, utrošenim lekovima, sanitetskom i medicinskom meterijalu i stacionarnim uslugama (tabela 5).

Ukupni troškovi izraženi su za po 50 bolesnika u obe grupe, za ceo period hospitalizacije.

Finansijski aspekt izražen je u dinarima i predstavlja razliku srednjih vrednosti cena iz obe grupe a izražen je i u procentu kao srednja vrednost uštede.

Postojala je statistički značajna razlika u svim ispitanim stavkama koje su činile ukupne troškove lečenja (tabela 6).

Tabela 5

Troškovi po stavkama kod bolesnika sa infekcijom urinarnog trakta (po bolesniku)

Struktura troškova	Troškovi pre upotrebe smernica (din) (kontrolna grupa)			Troškovi posle uvođenja smernica (din) (ispitivana grupa)		
	minimalni	maksimalni	$\bar{x} \pm SD$	minimalni	maksimalni	$\bar{x} \pm SD$
Bolesničko opskrbni dan	5322,36	170520,75	18515,71 ± 23271,06	773,0	24800,0	9339,09 ± 4168,15
Utrošeni lekovi	243,21	133044,87	15893,58 ± 24067,86	91,18	22396,05	6454,08 ± 5116,53
Sanitetski, medicinski meterijal	203,07	26730,50	3627,59 ± 5662,50	287,06	5574,84	1866,41 ± 1032,89
Stacionarne usluge	56,84	35471,48	7089,90 ± 7289,10	774,31	11978,08	3866,40 ± 2508,12
Ukupna cena	1866,49	332198,49	45126,78 ± 49483,17	1926,31	58692,30	21681,26 ± 10535,65

Tabela 6

Finansijski aspekti lečenja bolesnika sa infekcijom urinarnog trakta

Struktura troškova	Ukupna cena (din)		Finansijski aspekt (srednja vrednost uštede)	
	kontrolna grupa (k)	ispitivana grupa (i)	din	%
Bolesničko opskrbni dan	925785,49	466954,69**	9176,62	32,94
Utrošeni lekovi	794679,17	316152,18**	9441,5	43,08
Sanitetski i medicinski mterijal	18137,59	93320,73**	1761,18	32,06
Stacionarne usluge	354495,01	193320,09**	3223,5	29,42
Ukupna cena	2136636	1065069**	23445,52	35,67

***p* <0,01 u odnosu na k (*t*-test)**

Ušteda je evidentirana u korist ispitivane grupe u troškovima za bolesničko-opskrbne dane, utrošene lekove, utrošeni sanitetski i medicinski materijal, stacionarne usluge, te ukupne troškove lečenja.

Diskusija

Kod 11 (22,0%) bolesnika kontrolne grupe (antibiotska terapija prema ličnom izboru lekara) i 12 (24,0%) bolesnika ispitivane grupe (antibiotska terapija prema smernicama), antibiotska terapija bila je ordinirana za urinarne infekcije pre hospitalnog lečenja od strane lakara opšte prakse ili pedijatara. Kod obe grupe ispitivanih bolesnika prva dva mesta ambulantno ordiniranih antibiotika zauzimaju isti lekovi. Najviše je bila primenjena terapija gentamicinom, cefaleksinom i ampicilinom. Gentamicin se po preporukama iz literature koristi za lečenje pijelonefritisa [13–15] i čuva se za korišćenje u bolničkim uslovima, kada bi trebalo redovno da se meri njegova koncentracija u krvi zbog sprečavanja nastanka neželjenih dejstava aminoglikozidnih antibiotika. U ambulantnim uslovima i u nekim bolnicama kod nas, gentamicin se često koristi, što nije opravdano zbog toga što se ne zna koliko njegova primena izaziva neželjenih dejstava. Cefaleksin koji je na drugom mestu po upotrebi preporučuje se u lečenju nekomplikovanih infekcija urinarnog trakta [16]. Po istraživanjima rezistencije na antimikrobne lekove, uzročnika mokraćnih infekcija hospitalno lečenih bolesnika u Institutu za interne bolesti KC Vojvodine tokom 2006. godine na ampicilin je bio osetljivo od 22,7 do 35,7% sojeva *Escerichiae coli (E. coli),* 48,0% sojeva *Proteus mirabillis*, od 0,0 do 6,7% *Klebsiella pneumoniae* i 0,0% *Psudomonas aeruginosa* [17]. Stoga, upotreba ampicilina zbog velike rezistencije na najčešće uzročnike mokraćnih infekcija nije opravdana. Nije bilo istovremenog primenjivanja dva ili više antibiotika u ambulantnim uslovima, što je po svim preporukama.

U kontrolnoj grupi bolesnika (antibiotska terapija prema ličnom izboru lekara) sa infekcijom urinarnog trakta, kod svih 50 bolesnika pri prijemu uzeta je urinokultura. Kod 28 (56%) bolesnika nalaz urinokulture bio je negativan. Kod 22 (44%) bolesnika su u urinokulturi izolovane bakterije: *E. coli* kod 12 (54,0%) bolesnika, *Klebsiella pneumoniae* kod četiri (18,0%) i *Pseudomonas aeruginosa* kod 3 (13,6%). U ispitivanoj grupi bolesnika (antibiotska terapija prema smernicama), takođe kod svih 50 bolesnika pri prijemu uzeta je urinokultura. Kod 27 (54%) nalaz urinokulture je negativan. Kod 22 (44%) bolesnika su u urinokulturi izolovane bakterije: *E. coli* kod 15 (65,2%) bolesnika, *Enterococcus spp.* kod 4 (17,4%) i *Pseudomonas aeruginosa* kod 2 (8,7%). Pojava negativnih urinokultura može se objasniti primenom antibakterijskih lekova u ambulantnim uslovima ili samoinicijativnim lečenjem od strane bolesnika.

Tokom 2006. godine u Sektoru za bakteriologiju i parazitologiju Instituta za javno zdravlje Vojvodine praćena je rezistencija na antimikrobne lekove najčešće izolovanih uzročnika mokraćnih infekcija, kod svih bolesnika lečenih u Institutu za interne bolesti KC Vojvodine. Rezultati su pokazali da je na prvom mestu po zastupljenosti uzročnika *E. coli* od 43 do 51% zatim *Klebsiella pneumoniae* sa 16–21%, *Proteus mirabillis* sa 10% i *Pseudomonas aeruginosa* sa 10% [17]. Ovi rezultati slažu se sa rezultatima našeg istraživanja.

Klinička slika infekcije urinarnog trakta karakteriše se: povišenom telesnom temperaturom, prisutnošću dizuričnih tegoba, bola u lumbalnoj regiji i promenama u laboratorijskim nalazima. Stoga je efikasnost terapije praćena određivanjem telesne temperature i praćenjem subjektivnih tegoba: bola u lumbalnoj regiji, prisutnosti dizuričnih tegoba, kao i biohemijskim parametrima.

U našem istraživanju svi bolesnici pri prijemu imali su povišenu telesnu temperaturu, a sedmog dana lečenja došlo je do značajnog sniženja telesne temperature. Kod svih bolesnika prisutnost dizuričnih tegoba nakon sedmog dana lečenja bila je značajno manja nego pri prijemu, kao i prisutnost bola u lumbalnoj regiji nakon sedmog dana lečenja. Rezultati pokazuju da antibiotska terapija koja je primenjena u lečenju infekcija urinarnog trakta, bila ona po ličnom izboru ordinirajućeg lekara ili data po farmakoterapijskim smernicama, dovodi do jednako efikasnog sniženja telesne temperature, smanjenja broja bolesnika sa prisutnim bolom u lumbalnoj regiji i dizuričnim tegobama, sedmog dana bolničkog lečenja. Svi bolesnici otpušteni su kući izlečeni.

Od biohemijskih parametara praćen je broj bolesnika sa povišenim ukupnim brojem leukocita i vrednost leukocita (koliko je bolesnika imalo povišene vrednosti i koje su to vrednosti), broj bolesnika sa povišenom sedimentacijom eritocita i vrednostima fibrinogena. Broj bolesnikasa sa povišenim vrednostima ukupnog broja leukocita, kao i povišenim vrednostima fibrinogena nakon sedmog dana lečenja bio je značajno manji nego pri prijemu u obe grupe. Broj bolesnika sa povišenim vrednostima sedimentacije eritocita (prvi sat) pri prijemu i sedmog dana lečenja u obe grupe, nije pokazao značajnu razliku.

U grupi bolesnika koji su dobijali antibiotsku terapiju prema ličnom izboru lekara, kao lek izbora bio je najviše korišćen ciprofloksacin 24% , na drugom mestu bio je ceftriakson sa 23%, a na trećem gentamicin sa 13%. Prvo mesto ciprofloksacina opravdano je i preporučeno po svim svetskim preporukama [11–14, 16, 18]. Ceftriakson je preporučen za lečenje pijelonefritisa i njegova upotreba jedino je u tom slučaju opravdana [13, 14]. Gentamicin koji se nalazi na trećem mestu po upotrebi u našem istraživanju se, takođe, preporučuje [13, 14] u lečenju pijelonefritisa, ali u kombinaciji sa ampicilinom ili ciprofloksacinom, što kod nas nije bio slučaj.

Istovremeno davanje dva antibiotika kao početak bolničkog lečenja ordinirano je kod 14 (28,0%) bolesnika. Najčešće kombinacije bile su cefotaksim sa ciprofloksacinom, ceftriakson sa amikacinom i gentamicin sa cefaleksinom, ali nijedna od ovih kombinacija nije preporučena za lečenje urinarnih infekcija [11–14].

U ovoj grupi bolesnika najčešći nastavak antibiotske tarapije posle primene ceftriaksona bio je peroralni oblik ciprofloksacina kod osam (16%) bolesnika i posle primene gentamicina cefaleksin kod 5 (10%); oba antibiotika su preporučena u lečenju infekcija urinarnog trakta.

Broj dana antibiotske terapije kretao se od pet do 21, dok se po preporukama zemalja sa razvijenom farmakoterapijskom praksom za lečenje nekomplikovanih urinarnih infekcija preporučuje sedam dana antibiotske terapije, a za pijelonefritis 14 dana terapije [13, 14]. Promena antibiotske terapije kao posledica mikrobiološkog nalaza urinokulture, te započete neadekvatne empirijske terapije bila je kod dva bolesnika, što znači da je veliki broj bolesnika primao odgovarajuću terapiju.

U grupi bolesnika koji su dobijali antibiotsku terapiju po smernicama farmakoterapije, lek prvog izbora bio je ciprofloksacin, 32%, na drugom mestu je kotrimoksazol, 25%, a na trećem gentamicin, 14%, i ampicilin, 14%. Upotreba ciprofloksacina, koja je na prvom mestu, opravdana je i preporučena u lečenju infekcija urinarnog trakta [11–14]. Od 50 posmatranih bolesnika, kod 30 (70%) primenjen je samo jedan antibiotik. Kod 20 (40%) bolesnika ordiniran je drugi antibiotik posle primene prvog, kao prelazak parenteralne na peroralnu terapiju, što se preporučuje po smernicama [13, 14].

Ukupan broj dana antibiotske terapije kretao se od pet do 17, što je opravdano po preporukama zemalja sa razvijenom farmakoterapijskom praksom. Istraživanjem u Nepalu pokazano je da je dovoljan broj dana provedenih u bolnici 6,5 ± 3,3 za lečenje bolesnika sa urinarnom infekcijom (fluorohinolonima), a zatim nastavak antibiotske terapije, ako je potrebno kod kuće [19]. Pošto nemamo novije istraživanje praćenja rezistencije**,** tokom 2002. godine u Sektoru za bakteriologiju i parazitologiju Instituta za zdravstvenu zaštitu u Novom Sadu praćena je rezistencija na antimikrobne lekove najčešće izolovanih uzročnika mokraćnih infekcija. Rezultati su pokazali porast rezistencije *E. coli* na fluorohinolone, gde je više procenata rezistencije kod sojeva izolovanih iz mokraće ambulantno lečenih bolesnika (ciprofloksacin 45,2%), nego bolnički lečenih (ciprofloksacin 42,8%). Rezistencija sojeva *Proteus mirabillis* izolovanih iz mokraće ambulantno lečenih bolesnika, na ceftriakson veća je kod ambulantno lečenih bolesnika (17,7%) nego kod bolnički lečeni (12,7%) [20], što potvrđuje neopravdanu upotrebu ovog leka u vanbolničkim ustanovama, a često i u bolničkim.

Troškovi lečenja kod obe grupe bolesnika pokazuju velike raspone između maksimalnih i minimalnih troškova po računatim bolesničko-opskrbnim danima, utrošenim lekovima, sanitetskom i medicinskom materijalu i stacionarnim uslugama. U našem istraživanju pokazali smo da su u grupi bolesnika u kojoj su primenjene farmakoterapijske smernice u poređenju sa kontrolnom grupom, ostvarene uštede u svakom ispitivanom delu ukupne cene lečenja. Ušteda u ceni bolesničko-opskrbih dana bila je 32,94%, u ceni utrošenih lekova bila je najveća ušteda 43,08%, u ceni sanitetskog i medicinskog materijala 32,06%, ceni stacionarnih usluga 29,42% i ukupna ušteda cene lečenja infekcija urinarnog trakta, ako se primenjuju farmakoterapijske smernice, bila je 35,67%. U Italiji je rađeno istraživanje primenene protokola za lećenje cistitisa koje je pokazalo da se njihovom primenom troškovi lečenja po bolesniku sa 23 evra, smanjuju na 12,75 evra [21]. U ovom radu dobili smo slične rezultate jer je minimalna ukupna cena lečenja urinarnih infekcija bila 18,3 evra u ispitivanoj i 17,7 evra u kontrolnoj grupi. Istraživanje cene lečenja febrilnih infekcija urinarnog trakta kod dece, pokazalo je da se urinokultura kod dece koja su u hospitalnim uslovima primala antibiotsku terapiju i kod kuće, jednako negativizirala nakon pet dana. Uštede od 73% materijalnih sredstava zabeležene su u grupi bolesnika koji su lečeni kod kuće [22].

Troškovi lečenja su najmanji ako se lekovi primenjuju uz poznavanje rezistencije lokalnih sojeva *E. coli*, što je pokazano u radu iz Engleske [23], ali u našoj zemlji još ne postoji zakonska obaveza praćenja rezistencije. Vakcinacije bolesnika sa rekurentinim infekcijama urinarnog trakta, pokazala se kao povoljno ekonomsko rešenje. Posle šest meseci od vakcinacije troškovi lečenja ovih bolesnika smanjili su se sa 238 evra na 91 evro (po bolesniku) [24]. Kod nas još nije registrovan nov karbapenemdoripenem, koji se pokazao uspešnim u lečenju komplikovanih infekcija urinarnog trakta izazvanih *Pseudomonas aeruginosa* rezistenim na druge karbapeneme [25], a njegova primena bi dovela do značajnih smanjenja dosadašnjih materijalnih troškova u lečenju ove infekcije. Infekcije urinarnog trakta čine 25% svih infekcija, a godišnje na njihovo lečenje u Americi se potroši oko 1,6 milijardi dolara, zaključujemo da bi i kod nas pravilna upotreba antibiotika dovela do velikih ušteda [26].

Zaključak

Terapijski efekti pojedinih antibiotskih tretmana primenjenih u lečenju bolesnika sa infekcijom urinarnog trakta na Klinici za infektivne bolesti, KC Vojvodine su povoljni, jer se lečenje svih bolesnika završilo izlečenjem.

Formirani su principi lečenja infekcije urinarnog trakta po preporukama iz britanskog *British National Formulary* i američkog *Senford* vodiča za antimikrobnu terapiju, pošto u našoj zemlji ne postoje takvi vodiči. Efikasnost uobičajenog načina lečenja i lečenja prema aktuelnim farmakoterapijskim smernicama iz razvijenih zemalja podjednaka je.

Cena lečenja infekcija urinarnog trakta u našem istraživanju bila je povoljnija u grupi bolesnika u kojoj su primenjivane smernice.

U grupi bolesnika sa infekcijom urinarnog trakta, u kojoj su primenjene farmakoterapijske smernice u poređenju sa grupom bolesnika koji su dobijali antibiotike prema ličnom izboru lekara, zabeležena je ušteda u svakom ispitivanom delu ukupne cene lečenja. Ušteda u ceni bolesničko-opskrbih dana bila je 32,94%, u ceni utrošenih lekova 43,08%, u ceni sanitetskog i medicinskog materijala 32,06%, ceni stacionarnih usluga 29,42%, dok je ukupna ušteda cene lečenja infekcija urinarnog trakta, ako se primenjuju farmakoterapijske smernice, bila 35,67%.

Kombinacija savremenih farmakoterapijskih principa lečenja daje optimalne rezultate u lečenju infekcija urinarnog trakta. Primenjujući ove stavove u našem ispitivanju omogućeno je optimalno lečenje uz racionalnu potrošnju materijalnih sredstava.

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Clinical and functional evaluation of patients with acute low back pain and radiculopathy treated with different energy doses of low level laser therapy

Klinička i funkcionalna ispitivanja bolesnika sa akutnim lumbalnim sindromom i radikulopatijom koji su lečeni različitim dozama laseroterapije

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Abstract

Background/Aim. The main clinical phenomena in acute low back pain (LBP) with radiculopathy are pain and neurological disorders. Although some studies show that low level laser therapy (LLLT) has the ability to modulate inflammatory processes and relieve acute pain condition, the laser therapy dose protocol has not been yet completely established. The aim of this study was to investigate the effects of three different energy doses of LLLT in patients with acute LBP and radiculopathy. **Methods.** The study included 66 patients with acute LBP and radiculopathy who had been randomly divided into three groups (22 patients each) received three different doses of LLLT. The patients were treated 5 times weekly, for a total of 10 treatments, with the following parameters: wave length 904 nm, frequency 3,000 Hz, average diode power 25 mW; energy dose of 0.1 J per point in the first group, 1 J per point in the second and 4 J per point in the third group; daily treatment time and accumulated energy were 16 s and 0.4 J in the first group, 160 s and 4 J in the second group and 640 s and 16 J in the third group, respectively. The parameters of assessment before and after the therapy were: lumbar and leg pain measured by visual analogue scale (VAS), local and general functional changes (Schober test, manual muscle test, straight leg raise test and the modified North American Spine Society-Low Back Pain Outcome Instrument–NASS LBP). **Results.** Highly significant improvements ($p < 0.01$) were noted in all the groups after LLLT with respect to all the investigated parameters. The VAS scores were significantly lower in all the groups without a difference between the groups ($p > 0,05$). Functional improvements were better in the third group treated with the dose of 4 J per point than in other two groups ($p < 0.05$). **Conclusions.** Three different energy doses of LLLT were equally effective in alleviating lumbar and leg pain without side effects, but the dose of 4 J per point seemed to be more effective in improving the activities of daily living and lumbar mobility.

Key words:
lumbosacral region; pain; pain assessment; laser therapy; treatment outcome.

Apstrakt

Uvod/Cilj. Glavne kliničke manifestacije kod bolesnika sa akutnim lumbalnim sindromom i radikulopatijom (ALR) su bol i neurološki poremećaji. Mada su neke studije pokazale da terapija laserom male snage (LMS) menja inflamatorne procese i olakšava akutna bolna stanja, protokol lečenja laserom još uvek nije kompletno utvrđen. Cilj rada bio je da se ispita efikasnost tri različite doze LMS kod bolesnika sa ALR. **Metode.** U istraživanje je bilo uključeno 66 bolesnika sa ALR. Bolesnici su metodom slučajnog izbora bili podeljeni u tri grupe, po 22 bolesnika, kojima je primenjivana laseroterapija u različitim dozama. Bolesnici su tretirani pet puta nedeljno, ukupno 10 terapija, sledećim parametrima LMS: talasna dužina 904 nm; frekvencija 3 000 HZ; izlazna snaga 25 mW; doza od 0,1 J po tački u prvoj, 1 J po tački u drugoj i 4 J po tački u trećoj grupi; dnevno trajanje terapije i primljena energija iznosili su 16 s i 0.4 J u prvoj grupi, 160 s i 4 J u drugoj grupi i 640 s i 16 J u trećoj grupi. Parametri praćenja na početku i nakon dve nedelje terapije bili su bol u leđima i nozi, mereni vizuelnom analognom skalom (VAS), lokalni i opšti funkcijski status bolesnika (pokretljivost lumbalne kičme, manuelni mišićni test, test istezanja po Lazareviću, modifikovani *North American Spine Society Low Back Pain outcome* test). **Rezultati.** Kod sve tri grupe bolesnika uočeno je statistički

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visoko značajno poboljšanje svih ispitivanih parametara posle LMS terapije ($p < 0,01$). Skorovi VAS bili su niži u sve tri grupe, ali bez statistički značajne razlike ($p > 0,05$). Značajnije poboljšanje funkcijskog statusa uočeno je u trećoj grupi bolesnika koja je lečena dozom od 4 J po tački ($p < 0,05$). **Zaključak.** Tri različite doze LMS bile su podjednako efikasne u smanjenju bola u leđima i nozi bez neželjenih efekata, ali je doza od 4 J po tački bila efikasnija u poboljšanju aktivnosti dnevnog života i pokretljivosti lumbalne kičme ispitivanih bolesnika.

Ključne reči:
lumbosakralni predeo; bol; bol, merenje; lečenje laserom; lečenje, ishod.

Introduction

The point prevalence of low back pain (LBP) is reported to be as high as 33% and 50% of people whith LBP are expected to seek care [1, 2]. Acute episode that lasts less than 4 weeks is both a major cause of temporary disability and a challenge to correct medical treatment decision [3, 4]. The main clinical phenomena in acute LBP with radiculopathy are pain and neurological disorders that affect daily activities [5].

Data strongly support the role of inflammation alone or in association with root compression in pain etiology of lumbar radiculopathy that is associated with herniated discs [6, 7].

Laboratory studies show that low level laser therapy (LLLT) has the ability to modulate inflammatory processes and relieve acute pain conditions triggered by lesions in soft tissues [8–10]. This activity may occur through the decrease in nerve conduction, release of endogenous opioids, increase in angiogenesis and, consequently, increase in local microcirculation. It may also have inhibitory effects on the release of prostaglandins, cytokine levels and cyclooxygenase (Cox) 2 and it may accelerate cell proliferation, collagen synthesis and tissue repair [9, 11–13].

One of the most important aspects of laser applications is the dose, which is defined as the quantity of radiation emitted to the tissue. With regard to clinical studies, it is agreed that dose should be express in Joules (J) [14].

The literature data and reviews show a wide range of doses that are used in the treatment of acute and chronic musculoskeletal disorders [15]. The majority of recently created studies report the use of doses ranging from 1 J to 4 J [16–23].

Despite the increase in quality and volume of clinical studies of LLLT in recent years, a laser therapy dose protocol has not been completely established. This fact is due to the variable parameters of laser light that have been used in the investigations. Moreover, different equipment, experimental designs and techniques do not allow to compare the results of the clinical trials.

In *in vitro* trials higher energy doses have been reported to suppress inflammation and this effect was also reported to be dose-dependent, ranging from 0.3 J to 19 J per cm^2 (J/cm^2). The anti-inflammatory effect was highly significant after 5 days with daily laser treatment [8].

In the same review, Bjordal et al. [8] analysed clinical trials of LLLT and acute inflammatory pain, nine studies were methodologicaly acceptable and showed the adventage of LLLT groups over placebo groups and they emphasized the anti-inflammatory effect of LLLT in clinical settings.

It was also reported that energy doses that produced an anti-inflammatory effect were 1 J/cm^2 and 2.5 J/cm^2 and the dose of 2.5 J/cm^2 produced a better anti-inflammatory effect similar to those produced by diclofenac at the dose of 1 mg/kg [24]. Laser therapy and the dose of 2.1 J/cm^2 was more effective than 0.9 J/cm^2 and 4.2 J/cm^2 in the treatment of carrageenan-induced pleurisy in rat [25].

To our knowledge, there is a missing link between the results and effects of different protocol doses from LLLT in the laboratory and the results of clinical trials.

There are many papers reporting the use of LLLT for improvement of symptomatology of chronic, nonspecific LBP patients [19, 26–29] but there are no many trials concerning acute LBP with radiculopathy and no study has been conducted to determine the effect of different doses of LLLT in the treatment of LBP patients.

Based on these findings, the aim of the study was to assess the efficacy of LLLT given at three different doses and related functional short term changes in patients with acute LBP and radiculopathy.

Methods

The prospective double-blind randomized study included 66 patients, suffering from acute LBP with radiculopathy caused by disc herniation with the duration of symptoms less than four weeks. The diagnosis was made by clinical examination and additional investigations like plain radiography, magnetic resonance imaging and standard nerve conduction study and needle myography (NCS/EMG). Clinical characteristics for inclusion in the study were lumbar and unilateral leg pain, duration of symptoms less than four weeks, clinical signs of radicular lesion in dermatomal distribution and/or myotomal muscle weekness and/or diminished reflexes in lower limbs. The main criteria for patients exclusion were chronic low back pain and a previous spinal surgery.

Also, patients with neurological, metabolic, endocrine and neoplastic diseases were excluded from the study. Individuals who had received corticosteroids in the last 30 days were also excluded. Prior to treating with LLLT and baseline examination, all patients received nimesulide 200 mg/day during 7–14 days.

Of 84 referrals, 16 patients did not meet the entry criteria, 2 patients refused to participate and 66 patients were randomly assigned to three equal laser groups (A, B and C, n = 22 each) treated with different doses of laser light during two weeks (ten therapy sessions, five times a week except weekends).

The characteristics of laser beam included: wave length 904 nm; frequency 3000 Hz; power output 25 mW; spot size 1 cm²; dose 0.1 J per point in the group A, 1 J per point in the group B, and 4 J per point in the group C; daily treatment time and energy delivered were 16 s and 0.4 J in the A group, 160 s and 4 J in the B group and 640 s and 16 J in the C group, respectively; application mode – stationary in contact with skin, anatomical site local – 4 points, 2 cm laterally from spinous process of involved and next distal spinal segment. The doses were chosen according to recommended anti-inflammatory doses for Galium-Arsenide (GaAs) lasers by the World Association of Laser Therapy (WALT) [30] and energies that were used in clinical trials for lumbar spine pain [19, 26, 29].

Prior to commencing the study, ethics approval was obtained from the Medical School, University of Belgrade, Ethics Committee, and all patients gave informed written consent to participation in the study.

The outcome measures included:

1. Functional evaluation of the patients activities of daily living (ADL) according to a modified North America Spine Society Low Back Pain Instrument (NASS LBP) [31, 32]. The questionnaire measures symptoms, functional status, expectations from the treatment and satisfaction. The patients were asked to report how pain affected their activities such as walking, sitting and standing and each item was scaled from a complete ability to complete disability.

2. The visual analogue scale (VAS) was used in the measurement of lumbar and leg pain [33]. Pain levels were scored from 0 to 10, where 10 indicated unbearable pain and 0 indicated no pain at all.

3. Physical examination of the lumbar spine and legs [34]: a) measurement of lumbar spine flexion as the distance from the top of the third finger to the floor (cm); b) the Schober test was assessed by measuring the distance between two spinal landmarks.

Marks were made on the skin at the spinous process of L5 and 10 cm above as the participant stood in a neutral position. A participant then bent forward maximally, and the change in the distance between these marks was measured in cm; c) manual muscle testing (MMT) of crucial muscles according to the American Spinal Injury Association Protocol [35].

We performed and rated MMT from 5 to 0 (5 indicated that a patient could hold the position against maximum resistance and through a complete range of motion and 0 indicated no contractile activity in the gravity eliminated position). The tested muscles were: the iliopsoas for L2 miotome, the quadriceps muscle for L3, the tibialis anterior for L4, the extensor hallucis longus for L5 miotome and the gastrocnemius for S1 miotome; d) straight leg raise test.

To identify any adverse effects of the treatment, the subjects were asked to record any new symptoms.

The data were evaluated by using SPSS Version 17.0 for Windows. The results were expressed as the mean and standard deviation for data with the normal distribution, or as median and interquartile range for data that were not distributed normally. Significant differences among pre-treatment characteristics of the patients and baseline measurements among the groups were evaluated using χ^2 test, Mann-Whitney *U* test and Kruskal-Wallis test. The pain level scores and functional status of the patients in each group before and following therapy were tested using paired samples *t*-test and Wilcoxon Signed Ranks test.

Intergroup statistical analysis and comparison of differences among the groups for all outcome measures at the beginning and the end of the therapy were tested by the General Linear Model. The differences of p value < 0.05 were considered statistically significant.

Results

The main characteristics of the patients in the groups before the therapy are outlined in Table 1. There was no statistically significant difference among the investigated groups in terms of age and body mass index (BMI) ($p > 0.05$). Moreover, there was no difference in the levels of lumbar and leg pain ($p > 0.05$). The flexion of lumbar spine among the groups was similar without a significant difference ($p > 0.05$). The groups differed in MMT before the therapy, the patients in the group C had lower muscle strength as compared with the group A ($p = 0.044$) (Table 1). Electromyographic testing did not show a difference among the groups in terms of common affected nerve root levels and there was no difference in the severity of radicular lesions ($p > 0.05$) (Table 2).

Table 1

Characteristics of the patients before the low level laser therapy (LLLT)

Characteristics	Group	$\bar{x} \pm SD$	χ^2/F	*p* value
Age (yrs)	A	47 ± 10.711	0.873	> 0.05
	B	44 ± 8.763		
	C	45 ± 6.78		
Body mass index (kg/m2)	A	23,93 ± 2.43	2.545	> 0.05
	B	25.1 ± 2.78		
	C	25.10 ± 1.75		
Lumbar pain (VAS)	A	7 ± 1	1.149	> 0.05
	B	7 ± 3.5		
	C	6.5 ± 1		
Leg pain (VAS)	A	7 ± 1.5	1.031	> 0.05
	B	6.75 ± 3		
	C	6.5 ± 2		
Flexion (cm)	A	58.7 ± 20.8	0.285	> 0.05
	B	55.0 ± 16.9		
	C	55.7 ± 14.2		
Schober (cm)	A	2 ± 2	0.068	> 0.05
	B	2 ± 0.5		
	C	2 ± 0.5		
Manual muscle test	A	3 ± 1	6.225	0.044
	B	2 ± 1		
	C	2 ± 0.5		

SD – standard deviation; A – group treated by energy dose of 0.1J/point; B – group treated by energy dose of 1J/point; C – group treated by energy dose of 4J/point; VAS – Visual analogue scale

Table 2

The affected nerve root levels in the groups and severity of radicular lesions (electromygraphic study)

Affected root levels/severity of radicular lesions	Groups of patients			Statistics	
	A n (%)	B n (%)	C n (%)	χ^2	*p*
L4	6 (27.3)	5 (22.7)	0 (0)		0.085
L5	7 (31.8)	11(50.0)	13(59.1)		
S1	9 (40.9)	6 (27.3)	9 (40.9)	8.193	
Mild to moderate	3 (13.6)	0 (0)	0 (0)		
Moderate	10 (45.5)	10 (45.5)	7 (31.8)		0.162
Moderate to severe	7 (31.8)	7 (31.8)	11 (50.0)		
Severe	2 (9.1)	5 (22.7)	4 (18.2)	9.219	

A – group treated by energy dose of 0.1J/point; B – group treated by energy dose of 1J/point; C – group treated by energy dose of 4J/point

The baseline examinations of ADL did not show a significant difference among the groups ($p > 0.05$). The majority of patients in all groups improved the disability and discomfort during ADL following LLLT in relation to much better walking, sitting and standing and that was highly statistically significant ($p < 0.0001$) (Table 3).

There was no significant difference between the group A and the group B ($p > 0.05$), but the patients in the group C showed some statistically significant improvements in walking (F = 5.319; $p = 0.007$), sitting (F = 5.882; $p = 0.005$) and standing (F = 4.621; $p = 0.013$) as compared to the previous groups (Table 3).

After LLLT, we noticed pain reduction measured by VAS in all of the three investigated groups treated with different doses of laser light without a significant difference among the groups. Thus, all of the three doses were equally efective in relation to reduced lumbar pain (F = 2.161, $p > 0.05$) (Figure 1).

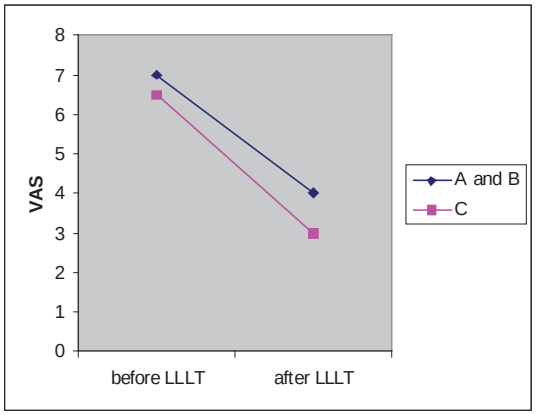

Fig. 1 – Lumbar pain in the groups before and after the low level laser therapy (LLLT)

VAS – Visual analogue scale; A – group treated by energy dose of 0.1J/point; B – group treated by energy dose of 1J/point; C – group treated by energy dose of 4J/point

Table 3

The reported activities of daily living (ADL) before and after low level laser therapy (LLLT)

ADL	Groups of patients (n = 22 in each group)						Statistics
	A (%)		B (%)		C (%)		
	before	after	before	after	before	after	
Ability to walk							
I can walk	0.0	4.5	4.5	9.1	0.0	13.6	
I can not walk >1 h	9.1	27.3	9.1	22.7	4.5	45.5	(C : A and B)
I can not walk >30 min	13.6	27.3	22.7	40.9	22.7	27.3	F = 5.319
I can not walk >10 min	45.5	40.9	36.4	22.7	31.8	13.6	$p = 0.007$
I can walk a few steps only	27.3	0.0	27.3	4.5	31.8	0.0	
I can not walk at all	4.5	0.0	4.5	0.0	9.1	0.0	
Statistics	Z=3.376*		Z=3.456*		Z=4.086*		
Ability to sit							
I can sit in every chair	4.5	9.1	0.0	4.5	0.0	4.5	
I can sit in special chair	0.0	0.0	0.0	0.0	0.0	36.4	(C : A and B)
I can not sit >1 h	9.1	36.4	13.6	13.6	13.6	45.5	F = 5,882
I can not sit >30 min	22.7	36.4	13.6	63.6	13.6	13.6	$p = 0.005$
I can not sit >a few min	54.5	13.6	45.5	13.6	36.4	0.0	
I can not sit at all	9.1	4.5	27.3	4.5	13.6	0.0	
Statistics	Z=3.491*		Z=3.080*		Z=4.142*		
Ability to stand							
I can stand	0.0	9.1	0.0	0.0	0.0	13.6	
I can stand with pain	4.5	9.1	0.0	22.7	4.5	27.3	(C : A and B)
I can not stand >1h	0.0	13.6	0.0	13.6	4.5	40.9	F = 4,621
I can not stand >30 min	18.2	45.5	13.6	31.8	27.3	18.2	$p = 0.013$
I can not stand >10 min	50	18.2	50	31.8	31.8	0.0	
I can not stand at all	27.3	4.5	36.4	0.0	31.8	0.0	
Statistics	Z=3.816*		Z=3.677*		Z=4.176*		

A – group treated by energy dose of 0.1J/point; B – group treated by energy dose of 1J/point; C – group treated by energy dose of 4J/point
***statistically significant difference ($p < 0.0001$)**

Similar results were noticed for leg pain (F = 1.978, $p > 0.05$) (Figure 2).

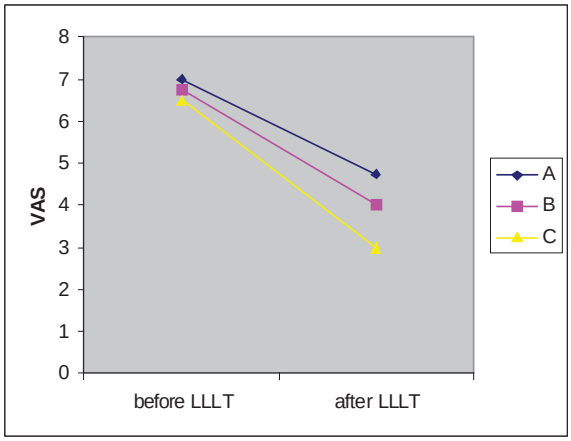

Fig. 2 – Leg pain in the groups before and after the low level laser therapy (LLLT)

VAS – Visual analogue scale; A – group treated by energy dose of 0.1J/point; B – group treated by energy dose of 1J/point; C – group treated by energy dose of 4J/point

Lumbar spine flexion was improved in all the groups after LLLT that was statistically significant ($p < 0.0001$). On the other hand, the patients in the group C treated with the dose of 4 J per point had better improvements in the flexion of lumbar spine (distance from the top of the third finger to the floor in cm) compared with A and B groups (F = 12.543, $p < 0.0001$) (Figure 3). The difference between A and B groups did not exist, patients in both groups improved flexion of lumbar spine equally ($p > 0.05$).

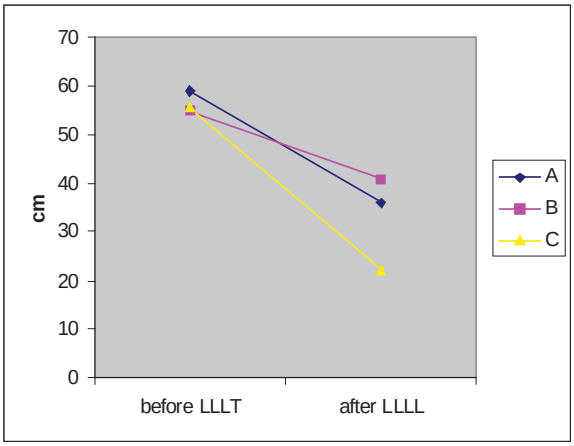

Fig. 3 – Flexion of lumbar spine before and after the low level laser therapy (LLLT)

A – group treated by energy dose of 0.1J/point; B – group treated by energy dose of 1J/point; C – group treated by energy dose of 4J/point

The patients in the group B and the group C had significantly higher values of the Schober's index (F = 4.329; $p < 0.05$) than the first group treated with the lowest dose of laser light, where we did not notice such an improvement following LLLT ($p > 0.05$).

At the end of the treatment, the patients from all groups equally improved muscle strength in their legs ($p < 0.0001$; figure 4) and showed better results in straight leg raise test ($p < 0.01$) without any differences among the groups (F = 3.066; $p > 0.05$; F = 2.922; $p > 0.05$).

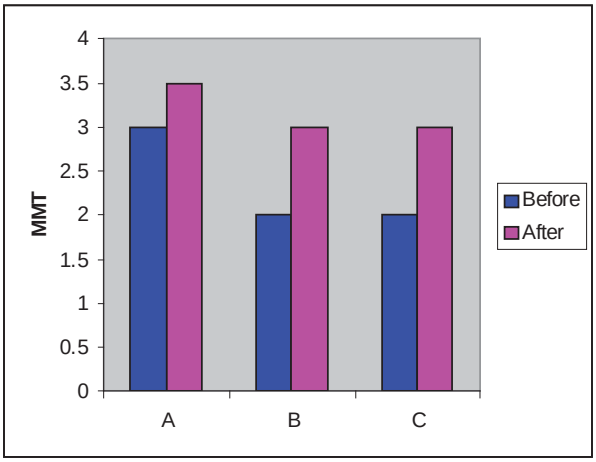

Fig. 4 – Manual muscle test (MMT) in the groups before and after the low level laser therapy (LLLT) therapy

A – group treated by energy dose of 0.1J/point; B – group treated by energy dose of 1J/point; C – group treated by energy dose of 4J/point

In this study, systemic or local side effects from laser treatment were not noticed.

Discussion

Prevention of recurrences and chronicity is identified as an important goal in the management of acute LBP [4]. Clinical guidelines recommend a series of steps in order to diagnose and treat patients presenting with LBP, including lumbar disc herniations [36]. The main criterion for judgment of treatment effectiveness includes pain and functional disability which have a considerable impact on overall health.

The present study investigated the use of different energy doses of LLLT for the treatment of acute LBP with radiculopathy. The doses of 0.1, 1 and 4 J per point showed a significant efficacy in relation to reduced pain and functional disability of the patients. Importantly, the patients treated with the dose of 4 J per point had significantly better results in terms of ADL and lumbar mobility.

The differences in the included patients and the applied regimes of LLLT were the main difficulty in comparing the results of this study with the results of other clinical LLLT trials.

Additionaly, there was no published research on the comparison of different energy doses in treating LBP. Most of the studies in the available literature included patients with non-specific chronic back pain [17, 19, 26, 28, 29]. We identified a meta-analysis by Yousefi-Nooraie et al. [37] considered nonspecific LBP, and there were no firm conclusions on the clinical effect of LLLT for LBP.

Soriano et al. [26] demonstrated the efficacy of LLLT in the treatment of chronic lumbar pain with following pa-

rameters of laser light: wave length - 904 nm, average power - 40 mW, frequency – 10,000 Hz, dose-4 J/cm^2.

Gur et al. [19] concluded that LLLT (producing energy of approximately 1 J/cm^2 improved pain and functional disability in the therapy of chronic LBP, but it did not bring any additional benefits to exercise therapy.

In the study that investigated acute lumbar pain associated with disc herniation, Gruszka et al. [27] showed positive results, improved pain relief and neurological status after LLLT with the dose of 9 J/cm^2. This study was supported by CT scans and conventional needle myography.

According to Konstantinovic et al. [18] treatment of acute LBP with radiculopathy at 904-nm LLLT at a dose of 3 J, proposed as additional therapy to nonsteroidal anti-inflammatory COX-2 drugs showed better improvement in local movements, more significant reduction in pain intensity and related disability, and improvement in quality of life, compared with patients treated only with drugs and with a placebo LLLT procedure. The study included 546 patients with symptoms for less than 4 weeks, caused by a prolapsed intervertebral disc, and confirmed by magnetic resonance imaging. The baseline characteristics, intensity of pain and functional disabilities of the patients were similar to our patients sample but the study showed positive clinical results of LLLT as additional therapy with nimesulide 200 mg/day without investigating the dose-dependent effects. Transitional worsening of pain was registered in 27 patients and 4 patients had persistent pain but the final results of side effects show the low risk nature of LLLT. In our study, the patients did not report the worsening of pain and symptoms.

Unlu et al. [38] investigated and compared LLLT (830 nm laser unit at a dose of 1 J/cm^2), ultrasound and traction therapy in the treatment of patients with acute lumbar and leg pain due to disc herniation. The study showed that all therapies were effective in reducing pain and disability scores but there was no significant difference among the 3 treatment groups. There were significant reductions in size of the herniated mass on magnetic resonance imaging after the treatment, but no differences among the groups.

The same design of the study was implemented in a a randomized controlled clinical trial by Monticone et al. [39] who compared two different methods (orthosis and exercises with a previous mesotherapy and LLLT) in treating patients with acute LBP. They found no significant pain relief in the group treated with LLLT, but treatment parameters and application technique were not reported.

In the very new prospective, placebo controlled study the Ay et al. [40] compared the effectiveness of LLLT (wave length of 850 nm and daily delivered energy of approximately 40 J) on pain and functional capacity in patients with acute and chronic LBP caused by disc herniation and found no differences between laser and placebo laser treatment. The authors did not explain precisely the clinical characteristics of the patients with acute LBP and duration of symptoms. They excluded patients with neurological deficits that was not in accordance with our study. All patients completed the study without side effects.

In summary, the results from our study suggest that LLLT given at three different doses, plays a significant role in reducing pain and functional disability in the treatment of acute LBP with radiculopathy. Although we did not find any statistically significant differences in pain intensity among groups, better improvements of physical function were observed in the group treated with the highest dose of LLLT.

The study has some limitations that must be considered. First, there was no placebo group for laser therapy. Second, the sample size was not enough to detect differences among the groups for some outcomes and evidences from this study suggest only the short-term effects.

In the evaluation of LLLT and LBP, the choice of the most optimal dosage presents a complex topic. For improved clinical results, the importance of LLLT dose as well as the pathophysiology of lumbar pain should be stressed.

Because of the positive results and different therapy regimes in the clinical evaluations of LLLT, further placebo-controlled studies with bigger homogeneous patients sample and longer follow-up periods should be performed in order to state precisely a laser therapy dose protocol and find possible interactions with other treatment modalities.

Conclusion

The results of this study show that the three investigated energy doses are equally effectve in reducing lumbar and leg pain without side effects in patients with acute LBP and radiculopathy, but the dose of 4 J per point seems to be more effective in improving the activities of daily living and lumbar mobility.

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Treatment of Achilles tendon rupture using different methods

Liječenje rupture Ahilove tetive primjenom različitih metoda

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Abstract

Background/Aim. Today there are controversies about searching for the ideal surgical method (conservatively with plaster cast, with open and percutaneous tenorrhaphy) for repairing a ruptured Achilles tendon. The aim of this study study was to examine the results of treating Achilles tendon ruptures in patients by using the following methods: percutaneous suturing, open surgery technique and non-surgical treatment by plaster cast immobilisation. **Methods.** Forty two patients treated at our facility in the period August 2003 – September 2010 for Achilles tendon ruptures were included in the study. They were operated on by using different orthopedic procedures (percutaneous reconstruction of the Achilles tendon, open surgery, plaster cast only) and two anaesthesia technique (spinal aneasthesia and local infiltrational anaesthesia). The following parameters were monitored after interventions performed and compared: duration of hospital stay, postsurgical complications, incidence of the reruptures of the Achilles tendon and time for full leg functionality. **Results**. The patients sustained their respective injuries in the following manner: 8 of them while pursuing sports activities, 24 while pursuing recreational activities, 4 at workplace, 4 while performing everyday activities, and 2 of the patients did not know how they had sustained their injuries. The average age of the patients was 40.5, with 37 (88%) men and 5 (12%) women. Surgeries were performed under spinal anaesthesia in 29 (69%) patients, and in 5 (12%) patients tenorrhaphy was performed under local anaesthesia. Anaesthesia was not used in 8 (19%) patients treated with plaster cast. We performed percutaneous reconstruction of the Achilles tendon in 19 (45%) patients. A total of 14 (33%) patients were treated under spinal anaesthesia, and 5 (11.9%) under local infiltrational anaesthesia with 2% xylocain. We treated 15 (36%) patients with open surgery. The patients treated conservatively stayed in hospital on average for up to 5 hours. Those who underwent an percutaneous surgery stayed 2 days and those who underwent an open surgery stayed 9 days. A total of 28 (66%) patients from the given series experienced no complications. The patients treated with open surgical reconstruction experienced skin complications ranging from inflammatory changes on the skin in 6 (14%) patients to dehiscence and skin necrosis in 3 (7%). The 5 (11.9%) patients whose ruptured Achilles tendon was treated percutaneously experienced temporary redness and delayed healing of the incision(s) longer than 5 mm. A total of 3 (7%) patients treated with open surgery and 1 (2%) patient treated with percutaneous tenorrhaphy had temporary peroneal nerve prolapses. A total of 7 (16.6%) patients had reruptures: 4 were treated with plaster cast, 2 underwent open surgery, and 1 was treated percutaneously. Out of the 8 patients who were treated with plaster cast, 4 sustained reruptures and 3 of the 4 had diabetes. **Conclusion.** Surgical treatment, percutaneous tenorrhaphy, performed in a small operating theatre under local anaesthesia, should be preferred in cases of fresh ruptures of the Achilles tendon.

Key words:
achilles tendon; rupture; orthopedic procedures; treatment outcome.

Apstrakt

Uvod/Cilj. Danas postoje kontroverze u vezi izbora idealne hirurške metode (konzervativno gipsom, otvorenom ili perkutanom tenorafijom) za reparaciju rupturirane Ahilove tetive. Cilj ovog rada bio je da se procijene rezultati liječenja rupture Ahilove tetive kod bolesnika metodom perkutanog šivenja, otvorenom operativnom tehnikom i neoperativnim liječenjem – gipsanom imobilizacijom. **Metode.** U studiju su bila uključena 42 bolesnika sa rupturom Ahilove tetive, liječena u našoj ustanovi u periodu avgust, 2003 – septembar, 2010. godine. Oni su liječeni različitim ortopedskim postupcima (perkutana rekonstrukcija Ahilove tetive, otvorena hirurgija, samo gips) i dvijema tehnikama anestezije (spinalna anestezija i lokalna infiltrativna anestezija). Pratili smo i uporedili slijedeće parametre poslije intervencija: dužinu boravka u bolnici, postoperativne komplikacije, incidenciju rerupture Ahilove tetive, kao i vrijeme potpune funkcionalnosti noge. **Rezultati.** Ispitanici su zadobili povrede: aktivnim sportom (8), na rekreaciji (24), na poslu (4), tokom obavljanja svakodnevnih aktivnosti (4), dok 2 ispitanika nisu znala razlog. Prosječna starost ispitanika bila je

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40,5 god. Muškaraca je bilo 37 (88%), a žena 5 (12%). Operativni zahvat izvođen je u spinalnoj anesteziji kod 29 (69%) ispitanika, a kod njih 5 (12%) tenorafija je urađena u lokalnoj anesteziji. Kod 8 (19%) ispitanika koji su liječeni gipsom, anestezija nije upotrebljavana. Perkutana rekonstrukcija Ahilove tetive vršena je kod 19 (45%) ispitanika, 14 (33%) ispitanika liječeno je u spinalnoj anesteziji, a 5 (11,9%) u lokalnoj infiltrativnoj anesteziji (2% Xylocain). Otvorenim operativnim pristupom liječeno je 15 (36%) ispitanika. Konzervativno liječeni ispitanici boravili su u bolnici u prosjeku do pet sati, perkutano hirurški liječeni, dva dana, a otvorenom hirurškom tehnikom liječeni, devet dana. Komplikacije nije imalo 28 (66%) ispitanika. Komplikacije kože imali su bolesnici liječeni otvorenom hirurškom rekonstrukcijom, u rasponu od upalnih promijena kože, šest (14%) pacijenata, do dehiscencije i nekroze kože, tri (7%) pacijenata. Bolesnici kod kojih je perkutano zbrinuta rupturirana Ahilova tetiva, pet (11,9%), imali su prolazno crvenilo i usporeno zarastanje one incizije čija je dužina bila veća od 5 mm. Prolazni ispadi nervusa peroneusa imala su tri (7%) ispitanika koji su zbrinuti otvorenom hirurškom metodom, i jedan (2%) ispitanik kod koga je tenorafija urađena perkutano. Rerupture je zadobilo sedam (16,6%) ispitanika: četiri liječena gipsom, dva liječena otvorenom hirurškom tehnikom i jedan perkutano. Od osam ispitanika koji su liječeni gipsom, rerupturu su zadobila četiri ispitanika, od kojih je troje bolovalo od dijabetesa. **Zaključak.** Kod svježe rupture Ahilove tetive prednost treba dati hirurškom liječenju, perkutanoj tenorafiji, koja se izvodi u maloj operacionoj sali uz primjenu lokalne anestezije.

Ključne reči:
ahilova tetiva; ruptura; ortopedske procedure; lečenje, ishod.

Introduction

The Achilles tendon connects the triceps muscle to the heel bone at the back of the lower leg and it plantar flexes the foot, lifting the heel and raising the entire body onto the toes. The Achilles tendon is exposed to physical strain and great stretch load while walking and moving [1].

Continuous activity of strong forces during increased physical strain (athletes, recreationists, manual workers) creates degenerative and infiltrative changes in the Achilles tendon, which makes it vulnerable and most often leads to ruptures of lower extremity tendons. These ruptures occur 2–5 cm above the calcaneal joint, they are found on both sides in approx. 25%–30% of cases, and occur five times more often in men than in women. Ruptures most often occur between the third and fifth decades of life [2].

Along with an increase in the interest of middle-aged people for recreation and taking part in sporting activities, spontaneous ruptures of the Achilles tendon occur more frequently than it was expected. The incidence of Achilles tendon ruptures in recreationists amounts to 61% [2].

The reasons for this increased incidence are unclear, but some of them could be the disproportion between body weight and Achilles tendon strength, intensified physical strain, increased use of corticosteroids, growth hormone and testosterone, microtraumas, illness- or age-related degenerative changes [1, 2.]

Ever since Achilles was killed after being shot at the calcaneal (Achilles) tendon people have been interested in it. Hippocrates came to the conclusion that this injury could even be fatal [1], and Jenings and Sefton [3] defined the functional importance of the Achilles tendon. In the 16th century, Parè provided the first description of an indirect rupture of the Achilles tendon [1]. Myerson [4] and Rostan [5] maintain that a normal tendon does not rupture and that this happens to a tendon already damaged in some way prior to the rupture. Burry and Pool [6] assumed that ruptures could only occur in abnormal tendons and in a combination of intratendinous degeneration and increased mechanical stress.

In 1959, Arner and Lindholm [7] favoured conservative treatment in their work, maintaining that the results were as good as those of surgical treatment. Ma and Griffith [8] put an end to the mutual dismissiveness between conservative and surgical treatment in 1977 by introducing percutaneous suturing of the Achilles tendon into practice. Percutaneous suturing of the Achilles tendon has since then been constantly improving, in an effort to get the best possible results The clinical signs are: strong pain when the tendon ruptures, palpable and sore "dent" in the Achilles tendon, and partial or complete loss of plantar flexion. The definite indication of a rupture is the Thompson "squeeze" test, i.e. the absence of plantar flexion of the foot on manually compressing the shank muscle [9]. Ultrasound confirms the clinical findings. Ultrasound is a highly sensitive and specific method for confirming the clinical diagnosis and monitoring the restitution of Achilles tendon ruptures [10]. A fresh Achilles tendon rupture can be treated both surgically and non-surgically [5].

The aim of the study was to examine the results of treating Achilles tendon ruptures in patients by employing the percutaneous suturing method, open surgery technique, and non-surgical treatment by plaster cast immobilisation and to point out the advantages of percutaneous surgical treatment of fresh Achilles tendon rupture over the open surgical technique and non-surgical treatment by plaster cast immobilisation.

Methods

Forty two patients treated at our facility in the period August, 2003 – September, 2010, for Achilles tendon ruptures were included in the study. They were operated on by using different orthopedic procedures (percutaneous reconstruction of the Achilles tendon, open surgery, plaster cast immobilization) and two anaesthesia technique (spinal aneasthesia and local infiltrational anaesthesia). The following parameters were monitored after interventions performed and compared: duration of hospital stay, postsurgical complications, incidence of the reruptures of the Achilles tendon and time for full leg functionality.

Results

The patients sustained their respective injuries in the following manner: 8 of them while pursuing sports activities, 24 while pursuing recreational activities, 4 at workplace, 4 while performing everyday activities, and 2 of the patients had sustained their Achilles tendon rupture for unknown reasons. The average age of the patients was 40.5, with 37 (88%) men and 5 (12%) women. Surgeries were performed under spinal anaesthesia in 29 (69%) patients, and in 5 (12%) patients tenorrhaphy was performed under local anaesthesia. Anaesthesia was not used in the 8 (19%) patients treated with plaster cast. On average, all patients were treated, either surgically or with plaster cast, within two days of the injury. All patients received medicamentous thromboembolism prophylaxis.

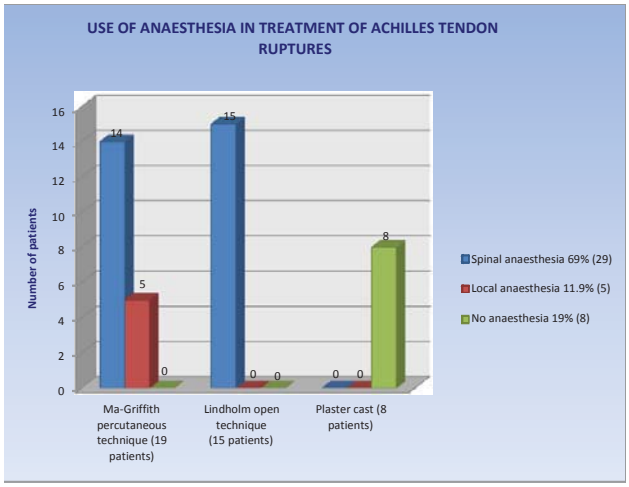

Fig. 1 – Use of anaesthesia in treatment of Achilles tendon ruptures

We performed percutaneous reconstruction of the Achilles tendon in 19 (45%) patients. Fourteen (33%) patients were treated under spinal anaesthesia, and 5 (11.9%) under local infiltrational anaesthesia, with 2% Xylocaine or Lydocaine. Having identified where Achilles tendon rupture occurred, we made 2 to 3 up-to-5-mm posteromedial and posterolateral skin incisions on both sides, distally to the depression in the Achilles tendon (Figure 2). Proximally to the depression in the Achilles tendon, we made 2 to 3 up-to-5-mm posteromedial and posterolateral skin incisions on both sides. Through skin incision, we penetrated diagonally in the proximal region through the skin of the tendon, from lateral to medial position, using a straight or slightly curved needle with slowly resorbing thread (Dexon, Vaykril or PDS) (0-1 thickness). At the point where the thread exited the skin, it went through both sides towards the distal position, making a Bunnell-type stitch. By this way the tendon was completely restituted and it did not take more than three stitches to establish and maintain the continuity of the Achilles tendon. The suture was tested by using the Thompson test. The skin was not sutured. Dermal concavities that stayed behind the needle puncture point was not a reason for concern because they subsided on their own in a couple of days. Knots were simply "pulled back" into the incision, using a small pair of scissors. An upper-leg definitive plaster cast with the knee in a flexed position and the foot in an equinus position was put on the operating table. In two weeks' time the plaster cast was cut shorter, below the knee. Two weeks later the lower-leg definitive plaster cast was put, with the heel positioned for full weight-bearing walking.

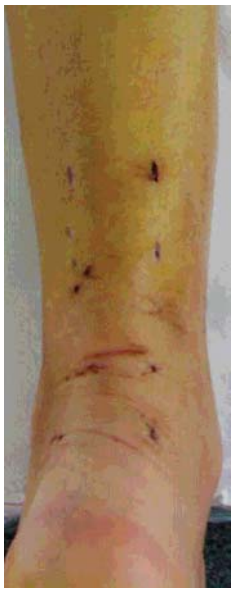

Fig. 2 – Posteromedial and posterolateral skin incisions on both sides, distally to the depression in the Achilles tendon

We treated 15 (36%) patients with open surgery. The approach was posteromedial, along the medial border of the Achilles tendon and between 10 and 12 cm in length. After the skin was incised and hemostasis controlled, the ruptured Achilles tendon was approached and restored using the Lindholm technique. Drainage was mandatory. An upper-leg plaster cast was put after the surgery, with the knee flexed and the foot in an equinus position. The average plaster cast immobilisation lasted 7.1 weeks.

Conservative treatment of a ruptured Achilles tendon commenced by putting the ruptured tendon in a total contact position and then by placing a high upper-leg plaster cast with the foot in the maximum equinus position, with the knee flexed 20°. The process of Achilles tendon cicatrisation takes three weeks [8], and our patients wore the plaster cast for four weeks so that the wound could completely cicatrise. During that time we recommended walking with crutches without weight-bearing through the leg, exercising toes from the very beginning, as well as exercises for strengthening the muscles of the upper leg [8]. After four weeks, the plaster cast was cut shorter, below the knee, and we maintained the foot equinus position for another four weeks. After eight weeks of wearing a plaster cast with the foot in an equinus position, the cast was taken off, and the heavy and sore foot was put in a neutral position in order to put a lower-leg definitive plaster cast with the heel in the walking position for two weeks. We treated 8 (19%) patients in this way.

All the patients were monitored in an outpatient setting for a year on average. The hospital inpatient stay was as follows: on average, the patients who were treated conservatively for Achilles tendon rupture stayed in hospital for up to 5 h; those who underwent percutaneous surgery stayed 2 days; and those who underwent open surgery stayed 9 days. Twenty eight (66%) patients from that series experienced no complications. The patients treated with open surgical reconstruction experienced skin complications ranging from inflammatory changes on the skin in 6 (14%) patients to dehiscence and skin necrosis in 3 (7%) of the patient (Table 1). The 5 (11.9%) patients whose ruptured Achilles tendon was treated percutaneously experienced temporary redness and delayed healing of the incision longer than 5 mm. The wounds healed when they were dressed with drained physiological gauze.

A total of 3 (7%) patients treated with open surgery and 1 (2%) patient treated with percutaneous tenorrhaphy had temporary peroneal nerve prolapses. A total of 7 (16.6%) patients had reruptures. A total of 4 of the 7 (16.6%) patients with reruptures were treated with plaster cast, 2 underwent open surgery, and 1 was treated percutaneously. Out of the 8 patients who were treated with plaster cast, 4 sustained reruptures (3 of the 4 had diabetes). Out of the 15 patients treated with the Lindholm open technique [1], 2 had Achilles tendon reruptures (Table 1). There was dehiscence prior to rerupture. Out of the 19 patients treated percutaneously with the Ma-Griffith technique [1], only 1 active athlete experienced an Achilles tendon rerupture during practice, four months after the percutaneous treatment. The analysis of rerupture established that the reason was the athlete's not following the doctor's orders (weight-bearing on the toes, going down stairs, slipping off smooth surfaces, early sporting activity).

The pain felt during surgical treatment, as well as occasional pain later on, are greatest in open surgical treatment of ruptured Achilles tendons, then in percutaneous surgical treatment and in conservative treatment. In open surgical treatment, patients on average take painkillers for three days, in percutaneous surgical treatment they take them for one day, and in plaster cast treatment, there is no need for painkillers (Table 1).

These treatments are accompanied by muscle atrophy.

The atrophy of the lower leg after surgical treatment of the Achilles tendon following the removal of a plaster cast (on average worn for 7.1 weeks) compared to the healthy lower leg amounts to 2 cm on average. Conservative treatment (plaster cast worn for 9.6 weeks) resulted in an average of 3.4 cm atrophy of the lower leg.

In one case, the tendon was elongated by plaster cast treatment. We had no tendon shortening or tendon elongation through surgical treatment.

In all patients treated with the Lindholm open technique the Achilles tendon thickened, which created minor or major clothing problems, due to compression at that point.

On average, full mobility of the ankle joint after percutaneous tenorraphy is established after 10 weeks, following the Lindholm open technique after 12 weeks and following plaster cast treatment after 16 weeks (Table 1).

We monitored the restitution of the Achilles tendon by ultrasound. We observed that in the first four weeks ultrasound examination did not detect any statistically significant differences between the surgically treated Achilles tendons and those treated with plaster cast. It suggested that surgically treated tendons were restored more quickly within that time. After twelve weeks, ultrasound did not show any difference between the tendons treated conservatively and those treated surgically.

In the surgical group there were no infections. One of the patients who were treated with the open surgical method had a pulmonary thromboembolism.

Table 1

Complications and time for the full leg functionality in patients surgically treated due to Achilles tendon ruptures

Parameters	Ma-Griffith percutaneous technique (n = 19)	Lindholm open technique (n = 15)	Plaster cast (n = 8)
Temporary inflammatory skin changes (n)	5	1	
Dehiscence and skin necrosis (n)		3	
Transitory paresis of peraneal nerve (n)	1	3	
Achilles tendon re-ruptures (n)	1	2	4
Thromboembolic complications (n)		1	
Pain duration during treatment (days)	1	3	
Full leg functionality (weeks)	10	12	16

Discussion

Tomak et al. [11] found percutaneous treatment of the Achilles tendon to be more successful than open surgery and that it could be performed under local anaesthesia and in outpatient conditions. In the period between 1991 and 1997, Cretnik et al. [12] made a prospective study about the modified percutaneous method of treatment of the Achilles tendon by monitoring patients over a two-year period. They monitored 134 patients, 124 men and 8 women after acute total ruptures. Postoperative care meant wearing a plaster cast for 6 weeks. The results were as follows: 1 (0.7%) complete re-

rupture, 4 (3%) partial reruptures, and ankle joint contractures were reported in 6 (4.5%) patients [12].

In 1981, Nistor et al. [13] published a study containing 105 cases of closed ruptures of the Achilles tendon treated surgically and non-surgically in which they showed that the treatment results were very similar. They gave preference to the percutaneous method. This treatment has certain advantages which are reflected in anatomic restitution of the tendon and maintenance of its length, reduction of the scar in the tendon tissue at the point of union and primary healing of the tendon within optimal time. Surgical treatment is usually preferred in younger people and active athletes [13].

The retrospective analysis conducted by Haji et al. [14] compared open and percutaneous treatment of ruptured Achilles tendons during a 14-year period. A total of 108 patients were monitored, 70 of whom underwent traditional surgical treatment, while 38 were treated by the modified Ma-Griffith treatment method. In the open method group there were 4 (5.7%) cases of rerupture occurrence, 4 (5.7%) cases of deep infection, 2 (2.9%) cases of palpable stitch knots and 1 (1.4%) lesion of the sural nerve. The complications following percutaneous treatment included 1 (2.6%) case of rerupture, 5 (13.2%) cases of palpable stitch knots, 4 (10.5%) cases of transitory lesion of the sural nerve, and there were no infections. Statistically speaking, there was no significant difference between the two groups [14].

The method used in the Goschewski et al. [15] study reduced the risk of complications arising from surgery, but it suggested faster postoperative mobilisation and functional treatment. That was percutaneous treatment of the Achilles tendon using two Lengemann extension wires for coadaptation of the ruptured tendon. Achilles tendon ruptures occurred in the course of sporting activities and, on average, were treated within 22 h. The outcome was very good in 98% of the cases. One (2%) patient suffered rerupture due to trauma, but there were no other complications [15].

Wallace et al. [16] found percutaneous treatment of the Achilles tendon to be more successful than open surgery treatment.

Josey et al. [17] presented a standardised protocol used in those who opted for non-surgical treatment or did not want to undergo surgery. Wallace et al. [16] presented the results of their non-surgical orthotic treatment which were better than publiched results of operative treatment of acute Achilles tendon ruptures. Weber et al. [18] presented the results of non-operative and operative treatments, which were equivalent. Additional pain was lesser, and return to unassisted walking and work went faster in the non-surgically treated group [18].

Conservative treatment was indicated in order to avoid surgical complications and reduce costs. That requires more time and immobilisation of the knee and ankle joint in an equinus position, which leads to lower leg muscle atrophy. The risk of an Achilles tendon re-rupture is much greater than after surgical treatment. Conservative treatment also implies the risk of tendon extension, which weakens the functioning of the muscle-tendon unit [1].

Conclusion

In case of fresh Achilles tendon rupture preference should be given to surgical treatment, percutaneous tenorrhaphy, performed in a small operating theatre under local anaesthesia.

Percutaneous tenorraphy establishes and maintains the contact between the ruptured ends of the Achilles tendon. This procedure is short, inexpensive, less painful, and the recovery of the muscle strength of the lower leg and the functionality of the ankle joint and the knee is faster.

Statistically, the occurrence of Achilles tendon reruptures is not considerable in either surgical treatment method, but is lesser than in conservative treatment.

Skin necrosis, as well as the extension or shortening of the Achilles tendon, is avoided by percutaneous suturing.

Percutaneously operated patients need less time to recover the muscle strength of the tendon and to restore full range of motion. The ultrasound findings in the patients who underwent surgery show better consolidation of the site of rupture of the Achilles tendon with less scar tissue.

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Efikasnost manevra Epley u lečenju benignog paroksizmalnog pozicionog vertiga zadnjeg polukružnog kanala

Efficacy of Epley maneuver in treatment of benign paroxysmal positional vertigo of the posterior semicircular canal

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Apstrakt

Uvod/Cilj. Benigni paroksizmalni pozicioni vertigo (BPPV) predstavlja jedan od najčešćih poremećaja perifernog čula za ravnotežu. Cilj istraživanja bilo je da se proceni efikasnost manevra Epley u lečenju benignog paroksizmalnog pozicionog vertiga zadnjeg polukružnog kanala (p-BPPV) i utvrde potencijalni uzroci neuspeha ovog tretmana. **Metode.** U ovoj prospektivnoj studiji ispitano je 75 bolesnika. Kod svih bolesnika anamneza je ukazala na, a pozicionirajući test po Dix-Hallpike-u potvrdio, dijagnozu p-BPPV. Svim bolesnicima je rađen i klinički ORL pregled, traganje za spontanim nistagmusom, vestibulospinalni testovi, kalorijski test i tonalana liminarna audiometrija. Bolesnici su lečeni modifikovanim repozicionim manevrom Epley, a kontrolni pregledi su zakazivani u intervalima od sedam i 14 dana, mesec, tri, šest meseci i godinu dana. Manevar je ponavljan, ako su vertigo i nistagmus na kontrolnom pozicionirajućem testu i dalje bili prisutni. Uspehom terapije smatran je prelazak „pozitivnog“ u “negativan” Dix-Hallipike-ov test nakon jednog ili dva Epley-eva manevra. **Rezultati.** Nakon inicijalnog Epley-evog manevra izlečenje je zabeleženo kod 90,7% bolesnika, a nakon sekundarnog kod 96%. Tri (4%) bolesnika sa sekunadarnim p-BPPV-om ni nakon drugog repozicionog manevra nisu imala prestanak simptoma. Etiološki faktori p-BPPV-a imali su značajan uticaj na stopu uspešnosti manevra ($p < 0,01$), dok dužina trajanja simptoma, starost i pol nisu ($p > 0,05$). Jedanaest (14,66%) bolesnika imalo je ponovljene epizode BPPV-a u periodu od godinu dana nakon uspešnog Epley-evog manevra. **Zaključak.** Manevar Epley pokazao se kao vrlo uspešna repoziciona metoda u lečenju p-BPPV. Bolesnici sa idiopatskim p-BPPV-om imali su bolje rezultate lečenja manevrom Epley nego bolesnici sa sekundarnim p-BPPV-om.

Ključne reči:
vertigo; dijagnoza; fizikalna terapija, modaliteti; lečenje, ishod.

Abstract

Background/Aim. Benign paroxysmal positional vertigo is one of the most frequent peripheral vestibular system disorders. The aim of this study was to examine the efficacy of the Epley maneuver in treating benign paroxysmal positional vertigo of the posterior semicircular canal (p-BPPV) and to discover possible causes of failure. **Methods.** This prospective study included 75 patients**.** In all the cases medical history showed and the positioning Dix-Hallpike test confirmed the diagnosis of p-BPPV. We also performed clinical ENT examination, searching for spontaneous nystagmus, vestibulospinal tests, caloric test, and audiometry. All the patients were treated by the modified Epley canalith repositioning maneuver. The patients were followed up at the intervals of seven and, fourteen days, and one, tree, and six months and one year. The maneuver was repeated if vertigo and nystagmus on control positioning test persisted. The transition from positive into negative Dix Hallpike test after one or two Epley maneuver was considered as success in treatment. **Results.** After the initial Epley maneuver the recovery rate was 90.7%, and after the second 96%. In three (4%) patients with secondary p-BPPV, symptoms did not cease even after the second repositioning maneuver. The etiology of p-BPPV had a significant effect on the maneuver's success rate ($p < 0.01$), whereas duration of symptoms, age and gender had no effect ($p > 0.05$). After a successful treatment 11 (14.66%) patients had recurrent attack of BPPV during the first year. **Conclusion.** The Epley maneuver is very successful repositioning procedure in treating p-BPPV. The patients with idiopathic form p-BPPV showed higher success rate with Epley maneuver than those with secondary p-BPPV.

Key words:
vertigo; diagnosis; physical therapy modalities; treatment outcome.

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Uvod

Benigni paroksizmalni pozicioni vertigo (BPPV) predstavlja sindrom koji se manifestuje iznenadnim kratkotrajnim napadima vrtoglavice koji su provocirani određenim položajem glave [1]. Ovo je jedan od najčešćih poremećaja perifernog čula za ravnotežu [2, 3]. Približno 43% perifernih vrtoglavica nastaje usled BPPV-a [4]. Godišnja incidencija BPPV-a iznosi oko 64 na 100 000 stanovnika [4, 5]. Sreće se u svim starosnim grupama. Najveća učestalost idiopatskog BPPV-a je između 50. i 70. godine života i dva puta češće zahvata ženski pol [5]. Raspodela u odnosu na pol je podjednaka kada se radi o sekundarnom BPPV-u.

Kod većine bolesnika (49–85,9%) uzrok BPPV-a ne može biti utvrđen, pa se govori o idiopatskom ili primarnom BPPV-u.[2] Etiološki faktori koji dovode do sekundarnog BPPV-a su povrede glave, bolesti unutrašnjeg uva (Menierova bolest, labirintitis, neuronitis vestibularnog nerva, akutna gluvoća, Koganov sindrom), bolesti srednjeg uva (hronično zapaljenje srednjeg uva, otoskleroza, stanje posle operativnog lečenja srednjeg uva), vaskularni poremećaji (vertebrobazilarna ishemija, dijabetička angiopatija) [5, 6].

Nakon histopatoloških nalaza bazofilnih depozita na kupuli zadnjeg polukružnog kanala, 1969. godine Schuknecht [7] je predložio teoriju kupulolitijaze kao patofiziološki mehanizam BPPV-a, dok su Parnes i McClure [8] pronašli slobodno plutajuće kalcijum-karbonatske čestice – otokonije u enodlimfi zadnjeg polukružnog kanala i tako postavili teoriju kanalolitijaze. Danas se kanalolitijaza smatra češćim oblikom BPPV-a od kupulolitijaze i pruža bolje objašnje za kliničke karakteristike ove bolesti [8, 9].

Napadi rotatornih vrtoglavica u određenim položajima glave glavni su simptomi bolesnika sa BPPV-om. Vrtoglavice traju od nekoliko sekundi do jednog minuta. Po prestanku vrtoglavice kod nekih bolesnika može se javiti i neodređeni osećaj nestabilnosti koji može trajati mnogo duže od vrtoglavice. Tegobe su ponekad praćene osećajem mučnine i povraćanjem. Bolesnici obično navode da se vrtoglavica javila u jutarnjim časovima pri pokušaju da ustanu iz kreveta. Vrtoglavica se može javiti i pri odlasku u krevet, zabacivanju glave unazad ili pri podizanju glave iz savijenog položaja. Ravnoteža je između napada obično očuvana. Izuzeci od ovoga su slučajevi kod kojih je BPPV udružen sa parcijalnim vestibularnim parezama, kada nagli pokreti glave bilo koje vrste mogu provocirati momentalni osećaj vrtoglavice. Vrtoglavice se ponavljaju određeno vreme i prestaju, jer BPPV ima tendenciju spontanog prestanka, obično posle mesec dana. Ako tretman nije započet, vrtoglavice mogu potrajati čak nekoliko meseci ili godina. Recidivi BPPV-a se, takođe, mogu javljati [10].

U poslednjih 20 godina, sa boljim poznavanjem i razumevanjem patofizioloških mehanizama BPPV-a došlo je i do značajnog napretka u lečenju. U lečenje prvog izbora spadaju različite vrste fizikalnih procedura. Repozicioni manevar Epley i njegove modifikacije primenjuju se od 1992. godine [11]. Manevar ima za cilj da pomeranjem glave i tela bolesnika kroz određene položaje, u ravnima u kojima se aktiviraju zadnji polukružni kanali, dovede do vraćanja otokonija iz zadnjeg polukružnog kanala kroz zajednički krak gornjeg i zadnjeg kanala nazad u utrikulus. U originalnom opisu ovog manevra preporučuje se premedikacija bolesnika jedan sat pre izvođenja manevra, nekim od vestibularnih supresanata u cilju smanjenja vegetativnih simptoma. Nejčešće se primenjuju dimenhidrinat, prometazin-hlorid (antihistaminici), diazepam, lorazepam i klonazepam (benzodiazepini). Modifikacije ovog manevra odnose se i na vreme zadržavanja bolesnika u određenim pozicijama. Epley i sar. [12] savetuju da vreme u svakoj od pet pozicija bude od 9 do 16 s, odnosno jednako zbiru latentnog perioda pre pojave nistagmusa i vremenu trajanja nistagmusa. Upotreba mastoidnih vibracija na zahvaćenom uvu u toku izvođenja manevra, kao i primena postmanevarskih instrukcija su još neke od modifikacija u odnosu na originalan opis manevra. Prema Epley-u primena standardnog elektromagnetnog koštanog vibratora i ručnog vibratora (80 Hz) pomaže da se izbegne adherencija otokonija za zidove polukružnog kanala [11].

Brojne studije pokazale su da je aktivni terapijski pristup efikasniji nego spontani oporavak BPPV-a. Kod bolesnika sa perzistentnim vrtoglavicama kod kojih terapija repozicionim procedurama nije imala uspeha i kod kojih godinama ne dolazi do oporavka primenjuje se hirurško lečenje. Od hirurških procedura rade se resekcija singularnog nerva ili okluzija zadnjeg polukružnog kanala [13].

Cilj ovog istraživanja bio je da se proceni efikasnost manevra Epley u lečenju benignog paroksizmalnog pozicionog vertiga zadnjeg polukružnog kanala (p-BPPV) i utvrde potencijalni uzroci neuspeha ovog lečenja.

Metode

U ovoj prospektivnoj studiji sprovedenoj u Audiološkom centru KBC „Zvezdara“ ispitano je 75 bolesnika. Kod svih je anamneza ukazala na, a rutinsko kliničko ispitivanje potvrdilo dijagnozu benignog paroksizmalnog pozicionog vertiga zadnjeg polukružnog kanala (p-BPPV) na pozicionirajućem testu prema Dix-Hallpik-u. Takođe, sproveden je i klinički otorinolaringološki pregled, traganje za spontanim nistagmusom, vestibulospinalni testovi, kalorički test, audiometrija, a prema potrebi i dodatna ispitivanja (neurološki pregled, kompjuterizovana tomografija i/ili nuklearna magnetska rezonanca).

Dix-Hallpike-ov test je podrazumevao naglo dovođenje bolesnika iz sedećeg položaja u ležeći, sa glavom u visećem položaju okrenutom desno ili levo pod uglom od 45°, sa predhodnim vraćanjem u sedeći položaj pre promene strane. Nistagmus je posmatran u srednjem primarnom položaju bulbusa, uz upotrebu Frencelovih naočara.

Neophodni kriterijumi za postavljanje dijagnoze p-BPPV-a bili su: postojanje latentnog perioda (2–15 sekundi) pre pojave nistagmusa, zamorljivost pri ponavljanju testa, vertikalno-rotatorni nistagmus sa smerom nagore i jasno prisustvo subjektivnog vertiga. Bolesnici sa BPPV-om lateralnog i anteriornog polukružnog kanala isključeni su iz ispitivanja. Epley-ev manevar (sa modifikacijama: bez premedikacije i bez mastoidnih vibracija) primenjivan je u lečenju svih bolesnika. Tokom svakog pregleda rađen je samo po je-

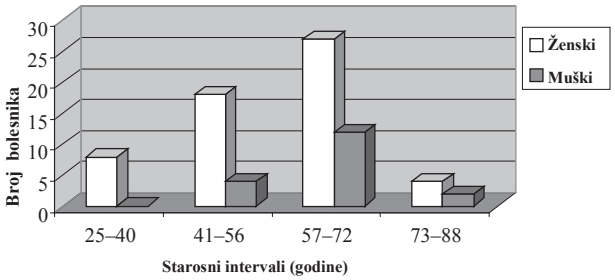
dan modifikovani manevar Epley koji je podrazumevao seriju od pet različitih položaja glave i tela, pri čemu je svaki položaj trajao približno oko 30 sekundi (dok nistagmus ne prestane). Prvi položaj je podrazumevao rotiranje glave bolesnika koji je u sedećem položaju na stranu obolelog uva za 45 stepeni. U drugom položaju kao u Dix-Hallpike-ovom testu, bolesnici su spuštani u ležeći položaj sa glavom okrenutom i dalje pod uglom od 45 stepeni na stranu obolelog uva i nešto ispod horizontale (glava u visećem položaju 30 stepeni). Treći položaj podrazumevao je okretanje glave za 90 stepeni u suprotnu stranu, ka zdravom uvu. U četvrtom položaju glava i trup bolesnika okretani su za još dodatnih 45 stepeni u istom smeru. Peti položaj je podrazumevao dovođenje bolesnika u sedeći položaj sa glavom okrenutom unapred i lako pognutom ka dole. Po završetku terapijske procedure, bolesnici su dobijali postmanevarske instrukcije: držanje glave u uspravnom položaju u narednih 8–10 sati, sedam dana spavanje na zdravoj strani sa visoko podignutim uzglavljem. Kontrolni pozicionirajući Dix-Hallpike-ov test rađen je nakon sedam dana. U slučaju pozitivnog Dix-Hallpike-ovog testa, Epley manevar je ponavljan istog dana, a kontrola je vršena 14 dana od postavljanja dijagnoze. Uspehom terapije smatrana je konverzija pozitivnog u negativan Dix-Hallpke-ov test nakon izvedenog jednog ili dva Epley manevra. S obziorom na to da BPPV može i spontano prestati u toku nekoliko nedelja, vreme od 14 dana dovoljno za izvođenje dva manevra, bilo je fiksno, posle čega oporavak nismo smatrali uspehom manevra. Praćenje bolesnika je nastavljeno na mesec, tri, šest meseci i godinu dana da bi zabeležili pojavu recidiva.

Analizirani su sledeći parametri: pol, starost, etiološki faktori, dužina trajanja simptoma do započinjanja lečenja, strana zahvaćenog polukružnog kanala, broj izvedenih Epley manevara u lečenju, ishod lečenja, subjektivna procena ishoda lečenja od strane bolesnika, recidivi, komplikacije manevra (mučnina, povraćanje i konverzija u BPPV nekog grugog kanala sa iste strane).

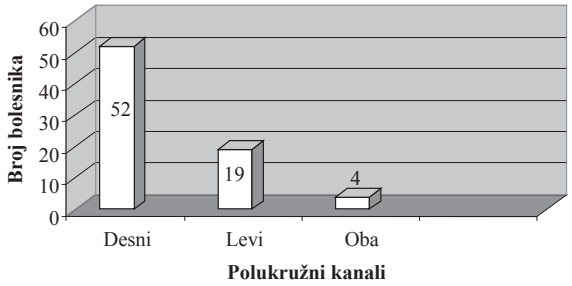
Od metoda deskriptivne statistike u radu su korišćene metode grupisanja, tabeliranja, mere centralne tendencije (aritmetička sredina, mod) i mere varijabiliteta (standardna devijacija i koeficijent varijacije). Od metoda analitičke statistike u radu su našli primenu χ^2-test, i Vilkoksonov test (Wilcoxon) ekvivalentnih parova – *W*. S obzirom da je veličina uzorka bila 75, značajnost razlike je kod Vilkoksonovog testa određena Zed-testom (*Z*), jer su se podaci ponašali po normalnoj raspodeli. Nivo značajnosti za sve primenjene statističke metode bio je 0,05.

Rezultati

Prosečna starost ispitanika bila je 57,19 ± 12,88 godina (26–81 god.). Najveća zastupljenost BPPV-a bila je kod bolesnika u 5. i 6. deceniji života (Mod = 56 god.) (slika 1). Razlika u učestalosti bolesnika prema polu bila je statistički visokoznačajna ($\chi^2 = 24{,}242$; df = 1; $p < 0{,}01$). Bolesnici ženskog pola tri puta češće (57 : 18) imali su BPPV (slika 1). Desni zadnji polukružni kanal daleko češće bio je zahvaćen nego levi (2,7 : 1) ili obostrano prisustvo bolesti ($\chi^2 = 39{,}909$; df = 2; $p < 0{,}01$) (slika 2).



Sl. 1 –Distribucija bolesnika u odnosu na pol i starost



Sl. 2 – Distribucija bolesnika u odnosu na stranu zahvaćenog polukružnog kanala

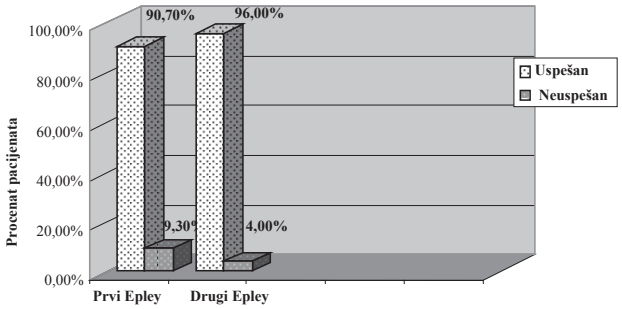
Uzrok BPPV-a bio je nepoznat kod 82,7% bolesnika (tabela 1). O sekundarnom BPPV-u radilo se kod 17,3% bolesnika. Kod četiri bolesnika radilo se o hroničnom zapaljenju srednjeg uva, kod tri o povredi glave i dijabetičkoj angiopatiji, a akutna gluvoća, vestibularni neuronitis i Menijerova bolest bili su prisutni u pojedinačnim slučajevima. Pod trajanjem simtoma podrazumevali smo vremenski period to-

Tabela 1

Etiološki faktori benignog paroksimalnog pozicionog vertiga (BPPV)

Etiološki faktori	Bolesnici		Ukupno	
	n	%	n	%
Nepoznati – idiopatski BPPV	62	82,70	62	82,70
hronično zapaljenje srednjeg uva	4	5,33		
povrede glave	3	4,00		
Poznati-sekundarni BPPV				
dijabetička angiopatia	3	4,00	13	17,3
akutna gluvoća	1	1,33		
neuronitis vestibularnog nerva	1	1,33		
Menierova bolest	1	1,33		
Ukupno	75	100	75	100

kom koga su bolesnici imali stalne epizode vrtoglavica izazvanih pozicijom. Ove vrtoglavice, do javljanja lekaru, u najvećem broju slučajeva trajale su do 15 dana ($\chi^2 = 35{,}091$; df = 3; $p < 0{,}01$) (tabela 2). Nakon izvođenja prvog manevra Epley konverzija pozitivnog u negativan Dix-Hallpike-ov test zabeležena je kod 68 (90,7%) bolesnika, a posle drugog kod 72 (96%). Kod tri (4%) bolesnika ni posle drugog manevra Epley nije postignuto izlečenje (slika 3). Analiza subjek-



Sl. 3 – Distribucija bolesnika u odnosu na ishod manevra Epley

bolesti i to kod bolesnika sa neuronitisom vestibularnog nerva i kod dva bolesnika sa hroničnim zapaljenjem srednjeg uva. U periodu od šest meseci rekurentni oblik bolesti registrovan je kod pet (6,66%) bolesnika (četiri sa sekundarnim i jedan sa idiopatskim BPPV-om), a kod 11 (14,66%) u periodu od godinu dana (kod pet bolesnika sa sekundarnim BPPV-om i šest sa idiopatskim).

Analiza ishoda manevra Epley, u odnosu na pol, starost bolesnika i dužinu trajanja simptoma bolesti, pokazala je da ne postoji statistički značajna razlika (tabele 2 i 3). Međutim, uočena je statistički značajna razlika između učestalosti primarnog i sekundarnog BPPV-a i učestalosti ishoda manevra Epley. Ova razlika je nastala usled većeg procenta uspešnosti manevra Epley kod ispitanika sa idiopatskim BPPV-om nego kod ispitanika sa sekundarnim BPPV-om. Ispitanici kod kojih nije zabeležen uspeh nakon dva manevra imali su sekundarni BPPV usled povrede glave.

Kod pet (6,66%) bolesnika postojala je ipsilateralna hipotonija na kaloričkom testu, kod 27 (36%) i ispilateralna senzorineuralna nagluvost različitog stepena, a kod 4

Tabela 2

Ishod manevra Epley u odnosu na dužinu trajanja simptoma bolesti

Trajanje simptoma bolesti (dani)	Ishod manevra Epley				Ukupno		*p*
	uspešan		neuspešan				
	n	%	n	%	n	%	
≤ 15	32	42,67	1	1,33	33	44,00	> 0,05 (Z = -1,342)
16–30	22	29,33	1	1,33	23	30,66	
31–60	10	13,33	1	1,33	11	14,66	
≥ 61	8	10,76	0	0	8	10,67	
Ukupno	72	96,00	3	4	75	100	

Tabela 3

Ishod manevra Epley u odnosu na pol, starost bolesnika i mogućnost utvrđivanja etioloških faktora

	Ishod manevra Epley		*p*
	uspešan	neuspešan	
Pol (n)			
ženski	56	1	> 0,05*
muški	16	2	
Starost (godine),			
x̄ (raspon)	57,83 (26–81)	44 (30–72)	> 0,05**
Etiologija			
idiopatski	62		< 0,01*
sekundarni	10	3	

***χ^2 test; **Z – test**

tivne procene ishoda lečenja od strane bolesnika pokazala je kompletnu rezoluciju simptoma kod 56 (74,67%) bolesnika, a poboljšanje sa još uvek prisutnim tegobama u vidu nestabilnosti ili straha i nesigurnošću kod 19 (25,33%) bolesnika. Tri bolesnika bila su bez promene dok sa pogoršanjem tegoba nije zabeležen nijedan bolesnik. Kod 10,7% bolesnika bio je prisutan neki od pratećih neželjenih efekata usled izvođenja manevra: nesvestica, muka, preznojavanje bledilo, strah. U jednom slučaju (1,33%) kao komplikacija manevra nastala je konverzija BPPV-a zadnjeg kanala u BPPV horizontalnog kanala sa iste strane. Rekurentni BPPV bio je prisutan u prva tri meseca kod tri (4%) bolesnika sa sekundarnim oblikom (5,33%) i ipsilateralna mešovita nagluvost. Hipotonija izostranog lateralnog polukružnog kanala sa afekcijom sluha nađena je kod tri (4,55%) bolesnika.

Diskusija

Epley manevar predstavlja repozicionu proceduru koja ima za cilj da serijom od pet uzastopnih pokreta glave i tela, koji se izvode pod kontrolom lekara, oslobodi zadnji polukružni kanal od slobodno plutajućeg otokonijalnog debrisa i pošalje ga nazad u utrikulus.Visok procenat izlečivosti BPPV-a zadnjeg polukružnog kanala objavio je veći broj

autora. Prema podacima iz literature, izlečivost se kreće između 30 i 100% [11–16]. Poređenje rezultata lečenja p-BPPV-a repozicionim manevrom Epley i njegovim modifikacijama je otežano jer se istraživanja dosta razlikuju u broju sprovedenih manevara u toku jednog tretmana, primeni premedikacije, mastoidnim vibracijama, postmanevarskim instrukcijama i dužini vremena praćenja. Kod ispitanika ove studije, sedam dana nakon izvođenja manevra Epley, konverzija pozitivnog u negativan Dix-Hallpike-ov test zabeležena je kod 90,7% bolesnika. Posle izvođenja drugog manevra Epley kod bolesnika kod kojih je na kontrolnom pregledu bio pozitivan Dix-Hallpike-ov test, procenat izlečenja se povećao na 96. Simhadri i sar. [14] na kontrolnom pregledu posle samo sedam dana zabeležili su izlečenje kod 95% bolesnika. Lopez i sar. [17] kod 89% bolesnika mesec dana nakon izvođenja manevra Epley, na pozicionirajućem testu po Dix Hallpike-u zabeležili su izlečenje. Za razliku od njih, Brevern i sar. [18] su ispitivali efikasnost Epley-evog manevra posle samo 24 časa od izvođenja i našli potpuni prestanak tegoba kod 80% bolesnika. Objavljen je i manji broj studija koje su upoređivale razliku između efikasnosti izvođenja samo jednog manevra Epleye u odnosu na ponavljano izvođenje, u jednom tretmanu dok tegobe ne prestanu (do četiri menevra) [1, 15]. Veća efikasnost ponavljanja manevara u jednom tretmanu još uvek je pitanje kotroverzi. Korn i sar. [15] navode da se postiže za 21,4% veća efikasnost izvođenjem četiri manevra Epley u jednom tretmanu u odnosu na izvođenje samo jednog manevra.

S obzirom na to da kod BPPV-a spontana remisija tegoba nije retka pojava, efikasnost pojedinih terapijskih procedura može biti i precenjena. Smatra se da usled prirodnih pokreta glave dolazi do spontane migracije otokonijalnog debrisa iz kanala u utrikulus gde mu je i mesto. Prosečno trajanje simptoma nelečenog BPPV-a zadnjeg polukružnog kanala je oko 39 dana [19]. Iz tih razloga u našoj studiji vreme od 14 dana, dovoljno za izvođenje dva manevra, bilo je fiksno, posle čega oporavak nismo smatrali uspehom manevra, iako smo bolesnike i dalje lečili nekim od terapijskih manevara.

U epidemiološkoj studiji koju su sproveli Caruso i sar. [20], uzrok BPPV-a bio je nepoznat kod 85,9% bolesnika. O posttraumatskom BPPV-u radilo se kod 14,1%. U našoj studiji uzrok BPPV-a bio je nepoznat kod 82,7% bolesnika, dok je postraumatski BPPV bio znatno ređe prisutan (4%). Dosadašnja iskustva pokazala su da se posttraumatski BPPV teže leči, zahteva ponavljanje terapijskih manevara do kompletne rezolucije simptoma, što je u saglasnosti sa našim rezultatima. Sva tri naša bolesnika kod kojih je lečenje posle dva manevra Epley bilo neuspešno, imala su sekundarni, posttraumatski BPPV koji se javio posle frakture baze lobanje. Pretpostavlja se da usled traume glave, veća količina otokonijalnog debrisa dospe u zadnji polukružni kanal [21]. Eksperimentalno je dokazano da otokonije mogu ponekad postati vrlo adherentne za zid kanala i da se ne pomeraju, ili da ostanu čvrsto zalepljene na površinu kupule [21]. Ovi fenomeni objašnjavaju zašto fizikalni tretman ponekad ne uspe. U takvim slučajevima preporučuje se primena liberatornog manevra Semont koji je efikasniji za lečenje kupulolitijaze od manevra Epley.

Gordon i sar. [21] našli su zastupljenost posttraumatskog BPPV-a kod 8,5% bolesnika sa stopom rekurencije 57%. Posle 10-godišenjeg praćenja bolesnika Brandt i sar. [22] su objavili pojavu rekurencije BPPV-a kod 80% bolesnika. Nunez i sar. [23] navode stopu rekurencije BPPV-a u prvoj godini 15%, a Gordon i sar. [21] 19%.' Nakon dve godine stopa rekurencije iznosila je 26% [23]. Zapažena je jedna ili više rekurencija BPPV-a posle manevra. Najčešće se javlja na istoj strani (65,9%), a moguća je i promena strane [17]. Kod ispitanika u ovom istraživanju rekurentni BPPV posle uspešnog izlečenja bio je prisutan kod 4% bolesnika, posle tri meseca, kod 6,66%, posle šest meseci i kod 14,66% bolesnika, posle godinu dana. Kod svih bolesnika radilo se o istoj strani i istom polukružnom kanalu.

Rezultati ovog istraživanja slažu se sa rezultatima većeg broja autora i pokazali su da pol, starost bolesnika i dužina trajanja simptoma bolesti, nemaju uticaj na ishod lečenja BPPV-a [17, 20–23].

Benigni paroksizmalni pozicioni vertigo bio je tri puta češći kod ispitanika ženskog pola. Ne zna se tačno zašto je idiopatski BPPV češći kod ženskog nego kod muškog pola. Moguće je da pod uticajem hormona dolazi do formiranja kalcijum-karbonatskih depozita u endolimfi. Ovo je naročito izraženo kod postmenopauzalnih žena gde je BPPV i najzastupljeniji [24]. Očigledno je da ova pretpostavka zahteva dalje kliničke i eksperimentalne dokaze.

Veliki broj autora opisao je dominantu zastupljenost BPPV-a sa desne strane [20, 25]. Nije poznato objašnjenje za ovaj fenomen. Jedno od mogućih objašnjenja su navike u spavanju na desnoj strani [25]. Naši rezultati su pokazali da je desni zadnji polukružni kanal bio češće zahvaćen od levog (2,6 : 1), dok je obostrani BPPV bio prisutan kod 6,1% bolesnika. Katsarkas [24] je našao idiopatski obostrani BPPV kod 6,3% bolesnika, i zastupljenost ženskog u odnosu na muški pol 2,23 : 1. Prema nekim autorima, zastupljenost desnog zadnjeg polukružnog kanala u odnosu na levi je 1,6 : 1, zastupljenost BPPV-a kod ženskog pola u odnosu na muški je 1,7 : 1, dok je obostrani p-BPPV prisutan kod 7,4% bolesnika [20].

Bolesnici su dobro podneli izvođenje manevra Epley. Samo mali broj (10,7%) imao je mučninu, preznojavanje, bledilo,izražen strah ili nestabilnost po završetku manevra Uopšteno, tolerancija manevra Epley je dobra [24]. Neželjeni efekti nastaju usled aktivacije limbičkog sistema zbog ponavljanih provociranih vrtoglavica, tokom dijagnostičkog i terapijskog postupka [25, 26]. Ruckenstein i sar. [27] po završetku lečenja zapazili su nestabilnsot i neodređene smetnje kod čak 47% bolesnika. U jednom slučaju gde je došlo transformacije BPPV-a zadnjeg polukružnog kanala u BPPV horizontalnog kanala sa iste strane zabeleženo je izlečenje Gufonijevim terapijskim manevrom.

Zaključak

Uspeh modifikovnog manevra Epley bio je u korelaciji sa uzrokom BPPV-a. Bolesnici sa idiopatskim BPPVom češće su imali dobar rezultat lečenja nego bolesnici sa sekundarnim BPPV-om. Moguće objašnjenje neuspeha manevra Epley

u lečenju sekundarnog BPPV-a je veća količina otokonijalnog debrisa usled traume u zadnjem polukružnom kanalu, čvrsta adherencija za zidove ili kupulu zadnjeg polukružnog kanala.

Manevar Epley predstavlja siguran i efikasan metod u lečenju BPPV-a zadnjeg polukružnog kanala. Poznavanjem kliničke slike bolesnika sa BPPV-om, uz dobro vođenu anamnezu i primenu Dix-Hallpike-ovog testa moguće je veoma brzo i jednostavno postaviti dijagnozu, a jednokratnom primenom manevra Epley u najvećem broju slučajeva i izlečiti vrtoglavicu.

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Uporedna analiza uticaja različitih tipova Carbopol®-a na brzinu oslobađanja litijum-karbonata iz matriks tableta

A comparative analysis of the influence of different types of Carbopol® on the release rate of lithium-carbonate from matrix tablets

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Apstrakt

Uvod/Cilj. Tablete tipa hidrofilnog matriksa predstavljaju najpopularniji oblik među peroralnim terapijskim sistemima. Karbomeri, upotrebljeni u koncentraciji 10–30% pri formulisanju matriks tableta, mogu znatno uticati na profil oslobađanja leka, usled formiranja matriksa tipa hidrogela. Cilj studija bio je da se uporedi uticaj različitih tipova Carbopol®-a (farmakopejski: karbomera) na brzinu oslobađanja litijum-karbonata i ostale farmaceutsko-tehnološke i fizičko-hemijske osobine izrađenih formulacija matriks tableta. **Metode.** Metodom direktne kompresije izrađene su tri formulacije matriks tableta sledećeg sastava: karbomer; laktoza, monohidrat; magnezijum-stearat; litijum-karbonat u odnosu 75 : 120 : 5 : 300. Prva formulacija izrađena je sa Carbopol®-om 971P NF, druga sa Carbopol®-om 974P NF i treća sa Carbopol®-om 71G NF. U navedenim formulacijama, sadržaj litijum-karbonata određen je prema propisu BP 2009, farmaceutsko-tehnološke osobine ispitane su prema propisima Ph. Jug. V, dok je brzina oslobađanja litijum-karbonata iz formulacija ispitana primenom *dissolution* testa, propisanog u monografiji „Lithium Carbonate Extended-Release Tablets" u USP 26. **Rezultati.** Profil oslobađanja litijum-karbonata iz matriks tableta sa Carbopol®-om 974P NF u potpunosti ispunjava zahteve USP 26, dok su vrednosti dobijene analizom matriks tableta sa Carbopol®-om 971P NF i Carbopol®-om 71G NF znatno ispod propisanih. U sve tri formulacije sadržaj lekovite supstance, variranje mase i čvrstina tableta odgovaraju postavljenim farmakopejskim zahtevima. **Zaključak.** U formulaciji matriks tableta sa litijum-karbonatom, primenom karbomera u koncentraciji 15%, sa Carbopol®-om 974P NF postignut je odgovarajući profil oslobađanja litijum-karbonata, dok je u formulacijama sa Carbopol®-om 971P NF i Carbopol®-om 71G NF, oslobađanje znatno sporije od propisanog po USP 26.

Ključne reči:
tablete; lekovi, produženo dejstvo; litijum karbonat; komparativna studija; ekscipijenti.

Abstract

Background/Aim. Hydrophilic matrix tablets represent the most commonly used oral dosage form. Carbomers used in the concentration of 10%–30% for preparation of matrix tablets, may significantly affect the profile of drug release due to the formation of hydrogel matrix tablets. The aim of this study was to compare the influence of different types of Carbopol® (carbomers in the pharmacopoeia) on the release rate of lithium-carbonate and other pharmaceutical, technological, physical and chemical properties of the prepared formulations of matrix tablets. **Methods.** Three different formulations of matrix tablets were made according to direct compression method. The tablets were of the following composition: carbomer, lactose monohydrate, magnesium-stearate, lithium-carbonate in the proportion 75 : 120 : 5 : 300. The first formulation was made with Carbopol® 971P NF, the second one with Carbopol® 974 P NF and the third one with Carbopol® 71G NF. The quantity of lithium-carbonate was determined according to the BP 2009, pharmaceutical and tecnological properties were examined in accordance with the regulations of Ph. Jug. V, whereas the release rate of lithium-carbonate from the formulations was examined by the application of dissolution test, prescribed in the monography 'Lithium Carbonate Extended-Release Tablets' in USP 26. **Results.** The profile of lithium-carbonate release from matrix tablets with Carbopol® 974P NF entirely complies with the regulations of USP 26, whereas the values obtained from the analysis of matrix tablets with Carbopol® 971P NF and Carbopol® 71G NF were considerably lower than the prescribed ones. In all the investigated formulations the content of the drug, mass variation and tablet hardness comply with the regulations set in pharmacopoeia. **Conclusion.** In the formulation of matrix tablets with lithium-carbonate, by the application of carbomers in the concentration of 15%, with Carbopol® 974 P NF a favourable lithium-carbonate release profile was achieved, whereas in the formulations with Carbopol® 971P NF and Carbopol® 71G NF, the release rate was significantly lower than that given in the USP 26 monography.

Key words:
tablets; delayed action preparations; lithium carbonate; comparative study; excipients.

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Uvod

Poslednjih decenija, sve veća pažnja usmerava se na razvoj i usavršavanje terapijskih sistema sa kontrolisanim oslobađanjem leka, kako bi se ispunili prioritetni zahtevi savremene farmakoterapije i omogućila bezbedna, efikasna i racionalna primena lekova. Primenom konvencionalnih oblika doziranja, vreme održavanja farmakološkog efekta leka i efikasnost terapije uslovljeni su režimom doziranja, biološkim poluvremenom i brzinom oslobađanja leka iz doziranog oblika. Pri tome, farmaceutsko-tehnološke karakteristike same formulacije predstavljaju ograničavajući faktor za postizanje usporenog oslobađanja i održavanje terapijske koncentracije leka u krvi u dužem vremenskom periodu, bez većeg variranja [1].

Dozirani oblici sa kontrolisanim oslobađanjem leka formulišu se sa ciljem prevazilaženja pomenutih nedostataka konvencionalnih oblika doziranja, tj. sa ciljem postizanja reproduktivnog, planiranog oslobađanja leka i produženog održavanja ujednačene terapijske koncentracije leka u krvi, tkivu ili organu [2].

Preparati sa kontrolisanim oslobađanjem najčešće se primenjuju peroralnim putem, čime se postižu dodatne prednosti u odnosu na preparate iz iste grupe, koji se primenjuju nekim drugim putem [3].

Na osnovu mehanizma delovanja i metoda izrade, peroralni preparati sa modifikovanim oslobađanjem lekovite supstance mogu se podeliti na one kod kojih se oslobađanje lekovite supstance kontroliše fizičkim, hemijskim ili biološkim putem. Matriks sistemi su podgrupa preparata kod kojih se oslobađanje lekovite supstance kontroliše fizičkim putem. Tablete tipa hidrofilnih matriksa predstavljaju najpopularniji oblik među peroralnim sistemima. Jednostavne formulacije, koje se mogu izraditi i u galenskim laboratorijama, grade matriks tipa hidrogela upotrebom gelirajućih sredstava tipa karbomera, poznatih pod zaštićenim imenom Carbopol®.

Karbomeri su visokomolekulski sintetski polimeri akrilne kiseline, hemijski umreženi alil-saharozom ili alil-pentaeritritolom. Kao rastvarači za polimerizaciju, koriste se benzen, etilacetat ili smeše cikloheksan-etil-acetata [4].

Polimeri sa oznakom „*P*“ ispunjavaju zahteve kvaliteta supstanci koje mogu ući u sastav farmaceutskih peroralnih preparata, pošto zadovoljavaju stroge kriterijume u pogledu vrste i količine rezidualnog rastvarača, niskotoksičnog potencijala [4].

Pored brojnih funkcija koje imaju u izradi različitih farmaceutsko-tehnoloških oblika (geli, emulzije, suspenzije, tablete sa trenutnim oslobađanjem leka), karbomeri se primenjuju i kao sredstva za kontrolisano oslobađanje lekovite supstance iz tableta, u koncentraciji 5–30% [1, 4]. Najpoznatiji svetski proizvođač polimernih sirovina iz grupe poliakrilata (karbomera), Lubrizol, na tržištu nudi različite karbomere pod nazivom Carbopol® sa odgovarajućom oznakom, namenjene za izradu peroralnih preparata [5–7]. Za izradu oralnih matriks tableta sa kontrolisanim oslobađanjem, Lubrizol preporučuje Carbopol® 71G NF, Carbopol® 971P NF i Carbopol® 974P NF. Ovi polimeri su sintetisani u etilacetatu, rastvaraču koji spada u grupu „bezbednih“ rastvarača, sa niskim toksičnim potencijalom, pa se mogu koristiti u izradi tableta [5, 8–10].

Pored fizičko-hemijskih osobina matriks nosača i lekovite supstance, osobine odabranog punioca imaju ključni uticaj na postizanje odgovarajuće kinetike oslobađanja. Osnovni kriterijum za izbor laktoze kao punioca u formulacijama, je njena rastvorljivost u vodi bez bubrenja, što ide u prilog usporavanju oslobađanja lekovite supstance iz matriksa [11].

Cilj ove studije bio je da se uporedi uticaj različitih tipova Carbopol®-a na brzinu oslobađanja litijum-karbonata i ostale farmaceutsko-tehnološke i fizičko-hemijske osobine izrađenih formulacija matriks tableta.

Metode

U radu je korišćeno sledeće:

Supstance i reagensi: Litijum-karbonat, *Ph. Jug. V* [12]; Carbopol® 974P NF, Lubrizol; Carbopol® 971P NF, Lubrizol; Carbopol® 71G NF, Lubrizol; Laktoza, monohidrat, Merck; Magnezijum-stearat, Centrohem; 1 M NaOH, Merck; 1 M HCl, Merck; 0,01 M NaOH; 0,01 M HCl.

Aparati i oprema: Ekscentar tablet mašina EK O KORSCH, tip D 126s; Vaga, Tip AC 2000, Mettler; Vaga, Tip AC 100, Metller; Aparat za ispitivanje čvrstine tableta, tip TBT/S, Erweka; Aparat za ispitivanje habanja tableta, tip TA 3, Erweka; Aparat za ispitivanje brzine rastvaranja lekovite supstance iz čvrstih lekovitih preparata, PHARMA TEST PTWS 3CE; Millex HA membranski filtri, 0,45 μm, Millipore Co; Sito Ø1 mm.

Uzorci matriks tableta sa litijum-karbonatom izrađeni su metodom direktne kompresije, oficinalnom po Ph. Jug. IV [13]. Njihov kvalitativno-kvantitativni sastav prikazan je u tabeli 1.

Priprema direktno kompresibilne smeše za tabletiranje urađena je prema opštim principima izrade složenih praškova, na sledeći način: pojedinačno se odmere i proseju (sito Ø1 mm) potrebne količine laktoze, odgovarajućeg karbomera (Carbopol® 971P NF za prvu, Carbopol® 974P NF za drugu i

Tabela 1

Kvalitativno-kvantitativni sastav izrađenih matriks tableta

Sastav	Formulacija (masa u mg)		
	I (C_{971P})	II (C_{974P})	III (C_{71G})
Litijum-karbonat	300,00	300,00	300,00
Laktoza, monohidrat	120,00	120,00	120,00
Magnezijum-stearat	5,00	5,00	5,00
Carbopol® 971P NF	75,00		
Carbopol® 974P NF		75,00	
Carbopol® 71G NF			75,00

Carbopol® 71G NF za treću formulaciju), i litijum-karbonata, navedenim redosledom. Nakon mešanja u tarioniku, doda se prethodno prosejan (sito Ø1 mm) i odmeren magnezijum-stearat i nastavi sa laganim mešanjem smeše praškova narednih 5 minuta. Sve formulacije tabletirane su na mašini KORSCH, alatom Ø 13 mm, ravnih površina, bruto mase tableta 500 mg, sa sadržajem litijum-karbonata 300 mg.

Izrađene formulacije ispitane su fizičko-hemijskim i farmaceutsko-tehnološkim metodama. Fizičko-hemijskim metodama urađeno je određivanje sadržaja litijum-karbonata, a farmaceutsko-tehnološkim, ispitani su: izgled tableta, variranje mase, čvrstina, habanje i brzina oslobađanja litijum-karbonata.

Sadržaj litijum-karbonata u eluatima, nakon filtriranja (0,45 μm) određen je po propisu BP 2009 za monografiju: „Slow Release Lithium Carbonate Tablets“, metodom retitracije viška hlorovodonične kiseline natrijum-hidroksidom [14].

Izgled tableta ispitan je prema propisu Ph. Jug. V, koji nalaže da tablete moraju biti jednoličnog oblika, veličine i boje, glatkih površina i oštrih, neoštećenih ivica [12].

Određivanje variranja mase tableta urađeno je po propisu Ph. Jug. V. Farmakopeja propisuje da se pojedinačno odmeri masa 20 tableta i potom izračuna prosečna masa. Dozvoljeno je odstupanje od prosečne mase ± 5%, a samo dve pojedinačne mase smeju pokazivati veće odstupanje od dozvoljenog, u opsegu ± 5–10% [12].

Provera čvrstine tableta urađena je prema propisu Ph. Jug. V. Primenom aparata Erweka TBT/S izmerena je sila lomljenja tableta. Za svaku pojedinačnu formulaciju ispitano je po 10 tableta, postavljanjem tableta na isti način u ležište uređaja pod pravim uglom. Čvrstina tablete jedne formulacije prikazuje se kao srednja vrednost izmerenih sila za 10 tableta [12]. Minimalna čvrstina tableta koja obezbeđuje njihov transport odgovara sili lomljenja od 34 N [15].

Otpornost tableta na habanje ispitana je primenom modifikovanog propisa Ph. Jug. V (modifikacija: sa nagibom ose bubnja od 10°, bubanj se okreće brzinom od 20 o/min, 5 minuta, da bi se postiglo 100 rotacija). Otprašeno je 20 tableta i odmerena ukupna masa tableta, sa tačnošću ± 1 mg. Nakon završenog postupka, tablete su ponovo otprašene i izmerena im je ukupna masa. Rezultat je prikazan kao razlika u masi pre i posle obrtanja, izražena u procentima u odnosu na početnu masu [12].

Prema propisu USP 26 (test II) za ispitivanje brzine rastvaranja litijum-karbonata iz tableta sa produženim oslobađanjem lekovite supstance (*Lithium Carbonate Extended-release Tablets*), ispitano je oslobađanje litijum-karbonata iz svih analizovanih uzoraka. Ispitivanje je vršeno u korpicama, pri brzini rotacije 100 o/min, u 900 mL vode, pri temperaturi 37 ± 0,5°C. Farmakopeja propisuje (test II) sledeći profil oslobađanja lekovite supstance iz matriks tableta: posle I sata ≤ 40%, posle III sata 45–75% i posle VII sata ≥ 70% [16].

Rezultati

Na osnovu vrste ispitivanja formulisanih matriks tableta, rezultati ovog rada grupisani su kao rezultati fizičko-hemijskih, odnosno farmaceutsko-tehnoloških ispitivanja.

Fizičko-hemijska ispitivanja

Sadržaj litijum-karbonata u formulacijama matriks tableta prikazan je u tabeli 2.

Rezultati ispitivanja izgleda tableta prema propisu Ph. Jug. V. u odnosu na karakteristične parametre pokazuju da sve tri formulacije zadovoljavaju zahteve farmakopeje. U svim formulacijama tablete su bile jednoličnog, okruglog oblika, jednolične veličine i boje i glatkih površina (tabela 3).

Rezultati ispitivanja variranja mase matriks tableta prikazani su u tabeli 4.

U tabeli 5 prikazani su rezultati ispitivanja čvrstine i habanja matriksa tableta.

Rezultati ispitivanja brzine oslobađanja litijum-karbonata iz matriks tableta prikazani su na slici 1.

Tabela 2

Sadržaj litijum-karbonata u formulacijama sa različitim tipovima Carbopol®-a (C)

Formulacija	Sadržaj (mg/tbl.)	BP 2009 (95–105%)
C_{971P}	288,21	96,07
C_{974P}	290,06	96,69
C_{71G}	286,36	95,45

Tabela 3

Izgled tableta izrađenim sa različitim tipovima Carbopol®-a (C)

Formulacija	Izgled tableta
C_{971P}	okrugle, jednolične veličine i boje, glatke
C_{974P}	okrugle, jednolične veličine i boje, glatke
C_{71G}	okrugle, jednolične veličine i boje, glatke

Tabela 4

Rezultati ispitivanja variranja mase tableta sa različitim tipovima Carbopol®-a (C)

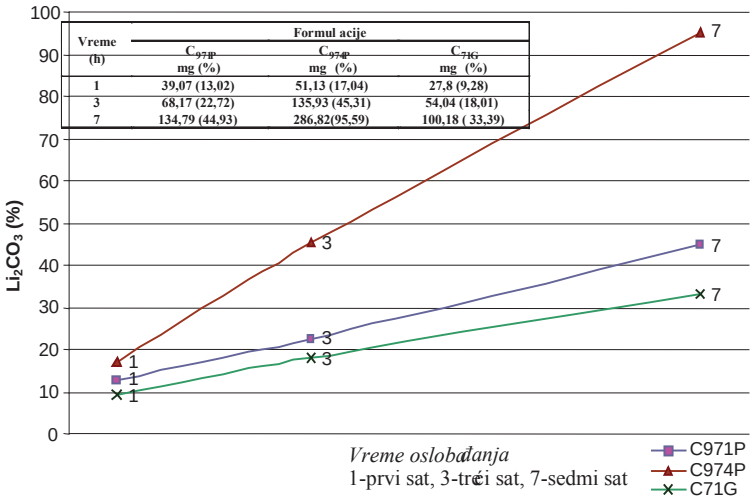
Formulacija	Prosečna masa (mg)	Min. ostupanje (%)	Maks. ostupanje (%)
C_{971P}	495,5	- 2,34	+ 4,39
C_{974P}	504,1	- 3,73	+ 2,38
C_{71G}	494,2	- 6,39	+ 2,97

Tabela 5

Rezultati ispitivanja čvrstine i habanja tableta izrađenim sa različitim tipovima Carbopol®-a (C)

Formulacija	Sila (F) lomljenja (N)			Habanje (%)
	F min	F max	$\overline{F}$	
C_{971P}	35,81	60,33	51,00	30,26
C_{974P}	25,99	62,29	37,96	30,29
C_{71G}	58,86	64,75	62,13	30,08

$\overline{F}$ **– prosečna sila lomljenja**



Sl. 1 – Ukupna količina oslobođenog litijum-karbonata (Li_2CO_3) iz formulacija izrađenih s različitim tipovima Carbopol®-a (C)

Diskusija

Osnovni cilj ove studije bio je da se ispita uticaj različitih tipova karbomera na brzinu oslobađanja lekovite supstance, kao osnovnog merila kvaliteta matriks tableta.

Ovi nosači efikasno usporavaju oslobađanje lekovite supstance i pružaju široke mogućnosti za izradu formulacije, u pogledu vrste i količine aktivnih i pomoćnih supstanci, kao i mogućnost izrade tableta malih dimenzija [5, 17].

Matriks tablete tipa hidrogela sa karbomerima, kao nosiocima matriks osobina, moguće je formulisati i izraditi na klasičnoj opremi za tabletiranje. Formulacije su rađene sa Carbopol®-om 71G NF, Carbopol®-om 971P NF i Carbopol®-om 974P NF.

Većina autora u izradi matriks tableta daje prednost karbomerima u odnosu na druge hidrofilne matrikse [18, 19]. Emami i sar. [18] navode da je pri ispitivanju različitih tipova sredstava za modifikovano oslovađanje lekovite supstance dobijen najbolji profil oslobađanja sa karbopolom. Postignuta je manja frekvencija doziranja i smanjeno je oscilovanje koncentracija lekovite supatance u plazmi. Ciftici i sar. [19] navode da je pri ispitivanju različitih formulacija tableta sa litijum-karbonatom, najveće usporavanje oslobađanja postignuto sa karbomerom, proporcionalno povećanju njegove koncentracije.

Osnovna razlika među odabranim polimerima je što Carbopol® 971P NF predstavlja sitan (veličina čestica < 75 μm) i voluminozan prašak, dok Carbopol® 71G NF sadrži do 80% čestica veličine 150–425 μm. U slučaju da se odgovarajuća kinetika oslobađanja lekovite supstance iz matriks tableta može postići samo primenom većih koncentracija karbomera (npr ≥ 15%), prednost se daje Carbopol®-u 71G NF, čija veličina čestica obezbeđuje znatno poboljšanje protočnosti i kompresibilnosti tabletne smeše [5–7].

Izrađene tablete bile su jednakog kvantitativnog sastava, pri čemu je tip karbomera bio jedini promenljivi parametar (tabela 1), pa je bilo moguće ispitati uticaj tipa karbomera na brzinu otpuštanja litijum-karbonata, kao i na ostale fizičko-hemijske i farmaceutsko-tehnološke osobine matriks tableta.

Metoda izbora za izradu matriks tableta, ukoliko dozvoljava sastav formulacija, je direktna kompresija, prvenstveno zbog postizanja usporenog profila oslobađanja, kao i zbog jednostavnosti i ekonomičnosti postupka izrade [8, 20, 21]. Pošto je profil oslobađanja uslovljen ne samo sastavom formulacije, već i svim parametrima koji definišu reproduktivnost postupka izrade, veoma je bitno vreme dodavanja i dužina mešanja sa upotrebljenim lipofilnim lubrikansom, kao i navedena veličina sita.

Karbomeri su efikasni ekscipijensi za formiranje matriksa. Aktivna supstanca se uniformno disperguje u polimernom matriksu [5]. To pokazuju i rezultati dobijeni određivanjem sadržaja litijum-karbonata u svim formulacijama, bez obzira na odabrani karbomer (tabela 2). Rezultati određivanja sadržaja u sve tri formulacije odgovaraju propisima BP 2009 za određivanje litijum-karbonata u matriks tabletama („Slow release lithium carbonate tablets“) [14].

Izgled svih tableta u potpunosti zadovoljava zahteve Ph. Jug. V u pogledu oblika, ujednoličnosti veličine, boje i glatkoće površina (tabela 3).

Variranje mase za sve formulacije tableta zadovoljava farmakopejski propis. Samo za jednu tabletu u formulaciji sa Carbopol®-om 71G NF masa odstupa ispod -5% (tabela 4), ali je ovo odstupanje u dozvoljenim farmakopejskim granicama [12].

Čvrstina i otpornost na habanje ukazuju na mehanička svojstva tableta. U pogledu čvrstine, za lomljenje tableta u svim formulacijama, bila je potrebna sila od 25 do 65 N. Najčvršće su bile tablete sa Carbopol®-om 71G NF ($\overline{F}$ = 62,13 N) a najmekše sa Carbopol®-om 974P ($\overline{F}$ = 37,96 N) (tabela 5), što se može povezati sa razlikom u fizičkim osobinama upotrebljenih karbomera. Carbopol® 71G NF namenski je pripremljen postupkom suve granulacije za izradu tableta direktnom kompresijom i ima 2–8 puta krupnije čestice od Carbopol®-a 971P NF. Uopšte, granulirani karbomeri imaju veličinu čestica u opsegu 150–425 μm [4, 6], što direktno utiče na protočnost tabletne mase i na čvrstinu tableta.

Dok je čvrstina tableta u ispitivanim formulacijama sa 15% karbomera zadovoljavajuća, njihova friabilnost je veoma visoka (tabela 5). Prema farmakopejskom propisu, za većinu tableta prihvatljiva vrednost za gubitak mase za vreme okretanja bubnja je 1% [12], a stepen gubitka mase u ispitivanim formulacijama je bio ≈ 30%.

Porozitet i mehanička otpornost gotovih tableta bitno su uslovljeni izborom pritiska kompresije i tipa mašine za tabletiranje. Međutim, sastav izrađenih formulacija može predstavljati ograničavajući faktor za ostvarivanje optimalnog pritiska kompresije, koji obezbeđuje izradu tableta visoke mehaničke otpornosti [11]. Korigovanje sastava ispitivanih formulacija, u cilju poboljšanja farmaceutsko-tehnoloških osobina tableta, nije bilo moguće, zato što je eksperimentalno ispitivan uticaj tipa karbomera na brzinu oslobađanja litijum-karbonata. Podaci iz literature govore u prilog tome da se optimalni pritisak kompresije za odgovarajuću formulaciju matriks tableta sa karbomerima određuje eksperimentalno, tako da čvrstina gotovih tableta treba da odgovara sili lomljenja od 8 do 10 kP (78,5–98,1 N), koja je dovoljna da obezbedi friabilnost manju od 1% [6]. U slučaju navedene tri formulacije ta pravilnost nije postignuta (tabela 5). U rasponu sile lomljenja od $\overline{F}$ = 37,96 do $\overline{F}$ = 62,13 N u izrađenim formulacijama sa različitim karbomerima, friabilnost tableta je ostala gotovo nepromenjena (≈ 30 %).

Najbitniji parametar za procenu uticaja tipa karbomera na kvalitet matriks tableta je brzina oslobađanja lekovite supstance. Na osnovu fizičko-hemijskih i farmakokinetičkih osobina litijum-karbonata [22] i fizičko-hemijskih osobina karbomera (anjonska priroda i pH zavisno bubrenje polimera) [5] ispitivanje profila oslobađanja rađeno je po propisu USP 26 – test II, datom u monografiji: „*Lithium Carbonate Extended-Release Tablets*“ [16].

Usporeni profili oslobađanja litijum-karbonata iz matriks tableta izrađenih sa Carbopol®-om 971P NF i Carbopol®-om 71G NF veoma su slični, ali ne odgovaraju zahtevima USP 26 [16] (slika 1). Sličnost profila se objašnjava njihovom identičnom hemijskom strukturom [23]. Veća brzina oslobađanja litijum-karbonata iz formulacije sa Carbopol®-om 971P NF, u svim vremenskim intervalima, u odnosu na formulaciju sa Carbopol®-om 71G NF (slika 1), pripisuje se razlici u veličini čestica i gustini korišćenih polimera. Podaci iz literature ukazuju na to da Carbopol® 971P NF, upotrebljen u istoj koncentraciji kao Carbopol® 71G NF, omogućava brže i obimnije bubrenje matriksa, što uglavnom ima za posledicu sporije oslobađanje leka. Ova pojava objašnjava se činjenicom da sitne čestice Carbopol®-a 971P NF predstavljaju mnogo veću kontaktnu površinu za bubrenje u medijumu u odnosu na granule Carbopol®-a 71G NF [8]. Kao uzrok razlike u kinetici oslobađanja lekovite supstance, ako su svi ostali parametri identični, i drugi autori navode razliku u veličini čestica ovih karbomera [20]. Rezultati dobijeni u ovom eksperimentalnom radu ukazuju na to da razlika u fizičkim osobinama između ovih karbomera ne mora imati ključni uticaj na kinetiku oslobađanja leka, već se faktori formulacije i postupak izrade moraju uzeti u obzir u tumačenju dobijenih profila oslobađanja. Tome ide u prilog i činjenica da samo formulacija sa Carbopol®-om 71G NF, nakon završenog *dissolution* testa, ostavlja gumasti ostatak u korpicama aparature.

Formulacija izrađena sa Carbopol®-om 974P NF daje najbrži profil oslobađanja litijum-karbonata, što se može objasniti visokim stepenom hemijske umreženosti polimera, odnosno građenjem rigidnih hidrogela, nehomogenih u pogledu viskoziteta u kontaktu sa vodenim medijumom. Nehomogen hidrogel ima veći viskozitet u poređenju sa Carbopol®-om 971P NF i Carbopol®-om 71G NF, pri čemu mikroviskozne oblasti imaju funkciju kanala za brži transport lekovite supstance iz nabubrelog matriksa [5, 8]. Preraspodela litijum-karbonata, kao teško rastvorne supstance u vodi [12], vrši se dispergovanjem u hidrofobnijim oblastima gela. Ova preraspodela je, uglavnom, ravnomerna u hidrogelu ujednačenog viskoziteta, kakav grade Carbopol® 971P NF i Carbopol® 71G NF, dok se u hidrogelu Carbopol®-a 974 P lek prevashodno nalazi u makroviskoznim oblastima. Pomenuta rastvorljivost leka ujedno je i najvažniji parametar koji uslovljava linearnu kinetiku njegovog otpuštanja, mehanizmom kontrolisanog bubrenja polimera [8]. U nabubrelom polimeru, postojeće mikrogel strukture deluju kao zasebne funkcionalne jedinice za kontrolisano oslobađanje leka [24]. Od velikog značaja za kinetiku otpuštanja je i primena nebubrećeg punioca, odnosno izvođenje *dissolution* testa u neutralnoj pH sredini medijuma. Anjonski polimer u neutralnoj sredini (pH = 5–7) maksimalno bubri, dolazi do odbijanja karboksilatnih anjona, a broj i veličina mikroviskoznih oblasti svode se na minimum [8, 11, 20]. Iz navedenog proizilazi da, ako je koncentracija karbomera 15%, svi nabrojani faktori favorizuju upotrebu Carbopol®-a 974P NF u izradi matriks tableta sa litijum-karbonatom.

Zaključak

Izrađene matriks tablete, koje su identičnog kvantitativnog sastava, a razlikuju se samo po tipu upotrebljenog karbomera, zadovoljavajućeg su kvaliteta u pogledu sadržaja litijum-karbonata, izgleda tableta, čvrstine i variranja mase.

Rezultati ispitivanja uticaja različitih tipova Carbopol®-a, upotrebljenih u koncentraciji 15%, na brzinu oslobađanja litijum-karbonata iz formulisanih matriks tableta, ukazuju na to da samo matriks tablete izrađene sa Carbopol®-om 974P NF imaju zadovoljavajući profil oslobađanja. Tablete izrađene sa Carbopol®-om 971P NF, kao i sa Carbopol®-om 71G NF pokazuju veoma slične osobine u pogledu kontrole oslobađanja litijum-karbonata, ali da bi se postigao zadovoljavajući profil oslobađanja u oba slučaja, potrebno je umanjiti koncentraciju karbomera.

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Asymmetries in numerical density of pyramidal neurons in the fifth layer of the human posterior parietal cortex

Asimetrije numeričke gustine piramidnih neurona petog sloja zadnje parijetalne kore čoveka

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Abstract

Background/Aim. Both superior parietal lobule (SPL) of dorsolateral hemispheric surface and precuneus (PEC) of medial surface are the parts of posterior parietal cortex. The aim of this study was to determine the numerical density (N_V) of pyramidal neurons in the layer V of SPL and PEC and their potential differences. **Methods.** From 20 (40 hemispheres) formaline fixed human brains (both sexes; 27– 65 years) tissue blocks from SPL and PEC from the left and right hemisphere were used. According to their size the brains were divided into two groups, the group I with the larger left (15 brains) and the group II with the larger right hemisphere (5 brains). Serial Nissl sections (5 μm) of the left and right SPL and PEC were used for stereological estimation of N_V of the layer V pyramidal neurons. **Results.** N_V of pyramidal neurons in the layer V in the left SPL of brains with larger left hemispheres was significantly higher than in the left SPL of brains with larger right hemisphere. Comparing sides in brains with larger left hemisphere, the left SPL had higher N_V than the right one, and then the left PEC, and the right SPL had significantly higher N_V than the right PEC. Comparing sides in brains with the larger right hemisphere, the left SPL had significantly higher N_V than left PEC, but the right SPL had significantly higher N_V than left SPL and the right PEC. **Conclusion.** Generally, there is an inverse relationship of N_V between the medial and lateral areas of the human posterior parietal cortex. The obtained values were different between the brains with larger left and right hemispheres, as well as between the SPL and PEC. In all the comparisons the left SPL had the highest values of N_V of pyramidal neurons in the layer V (4771.80 mm^{-3}), except in brains with the larger right hemisphere.

Key words:
parietal lobe; cerebral cortex; pyramidal tracts; humans; anatomy.

Apstrakt

Uvod/Cilj. *Lobulus parietalis superior* gornje spoljašnje strane hemisphere (SPL) i *precuneus* (PEC) na unutrašnjoj strani su delovi zadnje parijetalne kore. Cilj našeg rada bio je da se odrede numeričke gustine (N_V) piramidalnih neurona u petom sloju SPL i PEC i njihove eventualne razlike. **Metode.** Blokovi tkiva SPL i PEC sa leve i desne hemisfere uzimani su sa 20 mozgova (40 hemisfera) fiksiranih u formalinu (oba pola, 27–65 godina). Mozgovi su bili podeljeni u dve grupe: prema veličini hemisfera, prvu grupu činili su mozgovi sa većom levom (15 mozgova), a drugu grupu mozgovi sa većom desnom hemisferom (5 mozgova). Serijski rezovi (5 mμ) levog i desnog SPL i PEC bojeni po Nissl-u korišćeni su za stereološku analizu (N_V) piramidalnih neurona petog sloja. **Rezultati.** Numerička gustina u levom SPL kod mozgova sa većom levom hemisferom bila je statistički značajno veća nego u levom SPL kod mozgova sa većom desnom hemisferom. Upoređujući strane kod mozgova sa većom desnom hemisferom, levi SPL je imao značajno veću vrednost N_V od levog PEC, a desni SPL je imao značajno veću vrednost N_V kako od levog SPL, tako i od desnog PEC. **Zaključak.** Rezultati pokazuju obrnut odnos N_V piramidalnih neurona petog sloja između gornje spoljašnje i unutrašnje strane zadnje parijetalne kore. Dobijene vrednosti se razlikuju između mozgova sa većom levom i desnom hemisferom, kao i između SPL i PEC. Levi SPL imao je najveće vrednosti N_V u svim slučajevima (4771,80 mm^{-3}), osim kod mozgova sa većom desnom hemisferom.

Ključne reči:
parijetalni režanj; mozak, veliki, kora; piramidni putevi; ljudi; anatomija.

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Introduction

Since Rasdolsky [1] relationships between morphological and functional brain asymmetries have been confirmed by numerous investigators for various brain regions [2, 3, 4]. The parietal association cortex of primates comprises areas (Brodmanns area – BA) BA5 and BA7, also BA39 and 40. The area of the superior parietal lobule (SPL) contains BA5 and 7, which are marked as the area parietalis superior s. medialis [5]. Anatomically, both SPL of dorsolateral hemispheric surface and precuneus (PEC) of medial surface, are the portions of the same posterior parietal cortex (BA7), which comprises the greatest part of the parietal lobe behind BA2 on medial surface. By far the greatest part of human SPL belongs to BA7, but its detailed parcellation revealed 6 or 8 areas [6, 7] and several of them had a significantly higher variability in the left hemisphere and/or in men, and for some there was a hemisphere-by-gender interaction [7]. The cortex of PEC belongs to the medial part of BA7, but is not clearly defined by all authors as posterior parietal cortex [8]. SPL is a sensorimotor interface for visually guided movements [9], and the damage of BA7 leads to different complex types of agnosia [10].

This isocortical area has predominant six layered cortex of parietal type, with cinguloparietal transitional zone (BA31) from PEC to suprasplenial part of cingulate gyrus [11, 12]. In studies on the overall cortical connectivity and cortical networks the PEC and posterior cingulate gyrus were consistently observed as centrally connected regions, independent on age and sex [13]. Within the default brain network one of two prominent areas is the posterior midline region, which includes the posterior cingulate cortex (roughly BA31/30/29) and PEC (roughly medial BA7). Their activity has been associated with successful episodic retrieval, but also with unsuccessful episodic encoding [14]. The role of PEC (BA7) in man is specific in recall of episodic memory [15], and its activation is related to visual strategy of memory [16]. In early onset of Alzheimer disease, PEC and hippocampal atrophy are independent from each other and smaller PEC is associated with impaired visuospatial functioning [17].

In the cerebral cortex of humans there are two basic types of neurons: pyramidal (the majority of cortical neurons) and nonpyramidal ones, or pyramidal and inhibitory interneurons, and their numerical relationships are various in different brain areas [5, 18, 19]. Numerical density (N_V) as an stereological parameter indicates the number of neurons in a specific part of cortex, but in the available literature we did not find data about the number or density of neurons in the human posterior parietal cortex. We investigated N_V of pyramidal neurons of the layer V in two regions (SPL and PEC) of human parietal cortex, its variability, eventual differences and asymmetries.

Methods

This morphometric study on the cortex of SPL and PEC included a total sample of 20 brains (40 hemispheres) of adult persons (27–65 years) of both sexes. The brains used in this study (collection of the Department of Anatomy, Faculty of Medicine, Belgrade) were without visible macroscopic and pathological changes, and the cause of death was no disease of the nervous system. The brains removed by routine autopsies were perfused by physiological solution followed by 10% formaline solution through internal carotids and basilar artery. Then the brains were left in formaline solution with addition of glycerine (86–88% glycerolum) which formed a support for the stored brains on the bottom of the vessel. Brain tissue fixation period was about four weeks, and after this period we started this study.

After SPL and PEC identification, we measured their extrasulcal surfaces and fronto-occipital distance between the most prominent points of frontal and occipital lobes on each hemisphere, using a line parallel to intercommissural line [20]. A larger hemisphere was determined according to overlapping of two parameters: longer fronto-occipital distance and larger total (sum) surface of SPL plus PEC. If both of these parameters were larger in one hemisphere, that hemisphere was considered larger. For morphometric analysis in the first group (controls) we included 15 brains with the larger left hemisphere and in the second one five brains with the larger right hemisphere [21].

The tissue blocks (0.5×0.5 cm) removed from the middle of SPL and PEC, at equal (1 cm) distance from the hemispheric border in medial (PEC) and lateral direction (SPL), and at the midpoint between the parietoccipital and postcentral sulcus. After paraffin embedding, serial sections (5 μm thick) were stained by Cresyl violet (Nissl method) and used for stereology.

Stereology. For estimation of the density (number) of pyramidal neurons in the layer V of SPL and of PEC the relative stereological parameter, N_V was applied [22, 23].

The numerical density was determined on 5 μm thick sections stained by Cresyl violet, under magnification 40×, when a grid was inserted into the ocular of microscope (test system) M42 (Weibel), which was adjusted for the given magnification by an objective micrometer. The test system and microscope were calibrated by an objective micrometer 1:100 at the used magnification (ocular magnification 10× and objective 40×), and the determined surface area (At) of the test system was 0.058 mm2. The formula of Floderus [22] was used for the numerical density:

$$NV = N/A / (t + D – 2h),$$

where N_V is the numerical density of pyramidal neurons, N/A the number of pyramidal neurons on the test system surface, t is the thickness of a section (5 μm), D an average diameter of pyramidal cell (0.033 mm) and h is the constant (height of lost cap). This constant h is calculated according to the formula:

$$h = R – (R^2 – r^2)^{1/2},$$

where R is the maximal measured diameter (0.066 mm), and r the minimal measured diameter (0.0055 mm) of a pyramidal neuron. The average diameter of a neuron was determined by an objective micrometer 1:100 at the used magnification (ocular 10x and objective 40x) on 100 randomly selected pyramidal neurons of the fifth layer.

Pyramidal neurons counting was performed in 10 fields sampled in standardizied way, from the cortical surface to

the layer V, by moving the test system verticaly down from the cortical surface to this layer. After returning to the surface, the test system was moved horizontally for one field and movement was repeated down to the same layer [23]. The final values were obtained as middle values of these measurements.

In descriptive and analytical statistics (significance of differences by *t*-test, SD, SE) software "InStat 2" was used. We analyzed separately NV in SPL and PEC in brains with the larger left and in brains with the larger right hemispheres and compared the investigated structures on the left and right sides of these brains.

Results

The obtained values for N_V of pyramidal neurons of the layer V in SPL and PEC are shown in the Table 1 with significant differences marked by letters a-h.

Table 1

Numerical density (N_v) in the left and right superior parietal lobule (SPL) and left and right precuneus (PEC) in brains with larger right or left hemisphere

SPL/PEC	N_v (nm^{-3}), $\bar{x} \pm SD$ (min-max)	
	right hemisphere	left hemisphere
SPL		
left	3954.2 ± 187.5 [e] (3583–4089)	4771.8 ± 169.6 [a, b, c] (4510–4932)
right	4478.4 ± 59.3 [f, h] (4393–4553)	4257.4–145.9 [d] (4089–4468)
PEC		
left	3464.4 ± 330.2 (2993–3759)	3852.6 ± 43.1 (3793–3920)
right	4013 ± 162.9 [g] (3794–4218)	3675.1 ± 81.8 (3541–3794)

[a] $p < 0.01$ *vs* left SPL in the right hemisphere
[b] $p < 0.01$ *vs* right SPL in the left hemisphere
[c] $p < 0.01$ *vs* left PEC in the left hemisphere
[d] $p < 0.01$ *vs* right PEC in the left hemisphere
[e] $p < 0.05$ *vs* left PEC in the left hemisphere
[f] $p < 0.01$ *vs* left SPL in the right hemisphere
[g] $p < 0.01$ *vs* left PEC in the right hemisphere
[h] $p < 0.01$ *vs* right PEC in the right hemisphere

We found a significantly higher numerical density in the left SPL in the larger left hemispheres than in left SPL in larger right hemispheres, without other significant differences between the brains with larger left and right hemispheres.

In brains with the larger left hemisphere the left SPL had a significantly higher N_V than the right one, the left SPL had a significantly higher N_V than the left PEC, and the right SPL had significantly higher N_V than the right PEC.

In brains with larger right hemispheres the left SPL had significantly greater N_V than the left PEC, the right SPL had larger density than the left SPL, right PEC had higher density of neurons than the left one, and the right SPL had higher N_V than the right PEC.

In general, there was an inverse relationship between the lateral (SPL) and medial (PEC) parietal cortex, implying that when in one hemisphere one structure was larger, other was smaller, and between the sides. In addition, the left SPL appears to be specific, with the highest N_V of all investigated structures, except in brains with larger right hemispheres.

Discussion

The left hemisphere is dominant for language, and the right one for visuo-spatial orientation [2], and the larger dimensions of the left hemisphere include its larger cortical surface (left 840.0 cm^2, right 838.0 cm^2) [24]. Much more frequent findings of larger left hemisphere and of longer left Sylvian fissure are related to the great majority of right-handers in population, and to left hemisphere dominance, including the localisation of speech centers in left hemisphere [25]. We did not know the data about hemisphere dominance of the investigated brains, but according to detailed analysis of the literature and available morphological studies, our hypothesis that larger hemispheres were those with both, a longer fronto-occipital distance (brain length), and the surface of posterior parietal cortex is well established [21].

Our finding of greater N_V in the left SPL only in brains with the larger left hemisphere is in agreement with the majority of recent studies, which unfortunately did not consider the hemispheric dominance. So, between the two hemispheres there are globally and regionally specific differences, with the generally thicker cortex and with a larger number of neurons in the left hemisphere in both sexes [26, 27]. A significant leftward asymmetry was found in the precentral gyrus, middle frontal, anterior temporal and SPL, and under the condition of unconditioned love compared with the control condition the left SPL (BA7) was most significantly activated [27].

However, our results could be in discordance with the findings of significant rightward asymmetries of posterior brain regions on the medial surface [28], and that one of two hemispheric asymmetries for spatial attention control was a region in only right, but not left SPL [29]. Areas specifically

implicated in generating and playing scales (music) were posterior cingulate, middle temporal, right middle frontal, and right PEC cortices [30], what can be related to our finding of larger right PEC only in brains with larger right hemispheres. PEC is involved in the network of the neural correlates of self-consciousness, engaged in self-related mental representations during rest [31] and the most significant restoration of glucose metabolism (recovery of consciousness after severe chronic brain damage) occurs in cortices of PEC and cuneus [32].

The representative parietal cytoarchitecture of human BA7 is characterized by fully differentiated isocortex: a columnar pattern with conspicuous layers II, IV, V and VI [33]. Radial neuronal arrangement, horizontal dendritic branching and greater similarity to the majority of pyramidal (non-Betz) neurons are clear characteristics of BA7 large pyramidal neurons of lamina V [34]. The presence of several basal dendrites corresponds better to the majority of pyramidal (non –Betz) cells [35]. Horizontal orientation of both basal and apical dendritic branching fits well with the hypothesis about the role of lamina V pyramidal neurons in intracortical selection of impulses which would leave cortex [36] and indicate their role in associative processing [34]. In BA7 both stripes of Baillarger are visible indicating a considerable presence of horizontal axons, probably of long- range connections [37]. Therefore, regional differences in N_V of the layer V pyramidal neurons that we found are consistent with the existence of different subsets within the brain default mode network (long-range neuronal pathways), with the pivotal role of PEC/posterior cingulate cortex [38]. Additionally, findings that pyramidal neurons of the layer V of the adult rodent cortex fall into two major classes, type I cells and type II [18], lead to the question if their different distributions in parietal cortex cause the differences in the values of N_V.

In our previous study in brains with larger left hemisphere, the cortex of the left SPL was significantly thicker as compared to the left PEC, without other significant differences, what related to our present results further multiplies the number of neurons in the left SPL. In brains with the larger right hemisphere the cortex of SPL was bilaterally thicker than of PEC [8]. The lower N_V in the cortex of PEC we found, shows the more loose arrangement of neurons. Asymmetries in terms of cortical thickness reported for SPL (left > right) and PEC (right > left) with more pronounced differences in men [27], and findings of higher amounts of parietal gray matter in the left hemispheres [7], are in agreement with our results for brains with larger left hemispheres. In general, our results confirm the statement that differential parietal macroanatomy between genders and hemispheres still is a matter of debate [7]. In addition to the provided numerical data, our results lead to increasing complexity of knowledge about the relationships between morphological asymmetry and the function of human cortex.

Conclusion

Morphometric studies of human brain should unavoidably include the data about lateralization (handedness), cerebral dominance, or at least, about larger hemisphere.

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Diagnostical significance of dimethylarginine in the development of hepatorenal syndrome in patients with alcoholic liver cirrhosis

Dijagnostički značaj dimetilarginina u razvoju hepatorenalnog sindroma kod bolesnika sa alkoholnom cirozom jetre

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Abstract

Background/Aim. Chronic consumption of alcohol during a longer period of time leads to the development of cirrhosis with the reduction in metabolic liver function and disorders in arginine metabolism. Hepatorenal syndrome (HRS) is the most severe complication of alcoholic liver cirrhosis. The aim of the study was to analyze disorders in arginine metabolism by monitoring concentrations of asymmetric dimethylarginine (ADMA) and symmetric dimethylarginine (SDMA) in patients with liver cirrhosis and HRS. **Methods**. The study included three groups of subjects: a group of patients with cirrhosis and HRS (24 patients), a group of patients with cirrhosis without HRS (18 patients) and a control group composed of 42 healthy voluntary blood donors. Concentrations of ADMA, SDMA and L-arginine in plasma were measured in all groups using the high pressure liquid chromatography (HPLC) method. **Results.** The concentration of SDMA was significantly higher in the patients with HRS compared to the patients without HRS and it was also higher than the values obtained from the healthy participants (1.76 ± 0.3 μmol/L; 1.01 ± 0.32 and 0.520 ± 0.18 μmol/L, respectively; $p < 0.01$). The concentrations of ADMA were higher in the cirrhotic patients with HRS than in those without this serious complication of cirrhosis. The concentration of ADMA in all the examined cirrhotic patients was higher than those obtained from healthy volunteers (1.35 ± 0.27 μmol/L, 1.05 ± 0.35 μmol/L and 0.76 ± 0.21 μmol/L, respectively). In the patients with terminal alcoholic liver cirrhosis, the concentrations of ADMA and SDMA correlated with the progress of cirrhosis as well as with the development of cirrhosis complications. In the patients with HRS there was a positive correlation between creatinine and SDMA in plasma ($r^2 = 0.0756$, $p < 0.001$) which was not found between creatinine and ADMA. **Conclusion**. The obtained results demonstrate that the increase in SDMA concentration is proportionate to the progression of chronic damage of the liver and kidneys. Increased ADMA concentration can be a causative agent of renal insufficiency in patients with cirrhosis.

Key words:
liver cirrhosis, alcoholic; hepatorenal syndrome; diagnosis; prognosis; arginine; chromatography, high pressure liquid.

Apstrakt

Uvod/Cilj. Hroničnim konzumiranjem alkohola u dužem vremenskom periodu razvija se ciroza jetre sa smanjenjem metaboličke funkcije jetre i poremećajima metabolizma arginina. Hepatorenalni sindrom (HRS) je najteža komplikacija ciroze jetre. Cilj ove studije bio je da se analiziraju poremećaji metabolizma arginina praćenjem koncentracija asimetričnog dimetilarginina (ADMA) i simetričnog dimetilarginina (SDMA) kod bolesnika sa cirozom jetre i HRS. **Metode**. Istraživanjem su bile obuhvaćene tri grupe ispitanika: grupa bolesnika sa cirozom i HRS (24 bolesnika), grupu bolesnika sa cirozom bez HRS (18 bolesnika) i kontrolna grupa od 42 zdrava dobrovoljna davaoca krvi. Svim ispitanicima merene su koncetracije ADMA, SDMA, i L-arginina u plazmi, korišćenjem metode tečna hromatografija pod visokim pritiskom (HPLC). **Rezultati**. Koncentracija SDMA bila je znatno viša, kod bolesnika sa HRS, u odnosu na bolesnike bez HRS, i viša nego kod zdravih ispitanika (1,76 ± 0,3 μmol/L; 1,01 ± 0,32 μmol/L i 0,52 ± 0,18 μmol/L, respektivno; $p < 0,01$). Koncentracija ADMA bila je viša kod bolesnika sa HRS nego kod bolesnika bez HRS. Koncentracije ADMA kod bolesnika sa i bez HRS bile su više nego kod zdravih ispitanika (1,35 ± 0,27 μmol/L, 1,05 ± 0,35 μmol/L i 0,76 ± 0,21 μmol/L, respektivno, $p < 0,01$). Kod bolesnika u terminalnoj fazi alkoholne ciroze jetre, koncen-

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tracije ADMA i SDMA korelisale su sa stepenom progresije ciroze, kao i sa razvojem komplikacija ciroze. Kod bolesnika sa HRS postojala je pozitivna korelacija između kreatinina i SDMA u plazmi ($r^2 = 0{,}0756$, $p < 0{,}001$), ali ne i između kreatinina i ADMA. **Zaključak**. Dobijeni rezultati pokazuju da je povećanje koncentracije SDMA srazmerno progresiji hroničnog oštećenja jetre i bubrega. Porast koncentracije ADMA može biti uzročni faktor razvoja bubrežne insuficijencije kod bolesnika sa cirozom jetre.

Ključne reči:
jetra, bolesti izazvane alkoholom; hepatorenalni sindrom; dijagnoza; prognoza; amino kiseline, esencijalne; hromatografija, tečna, pod vp.

Introduction

Hepatorenal syndrome (HRS) is a potentially reversible syndrome which develops in conditions of chronic insufficiency and liver cirrhosis. It is characterized by renal dysfunction and severe changes in systemic circulation. Reduction in renal function is a consequence of reduction in blood circulation through the kidneys. It is manifested by the reduction in glomerular filtration. Renal failure is caused by the activation of specific vasoconstrictor systems involving activation of the sympathetic system, renin-angiotensin system and vasopressin [1]. Based on the new consensus concerning the definition, diagnosis and treatment of HRS, the International Ascites Club has established a new criteria for the diagnosis of HRS [2].

Dimethylarginins are formed by transmethylation modification, *via* reaction of enzyme protein methyltransferase (PRMT) on the remainder of arginine. During transmethylation, S-adenosylmethionine, which is a methyl group donor, transforms into S-adenosylhomocysteine. The methylated arginine remainder forms asymmetric dimethylarginine (ADMA) and symmetric dimethylarginine (SDMA) by proteolysis. The main metabolic pathway of ADMA takes place in the liver. ADMA is hydrolyzed by the action of the enzyme dimethylarginine dimethylaminohydrolase (DDAH) on citrulline and dimethylamine. A small part of ADMA enters the circulation and is removed as such through the kidneys [3]. ADMA is a direct inhibitor of the enzyme nitric oxide (NO) synthase, which participates in NO synthesis. NO participates in the maintenance of vascular tonus. Increased concentration of ADMA in blood of patients with decompensated liver cirrhosis reduces the synthesis of NO, whereby intrahepatic vascular resistance is increased [4]. Compared to ADMA, SDMA has indirect inhibitory effect on NO synthase. SDMA can disturb the synthesis by competing in the transport against L-arginine on the level of cell membrane [5–7].

Some studies [8] have demonstrated that increased ADMA level in blood of patients with decompensated liver cirrhosis is probably the result of DDAH enzyme activity exhaustion. Increased level of ADMA has a causative role in the development of HRS. Accumulation of ADMA in patients with liver cirrhosis causes liver damage. Accumulation of ADMA inhibits NO synthase thereby causing vasoconstriction of the kidney blood vessels. Thus, blood flow through the kidney is interrupted, in other words, glomerular filtration is reduced and SDMA is retained in the kidney. Compared to ADMA, SDMA is not broken down by the action of DDAH enzyme but is excreted as such through the kidneys [9, 10].

In patients with alcoholic cirrhosis increased level of ADMA is strongly correlated with the severity of liver disease, in accordance with the reduction of its metabolic function. However, the level of SDMA in plasma is within normal values in patients with alcoholic cirrhosis. The levels of dimethylarginine in plasma in HRS are not known. Therefore, the aim of this study was to estimate the level of dimethylarginine (ADMA and SDMA) in plasma, in patients with cirrhosis and HRS, as well as in patients with cirrhosis without HRS.

Methods

The study included two groups of subjects the target and control group. The group with cirrhosis consisted of 42 patients classified according to the presence of HRS. The patients were all male, aged 25 to 70 years, with an average age of 53.13 ± 23 and with history of more than ten years of alcohol abuse. All patients were in terminal stage of alcoholic cirrhosis with moderate to severe ascites. HRS was diagnosed in 24 patients with cirrhosis while 18 patients had no HRS. The control group consisted of 42 healthy examinees who were voluntary blood donors. All examinees in the control group were males, average age 50.76 ± 9.7 years with normal laboratory findings.

The diagnosis of cirrhosis was established in all the patients based on clinical, biochemical and ultrasound findings as well as liver biopsy. All the patients had moderate to severe ascites. The presence of ascites was confirmed by diagnostic paracentesis. HRS was diagnosed in accordance with the latest criteria, suggested by the International Ascites Club [3]. The criteria included: cirrhosis with ascites, low glomerular filtration rate, serum creatinine above 133 μmol/L (above 1.5 mg/dL), proteinuria below 500 mg/day, the absence of shock, the absence of bacterial infection, loss of fluid, poor kidney function after discontinuing diuretic treatment (serum creatinine remains at ≥ 133 μmol/L after at least 48 hours following the application of albumin dose of 1 to 100 g/kg a day), treatment without nephrotoxic drugs, the absence of parenchymal kidney disease (patient has no proteinuria > 500 mg/day, no microhematuria > 50 erythrocytes, as well as pathologic findings from echosonographic examination of the kidneys).

The study was conducted in accordance with the ethical standards of the Committee on Human Experiments or with the Declaration of Helsinki from 1975, revised in 1983. The study was prospective, in accordance with the Ethics Committee and it was conducted after obtaining consent from all the patients.

General biochemical parameters were obtained from patients' serum using standard biochemical methods of the International Federation of Clinical Chemistry (kinetic spectrophotometric methods performed on multichannel biochemical analyzer OLYMPUS AU680). Arginine and dimethylarginine were determined in all three groups using high pressure liquid chromatography (HPLC) method [11]. The method was performed in the following way: 50 μL of monomethylarginine as an internal standard (IS) was added to 0.2 mL plasma. This mixture was used in various phases in SPE cartridges with previous activation with 1 mL of methanol and 2 mL, of trichlovoaceticacid (TCA) 2%. After washing cartridges (1 mL TCA 2%; 1 mL phosphate buffer – 150 mmol/L, pH 8.0; 1 mL methanol), amino acids were eluated with 1.2 mL of 2% triethylamine dissolved in 70 : 30 solution of methanol / water. Eluates were dried in nitrogen, afterwards an aliquot of 0.4 mL buffer was added to dry residue (mobile phase A). Analysis was followed by derivatization with ortho-phthalaldehyde (0.1 mL, 2 min). For performing the HPLC method, a fluorescent detector (λ_{ex} 340 nm, λ_{em} 445 nm; photomultiplier (PMT) is 12 between 2.60 and 4.20 min.) was necessary as well as Zorbax SB-C18 column (150 × 4.6 mm, 3.5 μm). The basic separation of methylarginine was achieved by gradient between mobile phase A (sodium phosphate buffer- 40 mmol/L, pH 6.2) and phase B (methanol). The analysis began with 32% phase B for 4.0 minutes. It was then followed by mobile phase B which grew linearly up to 100% in the next 0.5 min. The whole process of washing a column lasted up to 7.5 min. After that, the content of the mobile phase returned to starting conditions. The whole process lasted for 9 minutes. Analysis of L-arginine was also performed within the process.

Readings for arginine were 2.90 min, for IS 3.50 min, for ADMA 3.85 min and SDMA 4.10 min. The concentrations of L-arginine, ADMA and SDMA in the samples were determined in comparison with the standards.

Data were entered in MS Excel. For analysis of data the statistical program SPSS 17.0 was used. The data were represented as mean values ± SD [95% confidence interval (CI) for medium]. The data were compared among the groups using the ANOVA test. Post hoc analysis by using Dunnett's T3 and Tuckey test was also used. Statistically significant difference was accepted with $p < 0.01$ risk. The ratio between the tested variables was determined by linear regression analysis and goodness of fit analysis, as well as Pearson correlation coefficient.

Results

Liver damage was more severe in the HRS group. This is manifested by de Ritis coefficient which was significantly greater in HRS patients, compared to patients without HRS and healthy examinees. Synthetic liver function, measured by albumin concentration, was significantly decreased in patients with cirrhosis without HRS. Excretory liver function, measured by bilirubin concentration, was significantly reduced in the patients with HRS as compared to the patients without HRS and healthy examinees. Kidney function parameters were considerably increased in the patients with HRS as compared to the patients without HRS and the healthy control (Table 1).

Table 1

Basic demographic, clinical and biochemical characteristics of the patients and healthy examinees

Paremeters	Cirrhosis with HRS	Cirrhosis without HRS	Healthy controls
Males/females (n)	18/ 0	24/ 0	42/ 0
Age (years)	55.83 ± 12.41	50.58 ± 11.08	50.76 ± 9.7
AST/ALT (U/L)	3 ± 1.4*	1.8 ± 0.6*	1.0 ± 0.2
Albumine (g/L)	25 ± 5.6*	27.1 ± 6.6*	40.9 ± 4.2
Total bilirubine (μmol/L)	115.8 ± 81.1*	54.7 ± 35.8*	5.7 ± 1.9
Indirect bilirubine (μmol/L)	61.0 ± 46.0*	29.9 ± 16.6*	5.1 ± 1.5
Direct bilirubine (μmol/L)	54.7 ± 38.4*	24.8 ± 21.2*	0.6 ± 0.5
Urea (mmol/L)	15.05 ± 7.8*	6.7 ± 3.2*	4.58 ± 1.5
Creatinine (mmol/L)	218.6 ± 109.6*	94.5 ± 17.2	84.4 ± 15.2

Data are presented as n/n or mean±SD; *$p < 0.01$ vs. other groups
HRS – hepatorenal syndrome; AST – aspartate aminotransferase; ALT – alanine aminotransferase

In cirrhosis with reduced kidney function the level of ADMA in serum rose with the increase in creatinine level (Pearson correlation coefficient, C = 0.45). With the manifested renal insufficiency in HRS this correlation was lost and the level of ADMA was relatively constant as compared to increase in creatinine (Figure 1).

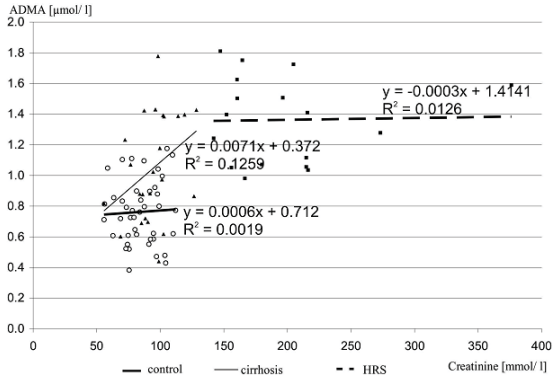

Fig. 1 – Analysis of the correlation and linear regression equitation between asymmetric dimethylarginine (ADMA) and serum creatinine in the tested groups

HRS – hepatorenal syndrome

In the group with cirrhosis, the increase in ADMA was followed by the increase in urea which was in accordance with the reduced metabolic and detoxification liver function

(C = 0.36). Further on, the level of ADMA was relatively constant (Figure 2).

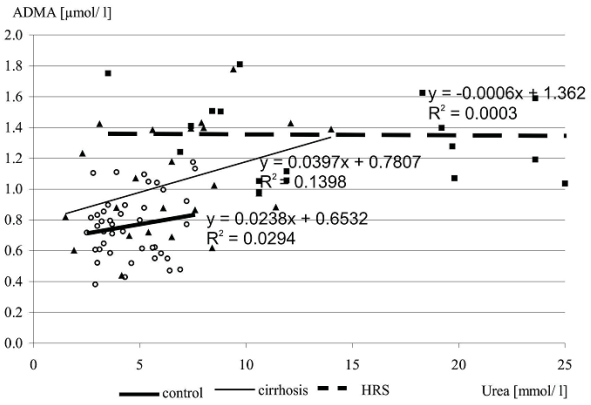

Fig. 2 – Analysis of the correlation and linear regression equitation between asymmetric dimethylarginine (ADMA) and serum urea in the tested groups

HRS – hepatorenal syndrome

In cirrhosis, the level of SDMA in serum rose with the increase in creatinine level (C = 0.83). With manifested renal insufficiency in HRS this correlation continued (C = 0.43, $p < 0.05$) (Figure 3).

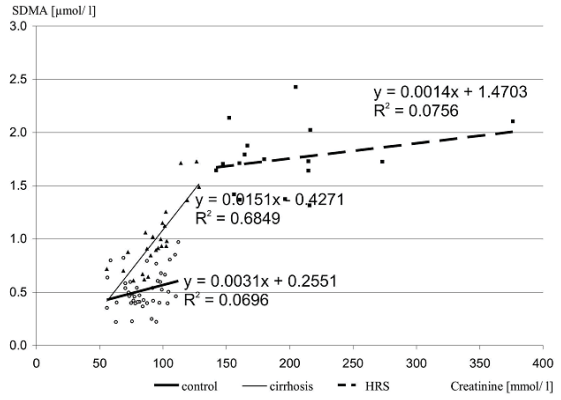

Fig. 3 – Analysis of the correlation and linear regression equitation between symmetric dimethylarginine (SDMA) and serum creatinine in the tested groups

HRS – hepatorenal syndrome

In the group with cirrhosis, with and without HRS, the level of SDMA was increased with increased urea level (C = 0.66 and C = 0.78, respectively; $p < 0.01$). The increase was more intense in the group with HRS (Figure 4).

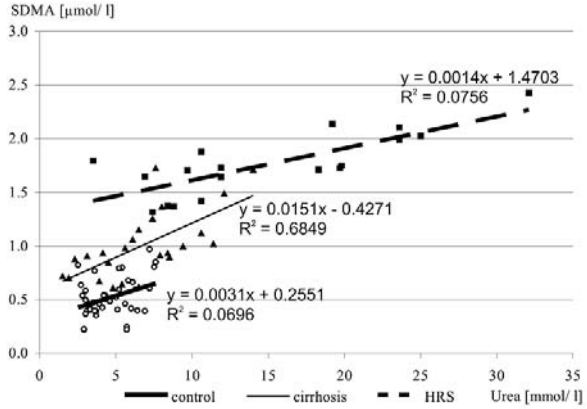

Fig. 4 – Analysis of the correlation and linear regression equitation between symmetric dimethylarginine (SDMA) and serum urea in the tested groups

HRS – hepatorenal syndrome

The lowest values of arginine were obtained in the group with cirrhosis and HRS. ADMA and SDMA were the highest in patients belonging to the groups with cirrhosis with and without HRS (Table 2).

Table 2

Arginine and dimethylarginine in tested groups

Parameters	Cirrhosis with HRS	Cirrhosis without HRS	Healthy controls
Arginine (μmol/L)	60.69 ± 16.8*	79.17 ± 21.7	91.98 ± 27.6
ADMA (μmol/L)	1.35 ± 0.27*	1.05 ± 0.35*	0.76 ± 0.21
SDMA (μmol/L)	1.76 ± 0.3*	1.01 ± 0.32*	0.52 ± 0.18
ADMA/ SDMA	0.79 ± 0.2*	1.09 ± 0.36*	1.58 ± 0.48

Data are presented as mean ± SD; *$p < 0.01$ vs. other groups
HRS – hepatorenal syndrome; ADMA – asymetric dimethylarginine; SDMA – symmetric dimethylarginine

Discussion

ADMA and SDMA are arginine metabolites which have great influence on liver and kidneys damage in chronic alcoholism. In order to prevent the progress of damage and development of HRS, it is important to maintain their levels within normal. The liver has an important role in ADMA metabolism. Great amounts of ADMA from systemic circulation are broken down in the liver by the effect of DDAH enzyme. In this study, in the group of patients with cirrhosis, high values of ADMA were obtained as compared to values in control group. High levels of ADMA appear to be caused by the reduction in metabolic function of the liver. Thereby, ADMA may represent a marker for the degree of liver damage [12, 13]. Some studies have shown that increase in the level of ADMA is followed by increase in liver damage. Some results have shown that two groups of patients with different clinical pictures and similar pathologic conditions of the liver have different levels of ADMA. By direct inhibition of NO synthase, ADMA influences the NO deficiency. This leads to vasoconstriction in liver sinuses which causes the develop-

ment of ischemia in the liver and destruction of hepatocytes [13].

The results obtained in this study, show that in the group of patients with cirrhosis, along with increase in urea, the level of ADMA increased as well. This was confirmed by the reduction in detoxification function of the liver. In this group, the level of ADMA was increased along with the increase in creatinine level which means that ADMA level can be a marker for impending kidney insufficiency. Some studies have shown that high concentration of ADMA in plasma, developed in cirrhosis, can be biologically effective in blood vessels of the kidneys [14, 15]. It is therefore believed that increased concentration of ADMA in liver dysfunction may have an important role in the development of kidney insufficiency in patients with cirrhosis. Some researches [16] have shown that increased concentration of ADMA can cause vasoconstriction effects in the kidney as well as cerebral arteries. Besides, by direct inhibition of NO synthase in the endothelium of renal blood vessels, ADMA causes vasoconstriction in the kidney. This leads to the reduction in glomerular filtration and damage in kidney function. Damage in kidney function causes the retention of SDMA [17–19]. The results of this study show no correlation between urea and ADMA, as well as creatinine and ADMA in the group of patients with cirrhosis with HRS. The level of ADMA is relatively constant which points out that the kidney has no significant effect on ADMA catabolism. The results also show a considerable increase in concentration of ADMA in the groups with cirrhosis with and without HRS. Therefore, ADMA may represent a marker for kidney and liver damage.

Compared to ADMA, SDMA is not broken down in the liver. It was catabolized in the kidney tissue and eliminated by urine. In the group of patients with cirrhosis, a significant correlation between SDMA level and urea may suggest a reduced liver detoxification function. Some studies have shown that in patients with cirrhosis but with normal range kidney function, SDMA in plasma does not correlate with clinical signs of liver damage. The values of SDMA also remain within normal range in patients with terminal phase of liver damage before liver transplantation [20]. The results of this study show a significant positive correlation between SDMA and creatinine in patients with cirrhosis. This shows that SDMA may be a marker for impending kidney insufficiency. In the group of patients with cirrhosis and HRS a significant correlation between SDMA and urea was demonstrated. This may point out to the severity of kidney insufficiency. In this group there was also a continued positive correlation between creatinine and SDMA, which may demonstrate the significant role of kidney tissue in the catabolism of SDMA. The results demonstrate that in the group of patients with cirrhosis, the concentration of SDMA is approximately two times higher than in the control group. In the group of patients with cirrhosis and HRS, the concentration of SDMA is approximately three times higher as compared to the control group. These results may point to the role of kidneys in SDMA catabolism. Similar results were obtained in other studies and they confirm the role of kidneys in the catabolism and elimination of SDMA [21]. It has also been demonstrated that the concentration of SDMA was returned to a normal value after kidney transplantation [22]. Some studies [20] have demonstrated that the increased level of SDMA may not be in correlation with clinical course of kidney damage in patients with terminal phase of liver cirrhosis before liver transplantation.

The obtained results demonstrated that the concentration of arginine decreases, which was followed by an increase in the concentration of ADMA and SDMA. In the group of patients with cirrhosis and HRS, the concentration of arginine had the lowest values, which may point to a significantly reduced liver function and severe kidney insufficiency.

Conclusion

In patients with alcoholic cirrhosis, in line with reduced metabolic liver function, ADMA may be a marker for the degree of chronic alcoholic liver damage.

In patients with cirrhosis, ADMA, as well as SDMA could be markers for kidney insufficiency development. Accumulation of ADMA in plasma causes kidney vasoconstriction and thereby retention of SDMA.

Considering that ADMA has several damaging effects, it can be concluded that modulation of the activity of enzyme which participates in ADMA catabolism may represent a new therapeutic goal which is intended to reduce the progress of liver and kidney damage and thus the development of HRS.

Further research should be directed toward establishing the referential values of ADMA and SDMA for liver and kidney damage.

Aknowledgments

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Odgovornost zdravstvenih ustanova za štete kao posledice lečenja

Responsibility of medical institutions for damages resulting from treatment

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Ključne reči:
zdravstvene ustanove; lečenje, greške; zakonodavstvo; medicina, sudska.

Key words:
health facilities; treatment failure; legislation; forensic medicine.

Uvod

U praksi obavljanja delatnosti u zdravstvenom sistemu različite su radnje i propusti kojima se može naneti šteta bolesnicima kao korisnicima usluga ili trećim licima. Razmatranje pretpostavki odgovornosti vezano za medicinsku delatnost stavlja težište na dopuštenost i regularnost postupanja zdravstvenih ustanova, odnosno njihovih zaposlenih koji pružaju zdravstvene usluge [1]. Sistematizacija radnji i propusta u pružanju zdravstvenih usluga kojima bi se mogla naneti šteta uglavnom je stvar usvojenog pravnog uređenja zdravstvene zaštite i zdravstvenog osiguranja građana svake pojedinačne države [2]. Profesionalno obavljanje zdravstvenih delatnosti nameće dužnost da se poznaju i savesno primenjuje znanje i iskustvo koje je čovek na tom području dosegao, kako bi od sebe otklonio moguću odgovornost za nepovoljan medicinski ishod. Postoji, takođe, dužnost da se poštuju sva pravna i moralna načela, posebno propisi koji se odnose na obavljanje zdravstvenih delatnosti. Svi ovi zahtevi, ako se pravilno shvate, nisu usmereni na to da sputavaju rad u svakodnevnoj medicinskoj praksi. Tako, lekar treba da se usredsredi na svoj posao, a ne da strahuje od odgovornosti i da neguje tzv. defanzivnu medicinu, koja nije u interesu ni bolesnika ni lekara. Loša pojava bi bila, takođe, ako bi lekar u svakom bolesniku video potencijalnog tužioca. S druge strane, izvesna doza opreza zbog eventualne odgovornosti ima preventivno dejstvo, jer podupire savesnost lekara i suprotstavlja se nemarnosti i lošem radu. Treba učiniti da odgovornost lekara bude razumna, pravična i podnošljiva, ali u isti mah da garantuje i potrebnu sigurnost bolesniku i poštovanje njegovih ličnih prava, a posebno ljudskog dostojanstva i prava na samoodređenje. Ta ideja je sa puno osnova postavljena, ali je njeno oživotvorenje u praksi često veoma teško, jer u sporu između lekara i bolesnika jedna strana izgleda da uvek ostaje nezadovoljna [3–11].

Postupanja u tretmanu bolesnika koja su protivna zakonskim propisima ili pravilima struke karakteriše protivpravnost. Oni povlače odgovornost za nastalu štetu u pravnom smislu, koja može biti višeznačna po vrsti, osnovu, kao i težini zaprećenih sankcija: građanska, imovinska ili odgovornost za štetu jeste oblik odgovornosti pod koji ulazi najveći broj slučajeva lekarskih grešaka. Iz tog razloga u anglosaksonskom pravu za ove slučajeve nepažnje razvio se poseban naziv – *medical malpractice* (pogrešna ili loša medicinska praksa), dok se u evropskoj terminologiji govori najčešće o pogrešnom postupanju, odnosno greškama lekara ili drugog medicinskog osoblja. Za građansku odgovornosti vezuje se pravni institut osiguranja od odgovornosti, što olakšava obeštećenje. Osnovna razlika između građanske i krivične odgovornosti jeste u standardu dužne pažnje koje lekar treba da se pridržava, jer bi u suprotnom usledila odgovornost. Krivična odgovornost sledi samo za grubu nepažnju, dok se kod odštetne odgovara i za običnu nepažnju. To objašnjava situaciju da je odgovornost za štetu zbog grešaka u medicini danas dominantan oblik odgovornosti i da daleko nadmašuje po broju krivične postupke. Smatra se da je to adekvatniji oblik sankcionisanja, budući da ovde nije u prvom planu društvena opasnost štetnih radnji (grešaka), već povreda ličnih dobara i ličnih prava nastalih kršenjem dužnog ponašanja nepažnjom. Staleška ili disciplinska odgovornost pokreće se kod kršenja pravila struke bez obzira da li se profesionalna delatnost obavlja u okviru javne ili privatne zdravstvene službe. Krivična odgovornost ima individualni karakter jer uvek odgovara lekar, a ne zdravstvena ustanova, i vezana je striktno za ispunjenje bića krivičnog dela, merilo za krivicu i pažnju je subjektivno, nema pretpostavke o elementima odgovornosti, nema dokaznih olakšica, niti osiguranja od odgovornosti [3]. Nekad se u počinjenoj grešci može desiti sticaj više protivpravnih radnji, što daje razlog za odgovornost po više osnova. U načelu, nijedna od više vrsta odgovornosti ne uslovlja-

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va drugu, jer svaka ima vlastite uslove i ciljeve, ali se često dešava da dokazivanje jednog pogrešnog, protivpravnog postupka bude zajednički element za sve. Ipak, bez obzira na to, različite odgovornosti se utvrđuju u različitim postupcima i od strane različitih organa, jedna drugu ne potiskuju i mogu se voditi paralelno, uz uvažavanje razloga praktičnosti i kvalifikacije po težini povrede, i poznatog pravila „*Ne bis in idem*“ (Ne sudi dvaput o istoj stvari). To je izvodljivo budući da je reč o više nivoa odgovornosti čiji su pravni osnovi i sankcije nejednaki, dopunjujući, a ne duplirajući. Praktično, krivičnu odgovornost i odgovornost za štetu utvrđuju i izriču redovni sudovi (krivica i parnica), a stališku odgovornost sudovi časti pri lekarskim komorama i strukovnim udruženjima pripadnika medicinskih profesija.

Osnov odgovornosti za štete kao posledice lečenja

Građanska odgovornost u domenu medicine označava obavezu naknade bolesniku one štete koja je nastala prilikom profesionalnog rada lekara i drugih službi. Ova vrsta odgovornosti smeštena je u kontekst postojanja ugovornog odnosa povodom nekog medicinskog tretmana, ali i opštih pravila obligacionog prava o ugovornoj i deliktnoj odgovornosti.

Za izvođenje odgovornosti zbog štete izazvane medicinskim procedurama ili drugim radnjama ne postoji poseban pravni režim, osim u malobrojnim izuzecima [4]. U okviru zemalja članica Evropske unije nastoji se jos od ranije da se ustanove i ujednače propisi koji regulišu odgovornost pripadnika slobodnih zanimanja, uključujući tu i profesije u zdravstvu [5]. Načelno, za građansku odgovornost u vezi za medicinskom delatnost važe opšti propisi o toj vrsti odgovornosti na nivou svake zemlje. Moderno pravo odgovornosti lekara gotovo svuda stvara sudsku praksu, koja je putem tumačenja već postojećih pravnih načela usavršila i dalje razvila i donekle modifikovala poznatu pravnu regulativu [1, 6]. Opšti je stav da ako bolesnik prilikom medicinskog tretmana pretrpi štetu, on svoje pravo na naknadu, može ostvariti kako po osnovu ugovorne, tako i po osnovu deliktne odgovornosti. U tom smislu „kršenje ugovora i nedopuštena radnja čine zajednički, stopljeni osnov odgovornosti lekara“ [7].

Tužbe po osnovu povrede ličnih prava, kao i pravne lekove koji se ulažu po njima, tradicionalno se pokreću kod građanskog suda, odnosno odgovara se po privatnoj tužbi u parnicama. Dva principa koja se ovde afirmišu jesu princip obeštećenja i princip kvaliteta zdravstvene zaštite. U razvijenim državama dešava se da od toga koliko je parnica u ostvarivanju ovih ciljeva uspešna, toliko zavisi i dalje krivično gonjenjenje pripadnika medicinskih struka, koje time dobija supsidijarni karakter. Razlozi mogu biti u tome da je tužilac odbijen, da nije u potpunosti obeštećen zbog ekonomskih gubitaka nastalih u parnici, ili da osnov krivičnog kažnjavanja počinioca postoji većinom onda kad je on aktivno učinio štetu, a manje kad je to bilo nečinjenje (propuštanje) koje isto tako može biti kažnjivo [8].

Odgovornost zdravstvene ustanove sagledava se i vezuje za odgovorno postupanje njenih zaposlenih. U zavisnosti od vrste postupanja koje se u konkretnom slučaju neke procedure ili zahvata duguje, izdvajaju se dva oblika kršenja dužnosti: u obliku greške u lečenju (veštini ili umeću) i u obliku greške u obaveštavanju (upozorenju, informisanju ili savetovanju) [9]. Prve se još nazivaju „klasičnim“ greškama, a druge greškama „na periferiji lečenja“. Bitno je da se prema pravnoj praksi i teoriji oba ova oblika pogrešnog postupanja po svom pravnom značaju izjednačavaju i jednako su podložne sankcionisanju. Ukoliko je lekar bez važeće saglasnosti, zbog propuštenog ili nedovoljnog informisanja bolesnika izvršio neki zahvat, i ako se rizik zbog koga je obaveštavanje bilo potrebno ostvario, onda lekar treba da plati punu naknadu nastale štete [10]. U okviru ove protivpravnosti dopušta se dokazivanje svakog pojedinačnog oblika kršenja dužne pažnje. Lekar postupa protivno svojoj dužnosti bilo da istovremeno ili nevezano krši postojeća pravila struke (lekarske veštine) ili ustanovljena pravila pažnje [11]. Lekar treba da postupa prema aktuelno važećim i ustaljenim medicinskim standardima i da upotrebi prikladnu, saobraznu meru pažnje. Na pitanje koju meru poznavanja stvari, odnosno stručnosti i koju meru pažnje lekar treba da pokaže odgovara se prema stanju medicinskih znanja i standarda u vreme tretmana, a ne pre ili posle toga. Lekar koji je zanemario pažnju koja je u području njegove delatnosti potrebna ne može se pozivati na druga ista takva lekarska mišljenja ili praksu, budući da vlastite greške ne gube svoj negativan kvalitet usled toga što ih čine i ostali. To, stoga, što je merilo za pažnju objektivno i predstavlja profesionalno merilo za pažnju, koje ne važi samo za lekare nego i za ostala slobodna zanimanja. Naime, pažljivost treba da bude takva da osigurava kvalitet lekarske usluge. Kao objektivno tipizirani standard pažnje uzima se pažnja koja se može očekivati od iskusnog i savesnog lekara istog ranga (nemačko pravo), odnosno dobrog stručnjaka iste kategorije i istog ranga kao i onog čije se ponašanje ocenjuje, lekara opšte prakse, specijaliste itd. (francusko pravo), odnosno razumno kompetentnog lekara (englesko pravo). Prema opštoj odredbi Zakona o obligacionim odnosima u Srbiji je merilo pažnje za zdravstvene poslenike pažnja dobrog stručnjaka, što znači povećanu pažnju prema pravilima struke i prema običajima [12]. Kad lekar ne postupa s pažnjom dobrog stručnjaka, radi se o običnoj nepažnji (*culpa levis*), a ako ne postupa ni onako kako bi postupao svaki prosečan lekar radi se o gruboj nepažnji (*culpa lata*) koja predstavlja viši stepen krivice [13]. Shodno tako visoko postavljenom merilu pogrešio bi svaki lekar koji bi postupao s manjim stepenom pažljivosti od standardno dobrog postupanja koje zakonodavac ima u vidu. Ipak, tako opisani standard pažnje ne bi trebalo shvatiti kao kruto pravilo koje ne trpi nikakva odstupanja u praksi. Zavisno od konkretnih okolnosti određenog medicinskog postupanja, smatra se da je dopuštena korekcija, kako u smislu ublažavanja, tako i u smislu pooštravanja dužnosti. Pravilo je da veća opasnost i veći rizik neke radnje zahtevaju i veću pažnju, a da hitnost i nužnost opravdavaju niži standard pažnje. Uvek treba poći od toga kako bi se iskusan i pažljiv lekar opšte prakse, odnosno specijalista, ponašao u datoj situaciji. Pri tome se, međutim, niži standard pažnje ne može opravdati praksom, koja može biti i dosta raširena, ako se radi o neurednom i aljkavom postupanju odnosno poslovanju. Na primer, nemački zakonodavac uvek govori o potrebnoj pažnji [14].

Zakonom nije moguće propisati u pojedinostima šta se smatra pažljivim ponašanjem, a šta nepažljivim, budući da to zavisi od konkretnog slučaja. Principe *lege artis* i indikovanog ponašanja određuje postojeće naučno saznanje u medicini. Za odgovornost je zato često presudan usvojen medicinski standard, pod kojim se podrazumeva ono što prosečno kvalifikovan, savestan i obazriv lekar može i treba da zna da učini u konkretnoj situaciji [15]. Za razliku od apstraktnog pravnog pravila, koje je generalno, važi načelno i vremenski je neograničeno, standard je promenljiv i predstavlja posredujući pojam između opšteg pravila o pažnji i prakse. Standard upućuje na to kako lekar u konkretnoj situaciji treba da postupi. On važi za datu situaciju, ali to ne znači da se ne može promeniti, budući da nova naučna saznanja mogu uspostaviti važenje drugačijeg standarda. Nova naučna saznanja nemaju uvek za posledicu da jedna do tada upražnjavana standardna metoda nadalje važi kao lekarska greška. Naime, može se desiti i obrnuto, da jedno ponašanje koje je do tada smatrano lekarskom greškom, prema novim saznanjima nije više lekarska greška. Propuštanje da se prati razvoj ili promena u metodama tretmana i postupanje po prevaziđenom metodu takođe se smatraju greškama u tretmanu. U nemačkoj sudskoj praksi standard se definiše kao dobra lekarska praksa, i ona čini pravno merilo za meritornu odluku suda, utvrđenu uz pomoć sudskih veštaka [15]. Osim postupanja prema medicinskom standardu, lekar je dužan da bolesnika obavesti o određenim činjenicama i da mu pruži potrebne savete i uputstva. Shodno tome, lekar ne sme preduzimati lečenje ili zahvat protivno volji bolesnika i dužan je da bolesnika sveobuhvatno obaveštava [16, 17].

U pogledu izvođenja odgovornosti pravni teoretičari vide određeni specifikum naročito kod pitanja dokazivanja lekarske greške [18]. Pre svega, tekovina je sudske prakse da odgovornost lekara predstavlja odgovornost za grešku. Kao što je već istaknuto, praktičar uvek duguje obligaciju sredstva kao što se svuda pravo odnosi prema staleškim normama u domenu tehnike. Greška posebno dobija na težini u medicinskoj struci, jer poseduje duplu aksiomatsku dimenziju u isto vreme i komplementarnu i različitu: medicinsko određenje gde je greška okarakterisana prema važećoj naučnoj normi, i pravno određenje koje je u vezi sa manjkavostima u izvršavanju pravno preuzetih obaveza i označava protivpravnu radnju. Otuda, profesionalna greška može da se analizira jednako sa medicinske tačke gledišta, da bi se naučno opravdalo postavljanje profesionalne odgovornosti, i sa pravne tačke gledišta da bi se to društveno potvrdilo i omogućila naknada štete bolesniku žrtvi. Razmatranje prava na zdravstvenu zaštitu dopušta da se obelodani stalna interakcija između ove dve dimenzije greške koja se naročito tumači redovnom saradnjom između sudija i medicinskih veštaka u parničnom postupku. Iz te interakcije konstatuje se uzajamni uticaj medicinske i pravne kvalifikacije profesionalne greške. Tako, medicinska kvalifikacija preuzima pravni zahtev za uzročnom vezom između nepropisne radnje i štete, dok je pravna kvalifikacija inspirisana medicinskim određenjem koje prethodno proglašava tu grešku. Profesionalna greška je onda pitanje jedne duple kvalifikacije, jedne analize u isto vreme naučne i pravne, a da ona ne provocira kritiku medicinsku, pravnu ili društvenu. Ipak, vremenom se sve više shvata da harmonizacija između dva tipa kvalifikacije greške treba da ustupi mesto pravnoj kvalifikaciji greške, naglašavajući da medicinska kvalifikacija služi sudu samo kao informacija u iznalaženju odgovornosti [19]. Prema većinskom shvatanju, a u cilju krajnjeg određenja i izvođenja odgovornosti, pojam lekarske greške predstavlja pravni pojam. Uopšte, izučavanje lekarskih grešaka od strane pravnika i svako meritorno postupanje nužno je radi utvrđivanja granica njihove dopuštenosti, radi razdvajanja protivpravnih medicinskih radnji od radnji koje su pravno irelevantne [20].

Treba zaključiti da pojam lekarske greške čini samo relevantna greška sa stanovišta prava, jer je jedino greška takve pravne kvalifikacije u stanju da pokrene neki od oblika odgovornosti. Pitanje da li je lekar počinio grešku u tretmanu ili prekršio dužnost pažnje nije po vrsti i obimu samo medicinsko nego je i pitanje u kojoj meri su ispunjene obaveze iz ugovora o lečenju, ili po opštim pravilima postupanja. To je, takođe i pre svega, pravno pitanje o kome merodavno odlučuje sud i gde medicinske kategorije pažnje predstavljaju samo polazne tačke. Iako sudija često samo pomoću medicinskih veštaka može da procenjuje, on nije dužan da preuzme svet pojmova lekara, koji može biti delom širi ali i uži, nego što su pravni pojmovi koji se prilikom primene zakona jedino mogu uzeti za osnov. Ovde se upravo naglašava normativno-pravni kvalitet objektivnog pojma pažnje, i zato je pojam lekarske greške u suštini pravni pojam. Osim toga, pojam lekarske greške jeste pravni pojam i u tom smislu da sudsko medicinsko veštačenje nije potrebno za sve vrste spornih lekarskih postupaka za koje se sumnja da su pogrešni. Takvi su slučajevi, na primer, nepribavljanje valjanog pristanka bolesnika ili neobaveštavanje usled čega je došlo do štete po zdravlje ili život. To pokazuje da svaka lekarska greška ne predstavlja ujedno i povredu pravila zdravstvene struke u užem smislu, već to može biti i povreda bolesnikovih prava i kršenje lekarskog dužnog postupanja. Ova konstatacija čini u današnje vreme široko prihvaćen stav u uporednopravnoj teoriji i praksi većine zemalja.

Osobenosti slučajeva odgovornosti zdravstvenih ustanova

Lekar koji se ogreši o svoju dužnost stručnog i pažljivog postupanja ili o bolesnikovo pravo samoodređenja krši svoje obaveze. To je osnovno načelo odgovornosti za štete nastale kao posledice lečenja. Prema vladajućem gledištu između zdravstvene ustanove i bolesnika postoji neposredna ugovorna veza, zbog čega odgovornost lekara nema javnopravni nego privatnopravni karakter [21].

Ako se na konkretan slučaj štete primenjuju isključivo pravila ugovorne odgovornosti, tada za štetu odgovara ugovarač koji se obavezao da pruži određenu zdravstvenu uslugu. To može biti zdravstvena ustanova ili onaj koji obavlja privatnu medicinsku praksu. Poslednji odgovara za svoje zaposlene i pomoćnike. Češća je, međutim, primena pravila deliktne odgovornosti, nezavisno od toga da li je odnos davaoca i korisnika ugovorne prirode. Pitanja odgovornosti mogu biti složenija ako u spornom lečenju bolesnika učes-

tvuje više lekara različitih specijalnosti, lekari asistenti ili nedovoljno kvalifikovani lekari, gde se nekad za zdravstvenu ustanovu kao osnovna postavlja odgovornost zbog propusta u organizaciji rada.

Kao odgovorna lica ovde, kao i kod ugovorne odgovornosti pojavljuju se zdravstvena ustanova odnosno njen vlasnik, kada je reč o privatnoj praksi. Nosilac privatne prakse odgovara za svoje zaposlene (lica u radnom odnosu) i za svoje pomoćnike (lica angažovana po osnovu ugovora). Ako za vreme njegove odsutnosti odredi zamenika, odgovara samo za njegov izbor i uputstva koja mu je dao (*culpa in eligendo et instruendo*) [19, 22].

Inače, zakoni odavno poznaju odgovornost za drugog i ona zbog subordiniranosti i institucionalizovanosti rada u medicini ovde nalazi svoju punu primenu. Tako, zbog nepažnje lekara koji je zaposlen u bolnici ili koji tu radi po ugovoru koristeći opremu i personal bolnice za lečenje bolesnika, odgovara bolnica. Opšta je zakonska odredba da za štetu koju zaposleni u radu ili u vezi sa radom prouzrokuje trećem licu odgovara preduzeće u kome je zaposleni radio u trenutku prouzrokovanja štete, osim ako dokaže da je zaposleni u datim okolnostima postupao onako kako je trebalo [21, 23]. Poslodavac odgovara za sve oblike krivice svojih zaposlenih (radnika). Preduzeće, odnosno ustanova poslodavca, ima pravo regresa isplaćenog na ime naknade štete, ukoliko je zaposleni postupao namerno ili sa krajnjom nepažnjom. Pored važećeg oblika odgovornosti za drugog, ustanova može da odgovara i za sopstveni propust, u kom slučaju je reč o povredi njegove primarne obaveze da se obezbedi odgovarajuća organizacija ustanove [24]. Propust u organizaciji čini poseban osnov odgovornosti, ali treba u svakom slučaju dokazati uzročnu vezu između protivpravne radnje i nastale štete.

Oštećeni ima pravo da zahteva naknadu štete i neposredno od radnika ako je on štetu prouzrokovao namerno [21, 25]. Ovo opšte rešenje ne prihvata odbranu tužene bolnice, naročito kod slučaja rada lekara po osnovu ugovora, gde navodi da je nepažljiv lekar nezavisan ugovarač za čije postupke bolnica nema odgovornost. Argumenti u prilog odgovornosti zdravstvene ustanove obično su bazirani na tome da se lekar pojavljuje kao zastupnik bolnice, na dužnost bolnice da kontroliše ključne aspekte rada lekara i na premisi da je počinjena nepažljiva radnja svojstvena delatnosti bolnice [22, 26]. Pristalice ovakvog stava ukazuju na realnost da je medicinska nega timska nega i da je zato više primereno fokusiranje odgovornosti na organizaciju nego osuđivanje individualnog lekara. To promoviše koordiniran pristup prevenciji grešaka i višem kvalitetu zdravstvene zaštite.

Iz prethodnog proizilazi da kada odgovara ustanova u nekim situacijama može doći do solidarne odgovornosti bolnice i lekara, i to kao izuzetak kada se tužilac pozove na postojanje namere u ponašanju tuženog. Ipak, slučajevi umišljajnog postupanja su krajnje retki i teško dokazivi, budući da je kod grešaka u medicini gotovo uvek u pitanju nepažljivo, tj. nehatno, postupanje na strani tuženog lekara. U literaturi ovi slučajevi opisuju se kao moguća paralelna odgovornost ustanove i lekara zaposlenog u ustanovi (bolnici). U nekim državama brojnije su tužbe protiv bolnica (Nemačka, UK), a u drugima protiv lekara (SAD 75% lekari a 25% bolnice) [23]. Ipak, tužioci u najvećem broju slučajeva odštetne zahteve podižu protiv zdravstvene ustanove. U regresnom zahtevu pored namere uzima se u obzir i krajnja nepažnja, i u tom smislu odgovornost neposrednog štetnika može biti od značaja. Kad zdravstvena ustanova isplati naknadu štete, ima pravo u roku od šest meseci od dana isplate da zahteva od lekara ili drugog pripadnika zdravstvenih profesija povraćaj isplaćenog iznosa, ako je štetu učinio namerno ili krajnjom nepažnjom [24]. U privatnoj praksi davaoc zdravstvenih usluga odgovara za štete koje počini lično i za štete zaposlenih s kojima je sklopio ugovor o radu. On, takođe, odgovara za lica koja su po njegovom nalogu radila na poslu koji se obavezao da izvrši, kao da ga je sam izvršio [21]. Izuzetak bi činio slučaj kad lekar koji postupa, na primer zbog odsutnosti ili drugih opravdanih razloga, imenuje svog zamenika, pošto se tada zamenik smatra samostalnim vršiocem obaveze i neposredno odgovara bolesniku za sve propuste [19].

U teoriji i praksi diskutuje se o pitanju objektivne odgovornosti za štetu nastalu u toku obavljanja medicinske delatnosti. Ona suštinski i sad postoji, ali u manjem obimu, na primer, u slučajevima odgovornosti zdravstvene ustanove prema učesniku kliničkih ispitivanja ili kod štete zbog transfuzije zaražene krvi, ili štete od medicinskih aparata [20]. Ako se posmatra praksa sudova u Srbiji, prema ranijoj praksi bilo je odluka u kojima se sama medicinska delatnost shvatala kao opasna delatnost i po tom osnovu se izvodila objektivna odgovornost bez obzira na krivicu. Po mišljenju teoretičara poređenje medicinske delatnosti sa nekim drugim opasnim delatnostima smatra se pogrešnim, jer je reč o delatnostima koje same stvaraju rizik od štete za druge, pa zato i odgovaraju ako se taj rizik ostvari. Kod medicinske delatnosti, upravo to postaje sporno, jer rizik po zdravlje ili smrt bolesnika nije prvenstveno izazvan od strane lekara, nego samom bolešću, gde lekar nastoji da tu opasnost po mogućstvu otkloni ili bar umanji [20]. U razrešenju ove dileme ranije su savezni i vrhovni sudovi republika i pokrajina izričito imali stav kojim odbacuju takvu mogućnost, premda su neke presude posle toga, pa i danas, prihvatile objektivnu odgovornost [1]. To iziskuje dodatni komentar sa stanovišta opravdanosti takvih sudskih odluka.

Razvoj drugih oblika obeštećenja bez obzira na krivicu (*no-fault compensation*) u domenu medicinske delatnosti vezuje se za vansudske postupke, odštetne fondove i jednim delom osiguranja [2]. Lekar je dužan da zaključenjem ugovora o osiguranju obezbedi dovoljno novčano pokriće za podmirenje zahteva za naknadu eventualne štete izazvane njegovom nepropisnom medicinskom intervencijom. U slučaju kad se steknu uslovi za imovinsku odgovornost lekara u sporazumu sa oštećenim i osiguravačem spor se rešava mirnim putem. U celom sistemu bitna je bolja šansa oštećenog da dobije kompenzaciju za štetu koju je u toku lečenja pretrpeo. Bolesnik nije prinuđen da okrivljuje bilo zdravstvenu ustanovu, bilo lekara koji je postupao kako bi ostvario pravo na naknadu, što je slučaj u sudskom postupku. Iz ukupnog odnosa između medicinskih usluga i njenih korisnika nema više konfrontacije i to je u razvijenim zemljama bio razlog da se podrži ovakav sistem obeštećenja.

Neki primeri iz sudske prakse Srbije i prakse inostranih sudova

Stanje sudske prakse u razvijenim državama karakteriše stalno nastojanje da se unapredi sudska zaštita bolesnika i da se sam sistem obeštećenja učini efektnijim. Ne radi se samo o priči o pohlepnim advokatima koji navode oštećene bolesnika da tuže. Problem je mnogo širi i najčešće leži u nedovoljnom razjašnjenju situacija da li je reč o nepažnji lekara ili o oštećenju bolesnika koje se nije moglo izbeći. To je, po mišljenju analitičara, razlog što prema statistici na jedan osnovan zahtev dolaze četiri neosnovana zahteva [26]. U praksi, ostvarenje prava na naknadu štete postaje tako zamršeno, da ići na sud izgleda kao „bacati kocku". Sudije nekad dobijaju zbunjujuća i suprotstavljena mišljenja od medicinskih veštaka o tome šta je u stvari standard *razumne pažnje* u medicini za datu situaciju i onda su prinuđeni da odlučuju kome poverovati. U odsustvu bilo kakvog jasnog vodiča da li je lekar pogrešio ili ne, dešava se da sud pokloni svoju veru teško oštećenom bolesniku. Dugoročno, oni gube jer to se odražava i na njihov pristup lekarskim uslugama visokorizičnih specijalnosti, kao što su ginekolozi, posebno u osiguranjima gde su premije najviše porasle. Sa druge strane, ni mnogi lekari ne veruju u sistem takvog pravosuđa, jer iz njega nekad dolaze nedosledne i nekorektne presude o medicinskoj praksi. Strah od toga da će biti tuženi i suočeni sa višim premijama osiguranja, lekari i drugi medicinski profesionalci često manifestuju na pogrešan način, tako što daju upute za skupe i nekad nepotrebne testove (defanzivna medicina), istovremeno odbacujući bilo kakvu slobodnu diskusiju o sopstvenim neuspesima i promašajima [26].

Za razliku od sudske prakse razvijenih zemalja, koja je bogata i po raznim pitanjima medicinskog prava ustaljena bez bitnijih kolebanja, takav stav se ne može izreći ako se za primer uzme Srbija. Sudska praksa o medicinskim predmetima u parničnim postupcima mnogo je više prisutna, ali broj utuženja još uvek vidno zaostaje za brojem krivičnih predmeta čije procesuiranje traje dugo i sa malo osuđujućih presuda.

Jedan od najranijih slučajeva iz sudske prakse bivših jugoslovenskih republika ticao se spora u vezi sa pribavljanjem pristanka bolesnika pre operacije [27]. Činjenice su bile sledeće: bolesnik, srednjih godina, muškog pola, sa tegobama koje je osećao zbog kile u predelu desne prepone bio je upućen na operaciju. Za tu operaciju je dao pristanak. Neposredno pre operacije lekari su konstatovali da postoji kila i na levoj strani, tj. obostrano. Po vlastitoj proceni izvršili su, upravo, operaciju leve kile. Posle operacije bolesnik je tvrdio da kod njega nije postojala kila na levoj strani i da za takvu operaciju nije dao pristanak, nego da se čak energično protivio operaciji. Zbog svih ovih okolnosti bolesnik se odlučio na utuženje. Prvostepeni sud je odbio tužbeni zahtev, pozivajući se na stanje zapisnika o izvršenoj operaciji i sprovedeno medicinsko veštačenje. Međutim, ceneći izneto činjenično stanje i priložene dokaze, drugostepeni sud usvojio je žalbu tužioca i ukinuo presudu. Sud je istakao više razloga za takvu svoju odluku. Iz pregleda celokupne medicinske dokumentacije u vezi spornog operativnog zahvata nije nigde bilo vidljivo da je tužilac bio obavešten da će mu biti operisana leva kila i da je dao pristanak za tu operaciju. Tužilac je, doduše, neposredno pre operacije obrijao i desnu i levu stranu prepone, i to na nagovor jednog bolesnika, a ne medicinskog osoblja, pa se stoga ne može sa sigurnošću izvesti nedvosmislen zaključak da je dao pristanak na operaciju leve kile. Bez pristanka bolesnika ne može se vršiti operativni zahvat, osim ako se radi o zahvatu hitne prirode, a bolesnik je u takvom stanju da se od njega ne može dobiti pristanak. Nedopustivo je i protivno načelu nepovredivosti fizičkog integriteta da se preduzme operativni zahvat na nekom licu protiv njegove volje, pa i onda kad bi to bilo od koristi za to lice, osim ako ne pretežu posebni razlozi koji opravdavaju takav postupak, kao što je životna opasnost ili stanje bolesnika kada ne bi bio u mogućnosti da dâ svoj pristanak.

Presuda ranije sudske prakse Srbije odnosila se na dužnost obaveštavanja od strane lekara i valjanog pribavljanja pristanka bolesnika za operaciju [28]. Predmet datira iz 1987. godine, ali je parnica o naknadi štete trajala više godina. Činjenično stanje bilo je sledeće: sredovečna žena koja je patila od urođene paralize desnog facijalnog živca, s namerom da ublaži svoje tegobe koje su se sve više potencirale, obratila se specijalistima vodeće opšte bolnice. Predložena joj je operacija koju je prihvatila i kojoj se ubrzo podvrgla. Lekar koji je operisao pratio je postoperativni tok i smatrao ga normalnim, da bi na prvom kontrolnom pregledu, 15 dana po operaciji, ustanovio da kod bolesnice postoji poremećaj vida, izražen kao pojava dvoslike pri pogledu na dole i horizontalno. Zbog toga je morao biti konsultovan očni lekar koji je potvrdio dijagnozu razrokosti, koja nužno iziskuje operaciju. Operacija obavljena na Očnoj klinici nije donela nikakvo poboljšanje i bolesnica je po drugi put sa ove klinike otpuštena sa zaključkom da se nad njom odlaže hirurška intervencija. Ovakav ishod lečenja bio je razlog za njenu tužbu protiv bolnice radi naknade štete. Tužbeni zahtev glasio je na naknadu od 200 000 dinara zbog umanjene opšte životne aktivnosti, 40 000 dinara zbog pretrpljenih fizičkih bolova i 50 000 dinara zbog narušenog estetskog izgleda, što je ukupno iznosilo 290 000 dinara. U tužbi je posebno istaknuto da je šteta nanesena zdravlju tužilje prouzrokovana krivicom lekara koji je operisao. U odgovoru na tužbu i na usmenoj raspravi pred sudom tuženi je osporio tužbeni zahtev u celosti. Tvrdio je da je operativni zahvat nad tužiljom obavljen prema pravilima medicinske nauke i etike, pa, stoga, šteta koju je tužilja pretrpela nije uzrokovana krivicom lekara. U razmatranju iznetih činjenica, diferencirajući ih na relevantne i irelevantne, sud se našao pred nekoliko pravnih pitanja: da li je u konkretnom slučaju postojala lekarska greška, imajući u vidu neuspešan ishod operacije i štetne posledice; kako pravno kvalifikovati postupanja stranaka pre i posle operacije; koji su bitni elementi za bolesnikovu odluku da se podvrgne operaciji. U tom smislu sud je naložio izvođenje dokaza veštačenjem, koje je obavio sudskomedicinski odbor Medicinskog fakulteta. Prema nalazu i mišljenju veštaka, razrokost i viđenje duplih slika posledica su operacije koju su nad tužiljom obavili lekari tuženog. Vid tužilje je usled toga smanjen za 20%, a opšta životna sposobnost za 50%, budući da ona stalno vidi duple slike i ne može da obavlja poslove koji pretpo-

stavljaju normalan vid. Operacija je, takođe, prouzrokovala veću fizičku i estetsku unakaženost tužilje. Zbog urođene paralize facijalisa, krivljenje usta je kod nje pre operacije bilo izraženo samo pri pokretima usta, a posle operacije unakaženje se ispoljavalo kako pri mimici lica, tako i kad je ono u stanju mirovanja. Prilikom obavljanja hirurških intervencija tužilja je osećala bolove jačeg do srednjeg intenziteta, koji su se postepeno smanjivali i gubili i koji su sastavni deo ovakvih intervencija. Nalazom sa pozivanjem na medicinsku dokumentaciju ističe se da je operacija u svemu izvršena *lege artis*, na način na koji se obavljaju operacije u oblasti savremene plastične hirurgije, tj. u skladu sa principima hirurške korekcije koja se radi u slučajevima pareze *n. facijalis*. Konstatovano je da postojeće posledice operacije u vidu razrokosti predstavljaju jednu od mogućih, iako izuzetno retkih operativnih komplikacija. Ceneći sve ove okolnosti, opštinski sud je zaključio da šteta koju je tužilja pretrpela predstavlja rizik koji je ona prećutno preuzela prihvatajući operaciju. Sud je odbio tužbeni zahtev, smatrajući da šteta koju je tužilja pretrpela nije uzrokovana lekarskom greškom, nego da pretstavlja neizbežan rizik operacije, koji mora da snosi svako ko na operaciju pristane. O žalbi na ovu presudu odlučivao je Okružni sud i potvrdio presudu Opštinskog suda. Međutim, po vanrednom pravnom leku, obe presude nižih sudova su ukinute. Vrhovni sud Srbije zauzeo je drugačiji stav, smatrajući proizvoljnim zaključak nižeg suda da je tužilja prećutno prihvatajući operaciju, preuzela na sebe i rizik od štetnih posledica koje su u konkretnom slučaju nastupile. Pred Opštinskim sudom nije ni utvrđivana činjenica da li je i u kom opsegu tužilji predočena mogućnost komplikacija i da li je ona preuzela na sebe rizik od njihovog eventualnog nastupanja. Vrhovni sud podvlači obavezu zdravstvenih radnika da bolesnika obaveste o suštini, značaju i domašaju medicinske intervencije na koju pristaje, kako bi bolesnik bio u mogućnosti da uzme u obzir razloge za i protiv intervencije i da na osnovu toga donese razumnu odluku koja se tiče njegovog lečenja. Po mišljenju suda obaveštavanje bolesnika ne podrazumeva iznošenje tehničkih detalja nego saopštavanje osnovnih podataka koji su bitni za njegovu odluku. Bitnim podacima sud je smatrao razjašnjenje delotvornosti predloženog zahvata i ukazivanje na mogući neuspeh i kad se on obavi propisno. U konkretnom slučaju tužilja je bila upozorena samo na uobičajeni rizik, i na njega je pristala, ali prema njenim tvrdnjama tuženi joj nijednog trenutka nije spomenuo mogućnost ovako katastrofalnog ishoda. Značaj ove presude Vrhovnog suda je u tome što ona po prvi put jasno izražava načelni pravni stav o pristanku bolesnika na medicinsku intervenciju i preuzimanju rizika od nje. Prema ovom stavu odgovornost lekara i medicinskih ustanova ne zavisi samo od stručnosti preduzimanja medicinske intervencije, već i od pridržavanja dužnosti da se bolesniku daju potrebna obaveštenja (pravo na obaveštenje), što čini poseban pravni osnov odgovornosti.

U razumevanju medicinskih sporova otišlo se doduše dalje o čemu svedoči skorašnji slučaj naknade štete zbog neutvrđivanja uzroka smrti bolesnika koji je preminuo u bolnici. U izreci presude Vrhovnog suda Srbije navedeno je da zdravstvena ustanova koja propusti da obaveznom obdukcijom utvrdi uzrok smrti bolesnika preminulog u zdravstvenoj ustanovi odgovara za štetu zbog nezakonitog i nepravilnog rada, jer bliski srodnici imaju pravo da saznaju uzrok njegove smrti i pravo da neizvesnost u pogledu ovih okolnosti ne traje neuobičajeno dugo. Iz obrazloženja: Sada pokojni DK, rođen 1962. godine, primljen je na Hirurško odeljenje tuženog zbog stomačnih tegoba i potom, 27. 6. 2001. godine, operisan, ali je 3. 7. 2001. godine tokom lečenja (reoperacije) preminuo. Sahranjen je bez potvrde o smrti, a izveštaj o smrti tuženi je sastavio naknadno 11. 9. 2001. godine, s tim što je, u međuvremenu 24. 7. 2001. godine tuženi dodelio porodici pokojnog DK 10 000,00 dinara. Osim toga, iz izveštaja Instituta za sudsku medicinu od 28. 9. 2004. godine proizilazi da se sa sudskomedicinskog stanovišta neposredni uzrok njegove smrti sa sigurnošću ne može utvrditi jer obdukcija nije izvršena. Imajući u vidu sve navedene okolnosti, Vrhovni sud nalazi da se zbog propusta tuženog u postupku utvrđivanja uzroka smrti sada pokojnog DK s obzirom na to da obdukcija, iako obavezna, nije izvršena i da je izveštaj o njegovoj smrti koja se dogodila 3. 7. 2001. godine sastavljen tek 11. 9. 2001. godine, za sada se ne može pouzdano, van svake razumne sumnje, zaključiti ni da li je tokom njegovog lečenja postupano prema standardnim pravilima medicinske struke, jer od ovih okolnosti zavisi odluka o isključenju odgovornosti tuženog za naknadu ove štete tužiocima. Iako su tužilje kao bliski srodnici sada pokojnog DK mogle zahtevati obdukciju radi utvrđivanja uzroka njegove smrti, to ne isključuje obavezu tuženog da uzrok smrti bolesnika preminulog u ovoj zdravstvenoj ustanovi utvrđuje obaveznom obdukcijom, budući da je postupak utvrđivanja smrti bolesnika propisan zakonom izostao i da je izveštaj o smrti sada pokojnog DK sačinjen naknadno. Zato i ovakav protivpravni postupak tuženog, ako je učinjen, može biti dovoljan za zasnivanje odgovornosti tuženog za naknadu štete u smislu člana 170. i 171. ZOO bez obzira da li je smrt bolesnika uzrokovana lekarskom greškom ili ne, budući da tužilje kao bliski srodnici umrlog lica imaju pravo da saznaju uzrok njegove smrti, a neizvesnost u pogledu ovih okolnosti ne sme trajati neuobičajeno dugo [29].

Predmet iz prakse inostranih sudova činjenično govori o tome da je gđa. D. bila lečena od dr P. i istoimenog privatnog udruženja lekara, gde je podvrgnuta hirurgiji raka jednjaka. Po završenom zahvatu ona je imala ozbiljan prigovor zato što je zbog hirurške greške morala biti kasnije podvrgnuta još jednom hitnom hirurškom zahvatu. Onda se kod nje razvila bolest u vidu trajnog oštećenja njenih pluća. To ju je učinilo nesposobnom za rad. Gđa D. je onda podigla tužbu protiv lekara P, istoimene hirurške asocijacije, kao i medicinskog poliklinič kog centra. Centar je kasnije izostavljen kao tuženi, ali je tužba zbog nepribavljanja pristanka informisanog i zbog nepažljivog postupanja procesuirana. Odbrana je odgovorila i usledila je žalba. U predmetu u ovom slučaju žalbeni sud je odbio da prihvati dokumentaciju i svedočenje veštaka koje je ponudila tužilja, vezano za broj pregleda na jednjaku obavljenih od strane tuženog, pre nego što je operisao tužilju. Naime, gđa D. je predložila dokaz svedočenjem u kome bi se ispitalo iskustvo lekara zbog okolnost da je on nju obavestio da obavlja isti zahvat u proseku jednom mesečno. U stvari, tuženi dr P. je to učinio samo pet puta u toku pet godina. Prvostepeni sud smatrao je ovu informaciju ire-

levantnom i isključio je iz dokaza svedočenjem. On se pozvao na slučaj Kaskie v. Wright, 589 A2d 213 (PaSuper. 1991), u kome je odlučeno da se od lekara ne zahteva da informiše bolesnika o tome koliko puta je obavio specifičnu medicinsku proceduru. Žalioci su dalje osporavali da prigovarači nisu predložili nikakvu medicinsku ekspertizu da li stepen neiskustva lekara sa tom vrstom hirurškog zahvata predstavlja stvarni rizik u odnosu na operativni zahvat. Međutim, Viši sud je odlučio da je ova činjenica relevantna za konkretno stanje stvari i da je medicinsko veštačenje bilo neophodno za slučaj nepažnje. Sud je ustanovio da je sporazum između lekara i bolesnika ugovorne prirode i obe strane moraju shvatiti značenje onoga što preuzimaju i očekivane rezultate. Sud je zaključio da bi razumno lice smatralo značajnim ako individualni hirurg da pogrešnu informaciju tako da je osnov tužbe bio u nedostajanju valjanog pristanka informisanog. Kompetentnost, iskustvo ili traženje za to relevantnih informacija bitni su za davanje pristanka. Hirurg koji onda pogrešno informiše bolesnika i dovede ga u uverenje da je u rukama iskusnog hirurga, nije stvarno pribavio saglasnost bolesnika. Sud je stao na stanovište da to ne znači da hirurg treba da bolesnika informiše o celom svom obrazovanju i iskustvu, nego u meri u kojoj je to potrebno da se dobije valjani pristanak. Sud je nadalje tvrdio da veštačenje nije bilo neophodno i vratio je predmet na ponovno suđenje.

Sporovi u domenu medicinske odgovornosti, takođe, česti su i u evropskim sudovima, kakav je bio slučaj koji se desio 1991. godine u Francuskoj u Opštoj bolnici u Lion-u i koji je svoj epilog dobio tek 2004. godine na Evropskom sudu za ljudska prava u Strazbourg-u [30]. Francuska državljanka vijetnamskog porekla koja je bila trudna pet meseci došla je u bolnicu na kontrolni pregled. Lekar je greškom zamenio karton sa kartonom druge bolesnice, istog porekla i veoma sličnog imena (Thi Nho Vo / Than Van Vo), koja je tog dana trebala da se javi radi intervencije vađenja ugrađene spirale za kontracepciju. Postupajući na osnovu zakazane intervencije uklanjanja spirale lekar je izazvao potpuno nepotrebno pobačaj kod žene trudnice i ona je izgubila bebu. Usledila je krivična prijava i optužba protiv lekara kome je stavljeno na teret nehatno ubistvo ploda u majčinoj utrobi. Prvostepeni sud doneo je osuđujuću presudu, a Apelacioni sud je preinačio izreku u pogledu kazne. Međutim, Kasacioni sud Francuske ukinuo je presudu. U daljem toku slučaja Evropski sud za ljudska prava, takođe, odbio je tužbu koja se pozivala na krivično delo, povredu prava na život fetusa i u tom smislu na kršenje obaveze iz člana 2 Evropske konvencije o zaštiti ljudskih prava i fundamentalih sloboda (ECHR). Uloga ovog suda kod tumačenja navedene odredbe Konvencije bila je delikatna i došlo se do stanovišta da čak i u slučaju važenja navedene odredbe, ne bi bio ispunjen uslov da država članica istovremeno nije povredila odredbe nacionalnog zakona. Sud je naglasio da podnosilac revizije ima još uvek opciju da podnese tužbu za naknadu štete administrativnom sudu shodno rešenjima nacionalnog prava. Ukoliko se dokaže nepažnja tuženog lekara, tužioci bi mogli da potražuju naknadu štete u novčanom iznosu. To se u ovom slučaju ipak nije desilo zbog čega je i sama presuda Evropskog suda za ljudska prava od strane nekih komentatora pretrpela kritiku [31]. Iz presude proizilazi da u slučaju smrtnog ishoda po plod, optužba treba da se usmeri na protivpravne radnje kojima se vređaju prava i dobra trudnice, tj. porodilje, a ne buduća prava samog fetusa, jer on još ne postoji u to vreme kao subjekt prava, tj. nije živorođen niti to, zbog nastupelog smrtnog ishoda, može biti. Sud je bio mišljenja da kompleksnost konkretnog slučaja i postojanje svojevrsnog trostranog odnosa u pogrešnom ginekološkom tretmanu uslovljava i vrstu optužbe, koja je dopustiva samo sa aspekta građanskog, a ne i krivičnog prava.

U jednom od slučajeva nemački sud je stao na stanovište da postojanje odgovornost zbog štete nastale u toku lečenja nepravilnim radnjama, kako hirurga, tako i anesteziologa, koji su presudom proglašeni solidarnim dužnicima naknade štete [32]. Iz činjeničnog stanja utvrđeno je da je kritičnog dana na Univerzitetskoj očnoj klinici glavni lekar obavljao operaciju razrokosti desnog oka na bolesniku kome je zbog toga data anestezija. U toku operacije bolesnik je dobijao čist kiseonik preko creva pričvršćenog na njegovoj bradi, dok mu je lice, sve do operativnog polja na desnom oku, bilo prekriveno sterilnim peškirom. Međutim, u jednom trenutku hirurg je radi zaustavljanja krvarenja uključio aparat *termokauter*. Pri njegovom radu iznenada je izbio plamen koji je naneo teške opekotine na bolesnikovom licu. Savezni vrhovni sud Nemačke osudio je oba lekara da visokim novčanim iznosima obeštete bolesnika kao solidarni dužnici. Sud je smatrao da je, usled istovremene upotrebe termokautera i čistog kiseonika, rizik od opekotina morao biti saznatljiv i predvidiv obadvojici lekara. Oni su bili dužni da se prethodno dogovore o metodama i instrumentima koji se u konkretnom zahvatu mogu primeniti bez rizika po bolesnika.

Zaključak

Tradicionalni način poimanja ogovornosti za štete u medicini zasniva se na strogoj etici, savesnosti i stručnosti pojedinca koji postupa u procedurama lečenja, gde se ističe odnos *intuitu personae* između lekara i bolesnika. Sa razvojem zdravstvenih delatnosti kao javnih službi taj odnos postaje sve depersonalizovaniji i vezuje se za uslugu koju zdravstvena ustanova ili nosilac privatne prakse daje bolesniku kao korisniku te usluge. To je bio razlog da se zdravstvena ustanova redovno pojavljuje kao odgovorna strana koja je i faktički i pravno, na osnovu pravila obligacionog prava, dužna da stane iza postupka svog zaposlenog. Posmatrano sa strane bolesnika u korist utuženja zdravstvenih ustanova govori i veća sigurnost i izvesnost pravne zaštite u spornim slučajevima lečenja.

U pravnoj praksi sudova slučajevi odgovornosti su prisutniji, ali se istovremeno vidi i težnja da štetu nadoknadi zdravstvena ustanova, jer to koristi odnosu lekar bolesnik umanjujući njihovu konfrontaciju. To donekle objašnjava činjenicu da u sudskim predmetima nema presuda o regresnim zahtevima zdravstvenih ustanova uperenih prema osuđenom lekaru čak i u slučajevima kad je reč o ozbiljnim posledicama po zdravlje bolesnika ili smrtnom ishodu. Sa pravnog gledišta može se konstatovati da u ovom delu nema dosledne primene zakona koji uređuje ta pitanja.

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GENERAL REVIEW

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Genetics of breast cancer: contribution of BRCA1/2 genes alterations to hereditary predisposition

Genetika karcinoma dojke: alteracije BRCA1/2 gena i njihov doprinos naslednoj predispoziciji

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Key words:
breast neoplasms; genetic predisposition to disease; genes, brca1; genes, brca2; mutation.

Ključne reči:
dojka, neoplazme; bolest, genetska predispozicija; geni, brca1; geni, brca2; mutacija.

Introduction

The term "hereditary cancer" refers to cancers associated with specific germ-line mutations in highly penetrant genes which are inherited as a Mendelian trait, whether through an oncogene, a tumor suppressor gene, or a DNA repair gene. Since the first association between germ-line mutations and hereditary predisposition for particular cancer types has been found in the mid of 90-ties, investigations pointed out a variety of tumor types with inherited predisposition to a high or moderate/low risk for development of disease (melanoma, gastric cancer, MEN I, MEN II, hereditary nonpolyposis colon cancer, etc) [1–4]. Data that hereditary predisposition, recognized by family clustering, has been found for the arising number of cancer types, together with introducing of screening for the mutations in responsible genes, makes different insight into cancer prevention and management of patients with malignant disease.

Breast cancer is the most frequent malignant tumor in females in Serbia. The incidence can be described with more than 4,000 newly diagnosed cases per year [5, 6]. Unfortunately, incidence and mortality trends show permanent increment in the few last years. Breast cancer can occur as sporadic, familial and hereditary. The majority of breast cancers are recognized as sporadic in patients with no cancer history in the family. The incidence of sporadic breast cancer rises in women over 50 years old. Minorities of breast and/or ovarian cancer patients (up to 5% to 10%) have a striking family history, suggestive of Mendelian autosomal dominant inheritance. An additional 20% of breast cancer cases are considered as familial describing situation with at least two cancer cases in extended family. In hereditary form of disease one of the two alleles of the gene responsible for the disease is altered by germ-line mutation. The off-spring of the mutation carriers has 50% chance of inheriting a mutant allele from either parent. The most common variant of hereditary breast cancer (HBC) is the appearance of breast as well as ovarian cancer cases in the same family (HBOC). The disease can also occur as site-specific breast or ovarian cancer. Other tumor types such as pancreatic cancer, Fallopian tube carcinoma, melanoma or prostate cancer in men can be commonly present in families with hereditary breast cancer [7–9].

Characteristics and functions of BRCA 1/2 genes

Discovery of the association between breast and ovarian cancer and BRCA1 (in 1994) and BRCA2 (in 1995) genes have made it possible to screen women for genetic predisposition to develop either one or both of these diseases [7]. BRCA1 and BRCA2 genes are highly, but not completely penetrant genes (about 80%). So far, more than 20 genes of low to medium penetrance that can modify the pentrance of BRCA1/2 genes in carriers of mutations (modifier genes), in that way modifying risk for hereditary disease, have been identified [10, 11].

BRCA1 and BRCA2 genes are classified as tumor suppressor genes. Both genes are large – BRCA1 has 22 and BRCA2 26 coding exons. For both genes exon 1 is noncoding, and both have unusually large exon 11. BRCA1 gene is located on chromosome 17q21 while BRCA2 is located on chromosome 13q12. BRCA1 encodes for 1863, while BRCA2 encodes for 3418 amino acid protein product [7]. Mu-

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tations are scattered throughout coding regions of both genes without clustering or "hot spots" resulting in a huge number of mutations detected in each gene – more than 1,600 in BRCA1 and 1,900 in BRCA2 mutations have been reported [7, 8]. The majority of them, but not all of them, are capable of disrupting the function of BRCA protein product in that way affecting the risk for malignant disease. So far, we identified 15 persons affected with BRCA1 (7 types in 11 persons) and BRCA2 (3 types in 4 persons) deleterious mutations in Serbian population. Other BRCA1/2 sequence variants (unclassified and polymorphic) were also found [12–16]. Among them, 4765del20 in exon 15 of BRCA1 and 4366insTT in exon 11 of BRCA2 gene are new deleterious mutations, firstly reported in our population [16].

Concerning mutation type, about 70% of detected mutations are frameshift mutations, while nonsense, as well as missense mutations contribute with about 10% each. Besides small changes in DNK structure such as frameshift or point mutations, in BRCA genes are also reported large genomic rearrangements. Somatic BRCA1/2 mutations are rare in sporadic breast cancer, but other mechanisms such as epigenetic inactivation by hypermethilation of BRCA1 promotor sequence were reported. BRCA1/2 somatic mutations are not so rare events in sporadic ovarian cancer [17].

BRCA1 and BRCA2 mutational spectra are population - specific and different founder mutations are reported in different populations [7, 18]. Data about ethnicity is also important since it has been shown that some ethnically isolated populations such as Ashkenazi Jews or Islanders, due to inbreeding, have limited number of BRCA1/2 mutations – more than 90% of BRCA mutation carriers of Ashkenazi Jewish women can be described with two BRCA1 (185delAG and 5382insC) and one BRCA2 (6174delT) mutations [19, 20]. In Iceland, which is geographically isolated, there is only one founder mutation [21]. This is the consequence of "founder effect" – some of rare mutations in small and isolated ethnic groups may become more frequent in the next generations due to reproductive isolation (founder mutations). All populations have their own founder mutations, but they can not be easily recognized due to the presence of additional BRCA variants that rose in reproductively mixed populations [15]. But, large proportion of BRCA mutations are detected only once – it can be said that the most of families at risk tend to have their own mutation. Besides common, population specific and family specific mutations are detected [16]. It is questionable if all deleterious mutations have the same penetrance [7]. Age-dependent penetrance of different germ-line mutations in BRCA1 genes was recently reported – the authors concluded that different BRCA1 mutations have distinct effects that influence age of onset of breast and ovarian cancer [22].

BRCA1/2 protein products are implicated in a variety of important cellular processes acting through interaction with other molecules in signalling pathways – DNA repair, transcriptional regulation, cell-cycle regulation and chromatin remodelling (reviewed in Figure 1). BRCA1 and BRCA2 protein products are included in repair of doublestrad DNA breaks by homologous recombination mechanism. For example, ionizing radiation, as well as cytotoxic agents cause DNA doublestrand breaks.

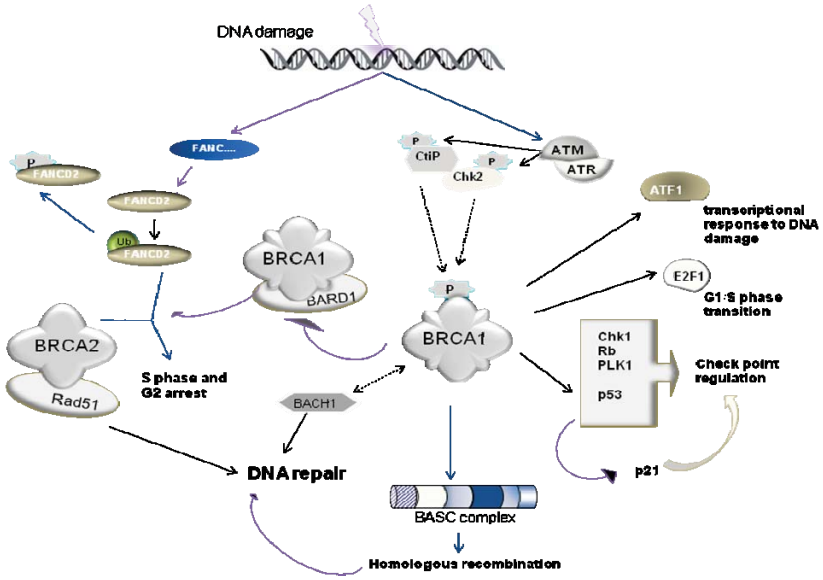

Fig. 1 – Schematic representation of BRCA1 and BRCA2 cellular pathways in interaction with other signalling molecules

Mutations in BRCA1/2 genes, especially frameshift mutations, cause the syntheses of proteins truncated at various extent. Such protein product, usually lack some domain crucial for its proper function (such as BRCT or BRC domains in BRCA1 or BRCA2), respectively, leading to genome instability and elevated cancer risk [7]. BRCT domains are crucial for BRCA1 interaction with a variety of proteins, forming complexes and enabling proper function of various important cellular processes. The fact that about 80% of BRCA1 germline mutations result in C ter-

minus truncation that include BRCT region and lead to increased predisposition for breast and/or ovarian cancer, point out the importance of BRCT domains for BRCA1 protein function. BRCA1 protein has a highly conserved RING domain at its amino terminus and two BRCT domains at the end of its carboxyl terminus. The fact that many clinically important mutations are located in parts of BRCA1 gene that encode these highly conserved domains indicates that they are very important for BRCA1 function. The RING domain of BRCA1 mediates its association with BRCA1-associated RING domain protein 1 (BARD1) [23]. BRCA1–BARD1 dimer has been implicated in the maintenance of genomic stability and tumor suppression through its involvement in DNA damage signalling, DNA repair and transcriptional regulation. BRCT domains interact with Rb tumor suppressor gene, as well as with other proteins associated with Rb, that are thought to be included in chromatin remodelling processes [24] that is required before and after DNA repair processes.

The main function of BRCA2 protein is DNA repair. BRCA2 protein in its structure has eight BRC repeats that represent conserved sequence motifs of about 30 amino acids each. BRC repeats are crucial for BRCA2 interaction with RAD51. BRCA2, by interacting with RAD51, plays a key role in DNA repair by homologous recombination. Lack of any of those domains disrupts BRCA2-RAD51 interaction, leading to DNA repair malfunction, elevating cancer risk [7].

Lifetime risk for the development of cancer in BRCA1/2 mutation carriers

It must be pointed out that the risk of BRCA-associated breast and ovarian cancer is related only to epithelial malignancies of both organs. As the consequence of limited penatrance of BRCA genes is the fact that all of BRCA1/2 mutation carriers will not develop malignant disease. So far, it is not possible to predict which of BRCA mutation carriers will develop disease, although genetic or environmental factors affecting penetrability of BRCA genes are intensively investigated [25–27]. Identification of BRCA1 and BRCA2 mutation can be used only for the risk estimation. But, it is obvious that the majority of women with inherited mutation in BRCA1 or BRCA2 gene will develop breast and/or ovarian cancer. Earlier estimates of lifetime risk were higher, especially if they were derived from families with a strong positive family history. Estimates of lifetime risk vary considerably depending on the group studied (for instance, if cases are selected for family history or not), type of mutations included in study, age selected etc. For instance, for Ashkenazi Jewish BRCA1 mutation 5382insC, which is also present in Serbian population, lifetime risk by the age of 70 is 67% and for ovarian cancer is 33% [28]. Generally, reported BRCA1 - and BRCA2 - related risk estimates by the age of 70 for breast cancer range from 45% to up to 87% – it can be said that the risk is elevated about 5 to 8 times in comparison to the risk for sporadic breast cancer. The risk of ovarian cancer by the age of 70 in BRCA1 mutation carriers range from 28% to 44%, while for BRCA2 carriers estimates are lower (from 11 to 27%) [29]. The risk for the development of ovarian cancer is elevated about 20 times in BRCA1/2 mutation carriers [29]. Characteristic of BRCA-related cancer is that hereditary breast cancer occurs at an earlier age than the sporadic form of disease. Women with BRCA1/BRCA2 mutation have a 33% to 50% chance to develop breast cancer before the age of 50 in comparison with general population with the chance of 2% only [30].

The presence of BRCA1/2 mutation elevates the risk for bilateral breast cancer. BRCA1 mutation elevates the risk for contralateral breast cancer up to 64% by the age of 70, while BRCA2 mutations elevates this risk to about 50% [31].

Besides this, elevated lifetime risk (up to 7%) for male breast and prostate cancer (up to 20%) is mostly related to BRCA2 mutation [32].

Hereditary predisposition identifying

Now it is clear that with BRCA1/2 alterations all hereditary predisposition for breast/ovarian cancer can not be covered. It was shown that BRCA mutations caused hereditary form of the disease in families with both tumor types clustering (breast/ovarian) (75%). In site-specific breast cancer the percent is lower – about 60% of female breast cancer families are caused by BRCA1/BRCA2 mutations [8]. This data depends on population studied. It is clear that besides contribution of alterations of some other genes such as p53 (Li-Fraumeni syndrome), PTEN (Cowden syndrome), ATM ataxia–telangiectasia i (mutated protein) etc., which rarely influence hereditary predisposition to breast/ovarian cancer, some now undefined genes will be discovered.

As major clinical benefits may occur through identifying clinical risk indicators of the hereditary cancer phenotype, it is necessary that attention be paid to [33]: positive family history of breast cancer, especially with early age of onset (at least two cases of breast cancer before the age of 50 from the same side (of family tree - about 50% of BRCA1-associated breast cancer cases are diagnosed by age of 41); breast cancer before the age of 35, without positive family history; bilateral breast cancer; ovarian cancer at any age associated with positive family history of breast and/or ovarian cancer; multiple cancers in the same person; male breast cancer at any age; relatives of a BRCA mutation carrier; Ashkenazi Jewish ancestry.

Genetic susceptibility testing

Hereditary breast and/or ovarian cancer belong to the group of hereditary syndromes with a high probability of linkage to known cancer susceptibility genes (BRCA1/BRCA2). It is accepted that identification of mutation carriers carry medical benefit, although due to limited penetrance of BRCA genes it can be only used for the risk estimation for malignant disease. BRCA1/2 genetic tests were among the first genetic tests to become widely available, due to high incidence and high mortality of breast cancer in Western countries. Genetic testing is performed in order to determine the molecular basis of the disease.

BRCA testing is performed on a peripheral blood sample due to the fact that we are searching for germ-line mutation present in all cells in organism. The most appropriate test for identification of BRCA1/BRCA2 mutations is a complete sequence analysis of the entire coding sequence and this remains the "gold standard" for mutation screening [34]. An ideal situation is the possibility to test a patient with breast/ovarian cancer as the first in the family with clustering of disease. In addition to the whole BRCA genes sequencing, other options are possible in certain situations [34]: for BRCA testing of relatives, when a specific type of mutation is confirmed in family member; for limited number of founder mutations in some populations such as Ashkenazi Jewish women; in 2%–12% of high-risk patients BRCA alterations are consisted of large genomic rearrangements and specific techniques such as multiplex ligation-dependent probe amplification (MLPA) are indicated.

BRCA1 and BRCA2 testing can result in the finding of deleterious mutation, with known clinical impact. The presence of benign polymorphisms, but also of unclassified variants in both genes was reported. Special problem in determining genetic susceptibility to breast and/or ovarian cancer are unclassified variants in BRCA genes [35]. These variants are missense mutations with uncertain influence on structure and function of BRCA1/2 protein products that result in their unknown clinical impact.

Bioethical principles of BRCA testing

Awareness of one's susceptibility to disease without an actual possibility of intervention can lead to an unacceptable use of such information (discrimination or social instrumentalization), or might have psychological impact on the person involved. The question that must be first asked is: Are the risks connected with the knowledge of susceptibility to genetic disease proportional to the benefits that such knowledge may provide? This problem is vast and involves medical, psychological, social and ethical dilemmas. These dilemmas are common to all predictive medicine, but the most evident in predictive DNA testing in hereditary breast cancer due to high risk for breast/ovarian cancer in healthy BRCA mutation carriers. All available preventive measures (follow-up, chemoprevention, bilateral prophylactic mastectomy or oophorectomy) are important but not definitive [36]. The choice of whether to pursue DNA testing belongs to the individual. Respect for the individual's autonomy is ensured by obtaining informed consent from that person. It is essential to offer pre-test counseling to evaluate individual capacity for autonomous decision-making [37]. Pre-test counseling also provides view of the risks and benefits, potential treatment as well as social and ethical implications involved. Genetic information has implications not only for the patients but also for their biological kin. Another big problem is to confront confidential setting between a patient and the physician and the importance of forwarding that information to biological kin who can easily be carrier of the same gene alteration. Appropriate pre-test counseling is finished with a person's signing the consent form, where the persons are asked to state that they fully understand the terms and have had adequate opportunity to ask questions [37] – our informed consent has been approved by the Ethics Committee of the Institute. It is imperative that counseling must be nondirective, allowing a patient full autonomy in deciding whether to be tested. Pre-test education should include the following information [36]: description of the patient's risk status; explanation of what it means to have inherited susceptibility to cancer; information about testing outcomes – results may be positive, negative or uninformative; appraisal of the risks, benefits and limitations of genetic testing; discussion on cancer surveillance and limitations of anticancer therapies; information about the risk of passing a mutation to children; review of psychological issues related to genetic testing; explanation of alternative to genetic testing.

In post-test counseling the counselor have to help patients to understand the results. A patient has also the right to decide not to be told about test results. Post-test counseling for mutation carriers must include a full explanation of a positive result accompanied by a description of surveillance and options for clinical management. It must be performed by a genetic counseling team, composed at least of a physician, genetic counselor, psychologist and registered nurse. Moral problem lies mostly in concerns how to make meaningful use of the available genetic information and it is necessary to weigh the risks against the harms in concrete cases.

Pathobiology of hereditary breast cancer

Breast cancer is heterogeneous disease in regard to pathobiological characteristics, prognosis of disease and predicting response to specific anticancer treatment. Growing data about different pathobiological characteristics among BRCA1- and BRCA2-related hereditary breast cancers, as well as especially BRCA1-related cancer compared to sporadic breast cancer with a consequent influence on the course of the disease, enforce the need for hereditary breast cancer characterization. Gene expression profiles of breast cancer have defined specific molecular sub-types with clinical, biological and therapeutic implications [38, 39]. According to pathobiological characteristics, the majority of BRCA1-related cancers can be classified in the group of „triple-negative breast cancer" (TNBC) since they are characterized with the lack of expression of steroid receptors (estrogen and progesterone) and lack of Her-2 receptor overexpression [40–42]. BRCA1-associated breast cancers are mostly pure differentiated carcinomas with ductal histology. About 10% of BRCA1-associated tumors show atypical medular histology. These cancers show also high mitotic index, pushing margins and the presence of necrosis. p53 mutations are more frequent in BRCA1-related than in sporadic breast cancer [42]. Although TNBC represents almost the exclusive phenotype in BRCA1-related breast cancer, it was recently reported that approximately 10 to 36% of BRCA1-associated breast cancers can be ER- positive [43]. It seems that TNBC BRCA1-related cancer is associated with younger age of onset (≤50), while ER+ BRCA1-related cancer occurs in elder mutation carriers [43]. It is suggested that ER+ BRCA- related cancer is

pathologically intermediate between BRCA1-related ER- breast cancer and ER+ sporadic breast cancer with the possibility that some of ER+ breast cancers in BRCA mutation carriers may be incidental [43]. Our previous investigation in Serbian population showed the presence of new BRCA1 mutation, previously not reported, in a patient with ER+ breast cancer [16]. It was found in older BRCA mutation carrier with strong family predisposition supporting an idea about ER+ BRCA1-related cancer as distinct entity of hereditary cancer rather than possibility that ER+ breast cancer in BRCA1 mutation carriers is not the consequence of BRCA1 dysfunction and can be considered as sporadic one. BRCA2- associated breast tumors are more similar to sporadic breast cancer, with predominant ductal histology, frequent carcinoma in situ and expression of ER (about 75%) [41]. BRCA1/2 mutations are common in high-grade serous papillary ovarian carcinomas [7].

The main question related to pathobiological characteristics of BRCA- associated cancer is if hereditary form of disease may have different course of disease in comparison to sporadic cancer, i.e. be more aggressive. Due to its characteristics, BRCA1- associated breast cancer has more aggressive phenotype and women with BRCA1-associated breast cancer seem to have worse prognosis of disease than women with sporadic cancer, while BRCA2-associated breast cancer is more similar to sporadic one.

Treatment options for hereditary breast/ovarian cancer

So far, BRCA-related cancer has been treated as sporadic cancer – in accordance to classic prognostic parameters (TNM, grade, histology etc) and breast cancer biomarkers (steroid and Her-2 receptors, Ki67 etc). BRCA1/2 status as predictor of various chemotherapy regimens was discussed in the literature [44, 45]. BRCA deficient tumors was shown to be more sensitive on platinum derivates regimens [45]. But, it seems that real revolution will be made with targeted therapy (PARP inhibitors) for patients with BRCA mutations. Poly(ADP-ribose) polymerase is nuclear enzyme family involved in base excision repair of single-stranded DNA breaks. When activity of PARP is disrupted, DNA replication can be stopped causing double-strand DNA breaks. Tumor cells with BRCA1/2 mutations are very sensitive to the lack of single-stranded breaks repair by PARP inhibition. By mechanisms of synthetic lethality which confers situation when there is lethal synergy between two originally non-lethal cellular events such as inhibition of PARP mediated repair of single-strand breaks, inducing double-strand breaks as well, in combination of loss-off-function of BRCA1/2 mediated homologous recombination, new targeted therapy for BRCA1/2 deficient tumors is constructed [46]. According to the results of phase II clinical trials with PARP inhibitor Olaparib (Astra-Zeneca), this approach is very promising for the treatment of BRCA1/2 mutated breast and ovarian cancer – complete or partial response was shown in more than 40% of BRCA1/2 deficient patients [47, 48].

What can be now recommended for healthy BRCA1/2 mutation carriers? Two main approaches are, so far recommended: clinical surveillance and prophylactic surgery. Chemoprevention, as the method also recommended for medical management of BRCA1/2 mutation carriers, was shown to be mostly effective for the prevention of contraleteral breast cancer in affected BRCA mutation carriers [49]. In surveillance for breast cancer, breast self-exam, clinical breast exam as well as radiological exams including magnetic resonance imaging in certain time-periods is recommended for healthy BRCA1/2 mutation carriers under the age of 18 [50, 51]. In surveillance for ovarian cancer pelvic exams, transvaginal ultrasound and CA-125 detection are included [50, 52]. However, prophylactic surgery is so far, the only approach with benefit in risk reduction for hereditary disease. Bilateral prophlactic mastectomy with breast cancer risk reduction greater than 90%, as well as bilateral salpingo-oophorectomy at the age of 35 or after childbearing is complete with nearly 100% risk reduction for ovarian cancer, but also up to 68% risk reduction for breast cancer is recommended for healthy female BRCA1/2 mutation carriers [53, 54].

Conclusion

Genetic testing for BRCA1/2 mutations is not a screening procedure for general population and is addressed to a selected part of population eligible according to including criteria. BRCA testing, since the presence of BRCA1/2 mutation is one of the best characterized genetic risk factor for disease, can give reliable result that help in risk estimation for development of breast/ovarian cancer in healthy individuals. Unfortunately, interpretation of BRCA testing results may be complex, especially due to posible presence of unclassified varients in both genes. Furthemore, only invasive prevention strategies such as profilactic surgery demonstrate risk reduction in healthy BRCA1/2 mutation carriers. Recent data that BRCA deficient tumors are target for treatment with PARP inhibitor rise possibility of targeted therapy in the treatment of BRCA-related cancers, but it is posible that this approach would be in future exploited for cancer prevention in healthy BRCA carriers.

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CASE REPORTS

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Severe acute caffeine poisoning due to intradermal injections: mesotherapy hazard

Teško akutno trovanje kofeinom usled intradermalnih injekcija: opasnost od mezoterapije

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Abstract

Introduction. Caffeine is indicated in the treatment of migraine headaches, as well as neonatal apnea and bradycardia syndrome. In mild poisoning, the most prevalent symptoms are nausea, vomiting, diarrhea, tremor, anxiety and headache. In more severe cases, symptoms consist of heart rythym abnormalities, myocardial infarction and seizures. Due to its common lipolytic effect, caffeine is used in mesotherapy, usually in combination with drugs of similar effect. We presented a patient with acute iatrogenic caffeine poisoning. **Case report.** A 51-year-old woman, with preexisting hypertension and hypertensive cardiomyopathy was subjected to cosmetic treatment in order to remove fat by intradermal caffeine injections. During the treatment the patient felt sickness, an urge to vomit, and a pronounced deterioration of general condition. Upon examination, the patient exhibited somnolence, hypotension and nonsustained ventricular tachycardia, which was sufficient enough evidence for further hospitalization. On admission to the intensive care unit the patient was anxious with increased heart rate, normotensive, with cold, damp skin, and visible traces of injection sites with surrounding hematomas on the anterior abdominal wall. Paroxysmal supraventricular tachycardia (PSVT) on electrocardiographic monitoring was found. The laboratory analysis determined a lowered potassium level of 2.1 mmol/L (normal range 3,5 – 5.2 mmol/L), and a toxicological analysis (liquid chromatography with ultraviolet detection) proved a toxic concentration of caffeine in plasma – 85.03 mg/L (toxic concentration over 25 mg/L). On application of intensive therapy, antiarrhythmics, and substitution of potassium, as well as both symptomatic and supportive therapy, there was a significant recovery. The patient was discharged without any sequele within four days. **Conclusion.** A presented rare iatrogenic acute caffeine poisoning occured due to massive absorption of caffeine from the subcutaneous adipose tissue into the circulation when injected directly into the tiny blood vessels, as evidenced by hematoma formation. Poisoning manifestations were registered in gastrointestinal, CNS (anxiety, somnolence) and cardiovascular (hypotension, ventricular tachycardia and nonsustained PSVT) system. In this era of mesotherapeutic treatment promotion, one should keep in mind toxic prevention, with application being carried out exclusively in a specialized institution

Key words:
caffeine; poisoning; cosmetic techniques; risk assesment.

Apstrakt

Uvod. Kofein se primenjuje u lečenju migrenozne glavobolje, a kod dece u lečenju neonatalne apneje i sindroma bradikardije. Kod lakših trovanja kofeinom najčešće se javljaju mučnina, povraćanje, dijareja, tremor, anksioznost i glavobolja, a kod teških trovanja poremećaji srčanog ritma, infarkt miokarda i konvulzije. Zbog poznatog lipolitičkog efekta kofein se koristi i u mezoterapiji, obično u kombinaciji sa supstancama koje slično deluju. **Prikaz bolesnika.** Bolesnica, stara 51 godinu, sa postojećom hipertenzijom i hipertenzivnom kardiomiopatijom, bila je podvrgnuta estetskom tretmanu uklanjanja masnih naslaga putem intradermalnog ubrizgavanja kofeina. Tokom tretmana osetila je mučninu, nagon za povraćanjem i izrazito pogoršanje opšteg stanja. Pri prvom pregledu utvrđeni su somnolencija i hipotenzija, a u EKG ventrikularna tahikardija *nonsustained*, zbog čega je upućena na bolničko lečenje. Pri prijemu u jedinicu intenzivne nege bolesnica je bila anksiozna, tahikardična, normotenzivna, sa hladnom i vlažnom kožom, a na trbuhu su bili vidljivi tragovi uboda sa okolnim hematomima. Elektrokardiografskom kontrolom regi-

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strovana je paroksizmalna supraventrikularna tahikardije (PSVT). Laboratorijskim analizama utvrđen je snižen nivo kalijuma – 2,1 mmol/L (3,5–5,2 mmol/L), a toksikološkim analizama (tečna hromatografija sa ultravioletnim detektorom) dokazan je kofein u toksičnoj koncentraciji – 85,03 mg/L (toksična koncentracija preko 20 mg/L). Na primenjenu intenzivnu terapiju, antiaritmike i supstituciju kalijuma, simptomatsku i suportivnu terapiju, došlo je do oporavka, te je četvrtog dana bolesnica otpuštena bez posledica. **Zaključak.** Opisano retko jatrogeno akutno trovanje kofeinom nastalo je atipično – zbog masivne resorpcije kofeina iz potkožnog adipoznog tkiva u cirkulaciju. Ubrizgavanje direktno u sitne krvne sudove potvrđeno je prisustvom hematoma. Manifestacije trovanja bile su prisutne u gastrointestinalnom, centralnom nervnom (anksioznost, somnolencija) i kardiovaskularnom (hipotenzija, ventrikularna tahikardija *nonsustained* i PSVT) sistemu. U eri promocije mezoterapijskih estetskih tretmana treba imati na umu takvu opasnost i estetske intervencije sprovoditi isključivo u visokospecijalizovanim ustanovama.

Ključne reči:
kofein; trovanje; kozmetičke tehnike; rizik, procena.

Introduction

The biochemical structure of caffeine is 1,3,7-trimethylxanthine. This compound belongs to a class of theophyllines with the chemical structure of 1,3-dimethylxanthine and theobromine, 3,7-dimethylxantine. Being an ingredient that is found in coffee, tea, cocoa and various drinks, caffeine is used routinely. The therapeutic use of caffeine in adults is an adjuvant therapy in combined analgesics for the treatment of migraine headaches, in children for the treatment of neonatal apnea, and in bradycardia syndrome. Caffeine, theophylline and theobromine belong to the group of methylxanthines, which cause the release of endogenous catecholamines, leading to the stimulation of adrenergic receptors. They are structural analogues of adenosine and pharmacologically function as adenosine antagonists. In higher doses, methylxanthines inhibit phosphodiesterase, the enzyme responsible for degradation of intracellular cyclic adenosine monophosphate (cAMP). The increase in cAMP leads to the clinical effects of adrenergic stimulation, muscle relaxation, stimulation of the myocardium, peripheral vasodilatation, stimulation of the respiratory center and the excitation of the central nervous system (CNS). Caffeine is bioavailable after oral, intravenous, subcutaneous, intramuscular and rectal application [1, 2]. Caffeine metabolism occurs *via* hepatic cytochrome P450 oxidase, the main processes including demethlylation and hydroxylation, with metabolic by-products (3,7-dimethylxanthine) teobromin, and (1,3-dimethyxsanthine) theophylline. For this reason, in patients with caffeine poisoning, serum concentrations of theophylline must be determined [1, 3]. Methylxanthines have a positive chronotropic and inotropic effect on the myocardium, leading to supraventricular tachycardia, atrial fibrillation, atrial flutter, multifocal atrial tachycardia, ventricular tachycardia and ventricular fibrillation. Electrolyte imbalances may be a factor in enhancing the development of arrhythmias. Caffeine and theophylline stimulate the respiratory center and increase respiratory rate (frequency of breathing), and therefore are used to treat sleep neonatal apnea syndromes. Effects on the CNS are manifested as headache, anxiety, agitation, insomnia, tremor, irritability, hallucinations and seizures. The effects exhibited on the musculoskeletal system result in an increase of intracellular calcium, muscle excitation, tremors, fasciculations and rhabdomyolysis [1]. The most common and mild clinical effects of caffeine toxicity are sinus tachycardia, hypertension, nausea, vomiting, anxiety, CNS agitation and palpitations. Severe clinical effects, fortunately less common, are seizure, dysrhythmias, myocardial infarction, hypertensive crisis, hyperthermia and delirium [3].

Treatment of patients with severe caffeine intoxication includes admission to the intensive care unit, electrocardiographic (ECG) monitoring, intensive therapy with isotonic solutions, as well as other forms of symptomatic and supportive therapy. In methylxantine severe poisoning, charcoal and hemodialysis are used in order to counteract caffeine's resistance. Indications for hemoperfusion through activated charcoal and hemodialysis are: serum levels of caffeine which are greater than 90 mg/L, severe poisoning with convulsions, hypotension resistant to parenteral infusion therapy, and heart rhythm disorders [1, 4].

Mesotherapy was discovered in Europe as a medical and cosmetic method for intradermal injection of a mixture of specific substances. Although traditionally used in the treatment of pain, it has recently been used for cosmetic purposes, especially in the treatment of cellulitis, as well as in the local reduction of fatty deposits [5]. In these procedures, the process of inhibition of phosphodiesterase contributes to its overall lipolytic effect.

Case report

A 51-year old woman, underwent aesthetic treatment of excess adipose tissue through lipolysis. The treatment took about sixty minutes and was performed in a beauty salon, under the control of a plastic surgeon specialist. It consisted of 20 intradermal injections of caffeine solution. The patient felt discomfort after the first two applications, and soon felt ill with anxiety, nausea and the urge to vomit. Because of a sudden disturbance of general condition, the patient was further examined in the Emergency Center, Clinical Center of Serbia, ascertaining suffering from somnolence and hypotension. Electrocardiographic (ECG) examination registered sinus rhythm and occasional nonsustained ventricular tachycardia. Due to suspicion of underlying systemic toxic effects during the treatment the patient was admitted to the Poison Control Center, Military Medical Academy.

On admission the patient complained of nausea, vomiting, and chest palpitations. The patient was anxious, afeb-

rile, hyperventilating, with cold/moist skin, and mydriatic pupils. The auscultatory findings in the lungs were normal. The patient's heart rate was 150 beats per min, tones cleares without additional sounds. Blood pressure on admission was 130/80 mmHg. Injection marks on anterior abdominal wall were present with surrounding hematomas (Figure 1). The personal history of the patient indicated treatment of previous hypertension with nifedipine. ECG recorded paroxysmal supraventricular tachycardia (PSVT) with the frequency of 146/min, changes in repolarization, ST segment depression of 6 mm in left-sided leads (V4–V6) D1 and AVL (Figure 2).

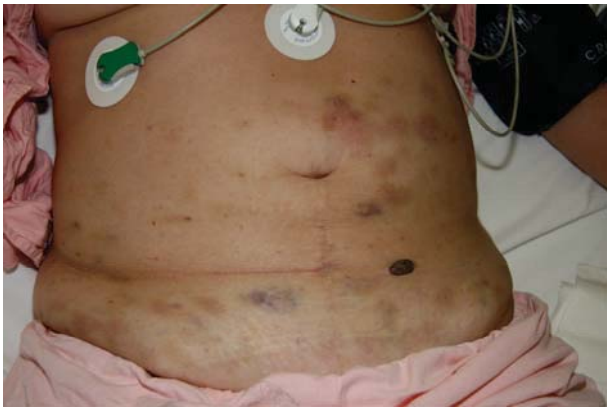

Fig.1 – Injection marks on the anterior abdominal wall with surrounding hematomas.

mal range 4.00 to 10.8 × 10^9)], with normal values of red blood cells, hemoglobin and platelets. Arterial blood gases indicated acute respiratory alkalosis with a hypocapneic level of carbon dioxide partial pressure (pCO2) 30.4 mmHg (normal range 32–48 mmHg), total pH 7.486 (normal range 7.35 to 7.45) and no underlying metabolic disorders.

Toxicology screening of the blood in the patient upon admission confirmed the presence of caffeine in the concentration of 85.03 mg/L (therapeutic cocentration of 1 to 10 mg/L (toxic being more than 25 mg/L) [using high performance liquid chromatography with ultraviolet scanning detection (HPLC-PDA)] and theophylline, 7.43 mg/L [therapeutic concentration of 8 to 20 mg/L immuno-fluorescence polarization method (AXYM)].

The patient was admitted to the intensive care unit with continuous ECG monitoring and parenteral therapy. The first 6 h of parenteral therapy included 5 mg of verapamil, diazepam 20 mg, 10 mg metoclopramide, infusion therapy with 3,000 mL of isotonic solution, and substitution with 100 mEq potassium chloride. Diuresis following this therapy was an amount of 1,800 mL. In addition to the therapy, symptoms included heart rate slowing to 90/min, confirmed by ECG finding (Figure 3), with repeated attack of PSVT at the frequency of 170/min, which is the reason for inclusion of beta blockers in the standard therapy.

On the second day of hospitalization the patient complained of nausea, warranting removal of metocloperamide.

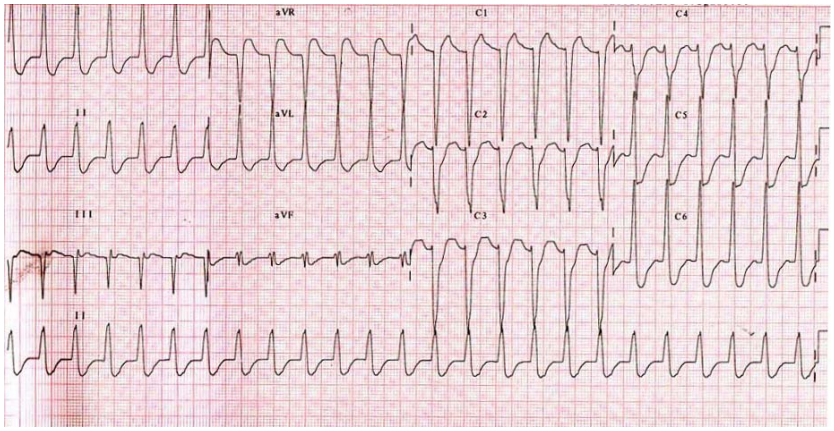

Fig. 2 – The ECG on admission showed sinus rhythm, frequency of 146/min, changes in repolarization, ST segment depression of 6 mm in left-sided leads (V4–V6, the D1 and AVL).

Biochemical analysis of the blood sodium level determined values of 147 mmol/L (normal range 135–147 mmol/L), potassium 2.1 mmol/L (normal range 3.5 to 5.2 mmol/L), chloride 99 mmol/L (normal range 98–111 mmol/L), glucose 17 mmol/L (normal range 3.5 to 6.4 mmol/L), urea 5.6 mmol/L (normal range 1.7 to 8.3 mmol/L), creatinine 69 mmol/L (normal range 50–124 mmol/L), aspartate aminotransferase (AST) 33 U/L (normal range 10–37 U/L), alanine aminotransferase (ALT) 49 U/L (normal range 20–65 U/L), creatinine kinase (CK) 79 U/L (normal range 21–232 U/L). The complete blood count showed elevated white blood cells [(the first day of 22 × 10^9, a second day of 15.7 × 10^9 (normal range 4.00 to 10.8 × 10^9)], with normal values of red blood cells, hemoglobin and platelets. Arterial blood gases indicated acute respiratory alkalosis with a hypocapneic level of carbon dioxide partial pressure (pCO2) 30.4 mmHg (normal range 32–48 mmHg), total pH 7.486 (normal range 7.35 to 7.45) and no underlying metabolic disorders.

From that day until hospital discharge, the patients ECG rhythm was at a normal frequency. Serum potassium level was 2.3 mmol/L. Detection of blood caffeine levels of 57.73 mg/L and theophylline at a concentration 6.59 mg/L were obtained.

On the third day, the patient complained of a headache, as well as pains in the neck area. Hypertension was established at 170/90 mmHg. Laboratory analysis determined hypokalemia (serum potassium level 2.8 mmol/L). The concentration of caffeine in blood was 27.43 mg/L, which was between the range of concentrations considered to be toxic. The concentration of theophylline was 7.43 mg/L. The

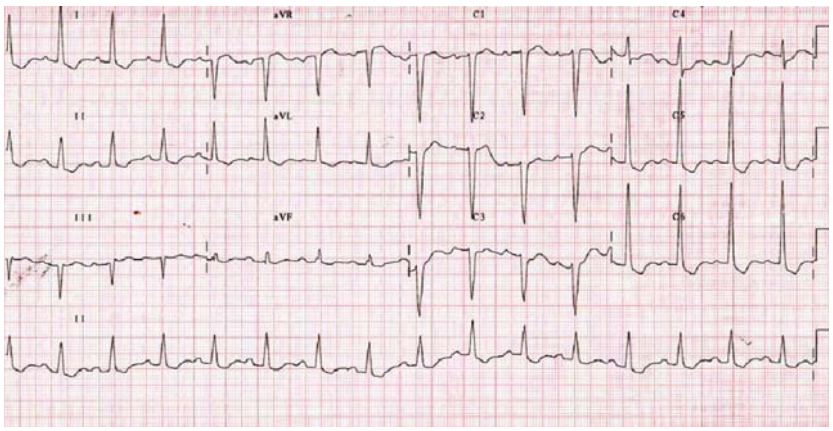

Fig. 3 – The ECG after beginning the treatment showed heart rate slowing to 90/min with changes in repolarization (the first day)

treatment started with an angiotensin converting enzyme (ACE) inhibitor, administered both parentally and orally, resulting in correction of hypertension, as well as hypokalemia.

On the fourth day of hospitalization the patient was in good condition and discharged. The ECG at discharge was found to be a sinus rhythm, at the frequency of 67/min (Figure 4), with the signs of hypertrophy and left ventricular overload. Normal values for biochemical parameters were recorded. The concentration of caffeine in blood was 8.39 mg/L and 1.86 mg of theophylline/L, which was at the therapeutic level. On echocardiographic examination, there was an enlarged left atrium of 4.3 cm, normal left ventricular dimensions, with concentric hypertrophy and a wall thickness of 13 mm. There was no failure of segmental contractility; ejection fraction was 65%. Diastolic function was altered by delayed relaxation.

acidosis with confirmation of toxic concentrations of caffeine. The symptoms gradually retreated after 7 days, and the concentration of caffeine was then between 60–70 mg/L [6, 7]. Ingestion of large amounts of caffeine can cause significant agitation, severe hypotension, tachycardia, ventricular arrhythmia, cardiac arrest, myocardial infarction, hypokalemia, rhabdomyolysis, seizures and acute renal impairment [8, 9]. Waring et al. [10] showed clinical data of 38 patients with caffeine ingested at an average dose of 1,040 mg (600 to 1,500 mg), which is equivalent to the amount found in about 10 cups of coffee. Out of them, 28 (73.7%) patients attempted suicide by deliberate self-poisoning, 8 (21.1%) patients ingested caffeine in order to enjoy (energy drinks), and 2 (5.3%) patients did it for weight loss.

We reported acute poisoning caused by intradermal caffeine intake by intentional injections for aesthetic purpose.

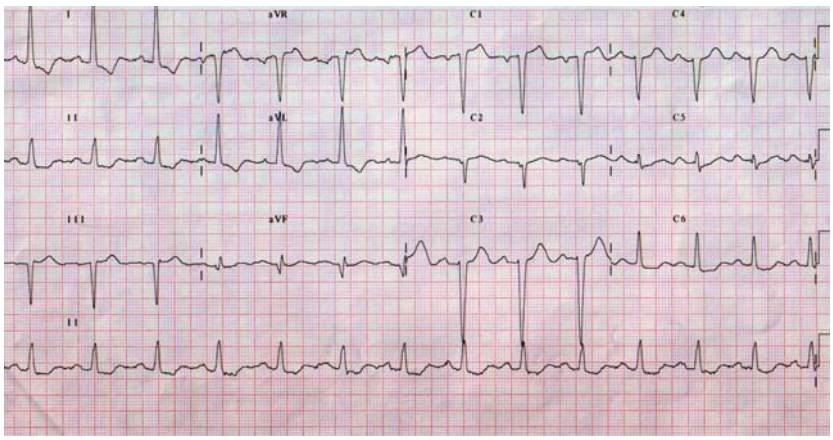

Fig. 4 – The ECG at discharge showed sinus rhythm, frequency of 80/min with signs of hypertrophy and left ventricular overload

Discussion

Caffeine side effects and systemic toxicity in adults is usually documented after oral administration, and during intravenous use in pediatric patients or neonates [1].

Intravenous caffeine in neonates has been presented with a number of severe toxic effects such as hypertension, tachycardia, tachypnea, tremor, opisthotonus, tonic-clonic convulsions, cardiac failure, pulmonary edema and metabolic

So, that differs from accidental poisoning with caffeine, usual entry of the toxin.

So far, it has not been proven that consuming caffeine from coffee increases the risk of cardiovascular disease. Also, there is no clear evidence that drinking moderate amounts of coffee, 3 to 4 cups per day (about 300 to 400 mg per day), poses a risk to health. However, certain groups of people, including people with hypertension, children and adolescents may be more sensitive to caffeine in terms of

side effects [11]. Before the treatment, the presented patient had already had hypertension, but this higher risk to adverse effects of caffeine was not taken into account.

The contraindications to mesotherapy are [12, 13]: pregnant and lactating females, insulin dependent diabetes mellitus, history of bleeding disorders, history of strokes, history of thromboembolic phenomena, patients on medication for cardiac arrythmias, aspirin, warfarin, heparin, history of recent cancer, severe heart disease, renal disease, any severe chronic systemic disease.

The main clinical effects at both, caffeine therapeutic doses as well as in case of poisonings with proven toxic concentrations, are from adenosine antagonism, beta adrenergic receptor stimulation and phosphodiesterase inhibition. On admission to the hospital, the presented patient's ECG showed repeated attacks of PSVT, with evidence of hypertensive cardiomyopathy and hypoklemia.

Severe caffeine poisoning is relatively rare and accompanied by unwanted hemodynamic complications, including a high mortality rate. Among complications are the most severe forms of cardiac abnormalities: sinus tachycardia, ventricular tachycardia and ventricular fibrillation, generalized convulsions, multiple organ failure (MOF) and cardiac arrest [1, 8, 9, 14]. The presented patient was initially observed to have hypotension, nonsustained ventricular tachycardia, and PSVT, fortunately with a favorable outcome. Sinus tachycardia is a common sign of poisoning, and is most likely benign in people with no previous cardiac disease. However, sinus tachycardia in methylxanthine poisoning, can progress to severe arrhythmias. Atrial fibrillation, atrial flutter, multifocal atrial tachycardia, ventricular tachycardia and ventricular fibrillation may result from methylxanthine poisoning [1]. Caffeine stimulates the respiratory center in the CNS, increasing the frequency of breathing, causing hyperventilation, respiratory alkalosis, respiratory failure, respiratory arrest and acute lung injury (ALI). On admission to the intensive care unit, arterial blood gas values described in the presented patient indicated respiratory alkalosis and hypocapnea, which was correlated with increased respiration and tachypnea.

In the article of Scottish authors [10], 24 (63.2%) patients showed only gastrointestinal symptoms, nausea and vomiting. In the first 6 hours of the treatment, the presented patient showed gastrointestinal symptoms, nausea and vomiting, which responded favorably to the use of metoclopramide.

It is known that caffeine causes psychiatric disorders under certain circumstances. Caffeine, which is widely used especially in younger population, is also found in many energy drinks, and can cause marked anxiety in otherwise healthy individuals. This is particularly true in sensitive persons with existing anxiety disorders. Caffeine may be associated with symptoms of depression, sleep disorders, and worsening of psychotic disorders in people with schizophrenia [15]. The presented patient was anxious upon admission, and later complained of a headache. According to the Scottish Poison Centre (for the period 2000 – 2008) dizziness, headache, tremor and agitation were much less common symptoms of caffeine poisoning in comparison to those with gastrointestinal symptoms [10].

Hypokalemia is a common manifestation of acute poisoning with methylxanthines resulting in beta adrenergic agonism and stimulation of Na^+/K^+ ATP-ase, which leads to a shift of potassium from the extracellular to intracellular space. This can be accelerated by vomiting and loss of potassium through the kidneys. In patients with theophylline intoxication, hyperkalemia occurs early and is independent of the initial laboratory analysis with vomiting [16]. The presented patient had a potassium concentration of 2.1 mmol/L, which was interpreted as a loss of potassium due to vomiting. After the first analysis of toxic concentrations of caffeine, hyperkalemia was interpreted as caffeine toxic effect. We performed a parenteral and oral potassium replacement, which exhibited parallel falls in toxic concentrations of caffeine, but not to completely normal levels. The concentration of caffeine in blood of the patient before mezotherapy remains unknown, but there are recommendations that coffee or caffeine-containing beverages must not be used for at least 12 h before the treatment [17]. In the presented patient, the concentration of caffeine was 85 mg/L immediately after mezotherapy, and 57.73 mg/L on the second day.

The immediate cause of death in severe caffeine poisoning is ventricular fibrillation, as has been shown by an experimental work [18]. Generally speaking, a concentration of caffeine in the blood of more than 100 mg/L is considered lethal [19, 20].

A case of sudden death has been documented involving a 25-year-old woman previously diagnosed with mitral valve prolapse. Cardiac arrest occurred immediately after drinking energy beverage. At autopsy screening, the presence of 19 mg/L caffeine was indicated in the aortic blood. The caffeine concentration was 10 g/L [21] upon further analysis. Swedish forensic experts during a year period witnessed four fatalities, demonstrating caffeine concentration of 80 to 100 mg/L [22] in post-mortem toxicological analysis.

Fatal caffeine overdose in adults is rare and involves more than 5 g of a drug containing caffeine to cause death. American toxicologists [23] from New Mexico, during a one year follow-up documented accidental caffeine poisoning as a cause of death in two patients: in a 39-year-old woman with the history of intravenous drug abuse with the caffeine concentration 192 mg/L in femoral blood and in a 29-year-old man with the disease history of obesity and diabetes mellitus, with caffeine concentration of 567 mg/L in femoral blood.

In both patients, the cause of death was accidental caffeine poisoning. At the begining of the 80's, articles were published about the cosmetic application of phosphodiesterase inhibitors and cAMP in the treatment of lipodystrophy [5]. In animal models, after subcutaneous application, the efficacy of methylxanthines themselves was tested, usually incorporating caffeine and theophylline, methylxanthines, or in combination with other substances that have a lipolytic effect. Their effect on the rate of absorption was monitored in accordance with artificially induced granulomas in adipose tissue. A better effect was achieved by combining preparations [5, 24].

Adverse effects of cosmetic treatments for cellulitis occur with intradermal injection of lipolytic substances, and can be presented as pain and erythema at the puncture site, vagal reactions, injury to nerves and blood vessels, skin necrosis and hematoma formation. Hematomas, which should not follow this type of treatment, are usually the most common side effect, and are a consequence of the effects of the applied substances interfering with the process of coagulation. According to the previously published data there are numerous local side effects associated with therapy [5]. Abdominal wall hematomas in the presented patient are shown as local side effects caused by substances in deeply applied injection (Figure 3). After application there was a massive absorption into the circulation as proved by the elevated concentration of caffeine 85.03 mg/L in the blood.

The most common local complications of mesotherapy are as follows: bruising and edema due to the chemicals used in mesotherapy [13, 24], skin necrosis [25–27], atypical mycobacterial infections [28], allergic reactions due to various chemicals [26, 29], atrophy and lipodystrophy [25], postinflammatory hyperpigmentation nodularity [25], after irregular lipolysis [29] etc.

Few papers describe systemic toxicity of substances applied during and after mesotherapy. Brazilian authors [30] describe the first case of systemic toxicity in a young woman presenting with thyrotoxicosis caused by mesotherapy with triiodthyroacetate acid. Alster and Tanzi [31] reported that in 2003, mesotherapy was banned by the Brazilian National Agency of Health due to its unwanted side effects. There are also systemic complications. "Systemic complications are allergic reactions, vagal syndromes, lipothymia, infections (HIV, hepatitis, etc) and liver toxicity with demyelination of nerves due to large doses of phosphatidylcholine" [24, 25].

In addition to supportive and symptomatic treatment for severe poisoning and systemic toxic effects, hemoperfusion and hemodialysis are strongly recommended [14, 32]. Fortunately, the presented female patient responded favorably to the treatment and did not require the action of extracorporeal detoxification. Cardiopulmonary resuscitation was needed in the worst case scenario. There were documented cases of survival in patients with cardiotoxicity induced by caffeine in which cardiopulmonary support was applied percutaneously [9].

Conclusion

The severe systemic toxic effects of caffeine applied intradermally in mesotherapy were seen in the presented patient. The cause of massive caffeine absorption from the subcutaneous tissue into the systemic circulation of the patient was partly due to the tiny blood vessels in the skin, as indicated by hematomas in the abdominal wall. The clinical picture showed mild gastrointestinal symptoms (nausea, vomiting), CNS disorders (somnolence, anxiety), and cardiovascular disturbances (hypotension, ventricular tachycardia and nonsustained PSVT). In this era of increasing popularity of mesotherapeutic aesthetic treatment, one should keep in mind the possibility of a significant absorption of the applied substances into circulation and their potential systemic side effects. Proper methods of intervention need to be applied in specialized institutions for cosmetic surgery that are staffed and equipped to respond in case of complications, as well as in poisonings.

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Successful resuscitation from two cardiac arrests in a female patient with critical aortic stenosis, severe mitral regurgitation and coronary artery disease

Uspešna reanimacija dva srčana zastoja kod bolesnice sa kritičnom aortnom stenozom, teškom mitralnom regurgitacijom i stenozom koronarnih arterija

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Abstract

Introduction. The incidence of sudden cardiac death in patients with severe symptomatic aortic stenosis is up to 34% and resuscitation is described as highly unsuccessful. **Case report**. A 72-year-old female patient with severe aortic stenosis combined with severe mitral regurgitation and three-vessel coronary artery disease was successfully resuscitated following two in-hospital cardiac arrests. The first cardiac arrest occurred immediately after intraarterial injection of low osmolar iodinated agent during coronary angiography. Angiography revealed 90% occlusion of the proximal left main coronary artery and circumflex branch. The second arrest followed induction of anesthesia. Following successful open-chest resuscitation, aortic valve replacement, mitral valvuloplasty and three-vessel aortocoronary bypass were performed. Postoperative pericardial tamponade required surgical revision. The patient recovered completely. **Conclusion.** Decision to start resuscitation may be justified in selected patients with critical aortic stenosis, even though cardiopulmonary resuscitation in such cases is generally considered futile.

Key words:
heart arrest; resuscitation; aortic valve stenosis; mitral valve insufficiency; coronary artery disease; treatment outcome.

Apstrakt

Uvod. Incidencija iznenadne srčane smrti kod bolesnika sa simptomatskom aortnom stenozom je 34%, a reanimacija tih bolesnika ima nepredvidiv ishod. **Prikaz bolesnika.** Bolesnica, stara 72 godine, sa kritičnom aortnom stenozom kombinovanom sa trosudovnom koronarnom bolešću, uključujući 90% stenozu glavnog koronarnog stabla imala je dva srčana zastoja, ali je uspešno reanimirana. Prvi zastoj bio je u toku koronarografije, a drugi posle uvoda u anesteziju. Uspešna reanimacija na otvorenom grudnom košu bila je praćena hirurškim zahvatom, zamenom aortne valvule, mitralnom valvuloplastikom i trostrukim aortokoronarnim *by-pass*-om. Postoperativna perikardijalna tamponada rešena je hirurškom revizijom. Bolesnica se uspešno oporavila. **Zaključak.** Postoji mogućnost uspešne reanimacije kod pojedinih bolesnika sa aortnom stenozom, mada se, uopšteno, smatra da je to uzaludno.

Ključne reči:
srce, zastoj; reanimacija; zalistak, aortni, stenoza; zalistak, mitralni, insuficijencija; koronarna bolest; lečenje, ishod.

Introduction

Severe aortic stenosis (AS) is defined as aortic valve area < 0.8 cm^2 (normal 2.5–3.5 cm^2) [1] whereas critical AS is defined as aortic valve index < 0.5 cm^2/m^2 [2]. Sudden death occurs in up to 34% of symptomatic AS patients [3] and cardiopulmonary resuscitation (CPR) is highly unsuccessful [1]. We presented a 72 year-old-female with critical AS, severe mitral regurgitation (MR) and three-vessel coronary artery disease with critical left main (LM) stenosis who, after successful resuscitation from two cardiac arrests, had emergency coronary artery bypass grafting (CABG), aortic valve re-

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placement (AVR) and mitral valve replacement (MVR), survived and went home in good condition.

Case report

A 72-year-old Caucasian female experienced dyspnea on exertion and retrosternal pain at the age of 70, and developed dyspnea at rest at the age of 72. The patient had no other medical problems. Administered medications included oral aspirin, atorvastatin, enalapril, metoprolol, furosemide and nitrates. Examination revealed 4/6 holosystolic murmur propagating to the axilla and neck. Electrocardiogram showed sinus rhythm, without Q waves or acute ST-T abnormalities. Echocardiography revealed aortic valve calcification, aortic value area 0.6 cm^2, peak pressure gradient 111 mmHg by Doppler, mild aortic regurgitation, severe MR and preserved left ventricular function (Table 1). Clinically, the patient was at the New York Heart Association (NYHA) III functional status.

Table 1
Transthoracic echocardiography findings before hospital admission

Variable	Value
Aortic valve area (cm^2)	0.6
Aortic valve index (cm^2/m^2)	0.353
Peak aortic gradient (mmHg)	111
Mean aortic gradient (mmHg)	89
Left ventricular end diastolic diameter (mm)	42
End systolic pressure (mmHg)	30
Left atrial diameter (mm)	40
Left ventricular ejection fraction (%)	60
Left ventricular septum wall thickness (mm)	13
Right heart chamber	Normal
Pericardium	Normal

During catheterization, immediately after contrast iohexol [4] (Omnipaque 350, GE Healthcare, Norway) was injected into the LM, the patient developed bradycardia and hypotension, rapidly deteriorating to severe dyspnea and asystolic cardiac arrest. Resuscitation started promptly, according to the American Heart Association guidelines. Twenty minutes following resuscitation, circulation was restored and spontaneous breathing returned. In the Intensive Care Unit (ICU), the patient regained consciousness, responded to instruction and was able to move all extremities after thirty minutes. Catheterization showed 90% LM, 60% left anterior descending and 90% circumflex stenosis. Left ventriculogram and right coronary artery angiogram were aborted.

Then, 95 minutes after the first arrest, the patient came to the operating room for emergency CABG-AVR-MVR.

General anesthesia was induced with diazepam 15 mg, sufentanil 25 μg and pancuronium 10 mg, and maintained with sevoflurane 0.7–1.0 ET MAC. Ten minutes after induction, the patient acutely developed hypotension and bradycardia unresponsive to *iv* epinephrine, and rapidly progressed to asystole. Resuscitation included emergency sternotomy, internal cardiac compressions and heparinization (400 units/kg). Heart exposure revealed 3 cm right ventricular wall laceration, likely from open heart massage. Following aortic and bi-caval cannulation, cardiopulmonary bypass (CPB) started. Myocardial protection included antegrade and retrograde cold blood cardioplegia. The patient had AVR (mechanical St. Jude 19, St. Jude Medical, Minnesota, USA), MVR (Duran Ancore ring 27, Medtronic, Minnesota, USA), three-vessel CABG (venous grafts to left anterior descending, circumflex and right coronary artery) and right ventricular (RV) wall laceration repair.

Cardiopulmonary bypass time was 230 min, aortic clamp time was 160 min, and the operation lasted 290 min. Intravenous epinephrine (0.067 μg/kg/min) and dobutamine (maximum 15 μg/kg/min) infusions were used, and the patient was stable after cardiopulmonary bypass (sinus rhythm, blood pressure 105/60 mmHg, central venous pressure 15 mmHg, hemoglobin 11.6 g/L, normal arterial blood gases). Postoperatively, a pulmonary artery catheter was inserted in the ICU (Table 2).

Table 2
Hemodynamic variables measured with a pulmonary artery catheter (PAC)

Variable	After surgery	Before PAC removal
PCWP (mmHg)	16	8
Cardiac index (l/m2)	3.0	2.5
Stroke volume (mL)	44.8	45
SVR (dyn/s/sec)	1199	
PVR (dyn/s/sec)	138	
SvO_2 (%)	71.8	64.7

***PCWP – pulmonary capillary wedge pressure; SVR – systemic vascular resistance; PVR – pulmonary vascular resistance; SvO_2 – mixed venous oxygen saturation**

Two hours after surgery, the patient developed atrial fibrillation and received three synchronized cardioversions and *iv* amiodarone loading, followed by oral amiodarone 1,200 mg/day. Despite postoperative troponin elevation (1.60 ng/mL), there were no wall motion abnormalities on echocardiography.

Four hours after surgery, chest tube drainage increased (1,000 mL/2 hours), central venous pressure increased to 22, urine output decreased, and hemoglobin dropped to 8.1 g/L. The patient received red blood cells 645 mL, fresh frozen plasma 610 mL, platelets 6 units, epinephrine increased to 16 μg/kg/min, dobutamine to 20 μg /kg/min and norepinephrine to 12 μg/min for hypotension. Emergency echocardiography revealed large (18 mm thick) pericardial effusion, diastolic RV collapse, but no vena cava collapse. Emergency reexploration revealed bleeding from the right atrial cannulation site. After bleeding stopped and tamponade was relieved, epinephrine infusion decreased to 0.05 μg/kg/min, norepinephrine stopped and urine output increased.

Approximately 8 h after the 2nd operation, the patient woke up and responded to commands. Despite postoperative liver dysfunction and non-oliguric renal insufficiency, the patient gradually improved, left the ICU on the day 27 and

went home on the day 33. Two weeks after discharge, the patient was neurologically intact, and walked 5 km/day.

Discussion

This is probably the first report on successful resuscitation from two distinct cardiac arrests in a patient with a combined critical AS, severe MR and severe coronary artery disease. A predicted perioperative mortality for patients with NYHA III functional status, the same as the presented patient initially had, is 4.81% (logistic Euroscore). The first arrest occurred after iohexol injection for coronary angiography. Non-ionic contrasts are considered safer than ionic media [5], and low-osmolar contrast is probably safe in patients with severe AS [6]. However, serious hemodynamic and electrophysiologic adverse events, including hypotension, myocardial dysfunction, arrhythmias, and cardiac arrest can occur after intraarterial or intracoronary iohexol injection [7], and the reported risk of death was 6.6–100/ million during angiography with iohexol [4]. Although disastrous anaphylactic reactions to contrast are rare (0.03%) [5], acute anaphylaxis cannot be excluded in this case. A predicted perioperative mortality (Logistic Euroscore) was at that moment 20.33%.

Emergency surgery was indicated in this case, due to symptomatic LM stenosis. As the second arrest occurred shortly after general anesthesia induction, myocardial ischemia, intraoperative myocardial infarction and arrhythmias [3] are all plausible etiologies. This particular patient had four reasons why resuscitation was unlikely to succeed: resuscitation from asystole has poor prognosis; external cardiac compressions are ineffective in severe AS, because overcoming the pressure gradient across the aortic valve is difficult [1]; creating adequate cardiac output with CPR is problematic due to MR; and achieving adequate coronary perfusion is difficult due to severe LM stenosis. However, this patient was revived twice. Immediate sternotomy and internal cardiac compressions may explain CPR effectiveness after the 2nd arrest [8]. Prompt CPB initiation likely contributed to good outcome [9], hypothermia during CBP probably provided some brain protection [10].

Limitations of this report include not measuring serum triptase to exclude anaphylaxis to contrast, and not using a pulmonary artery catheter or transesophageal echocardiography for perioperative hemodynamic monitoring.

Conclusion

This report suggests that despite a low likelihood of survival, full resuscitation is worth pursuing in otherwise healthy patients with severe AS.

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CASE REPORT

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Rapunzel syndrome

Repunzelov sindrom

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Abstract

Introduction. Trichobezoars are foreign bodies in gastrointestinal tract, composed of hair. They occur mainly in children and adolescents suffering from trichotillophagia. They commonly occur in the stomach, but as they enlarge over time, they can extend through the pylorus into distal parts of the small intestine resembling a tail. This rare form of trichobezoar is named Rapunzel syndrome. **Case report.** We presented a 19-year-old female patient, who suffered from trichotillomania and trichotillophagia, which led to trichobezoar formation. Intra-abdominal tumour was suspected after initial clinical examination. Abdominal echosonography, endoscopy and abdominal computed tomography (CT scan) in the pre-operational period revealed trichobezoar formation. The patient was operated on and subjected to further psychiatric treatment. **Conclusion.** Trichobezoar should be differentially diagnostically taken into consideration in younger women with abdominal pain, nausea, vomiting, palpable abdominal mass and psychiatric disorders. Most trichobezoar cases require surgical treatment, whereas the patients need long-term psychiatric treatment and monitoring.

Key words:
bezoars; trichotillomania; gastrointestinal neoplasms; digestive system surgical procedures; psychotherapy; treatment outcome.

Apstrakt

Uvod. Trihobezoari su strana tela u gastrointestinalnom traktu, sastavljeni od kose. Javljaju se najčešće kod dece i adolescenata koji pate od trihotilofagije. Najčešće se javljaju u želucu, ali kako vremenom rastu, mogu se prostirati kroz pilorus u distalne delove tankog creva u vidu repa. Ova retka forma trihobezoara predstavlja Rapunzelov sindrom. **Prikaz bolesnika.** U radu je prikazana bolesnica, stara 19 godina, koja je patila od trihotilomanije i trihotilofagije, što je dovelo do stvaranja trihobezoara. Kliničkim pregledom postavljena je sumnja na intraabdominalni tumor. Ehosonografija abdomena, proksimalna endoskopija i kompjuterizovana tomografija abdomena, pokazali su da se radi o trihobezoaru. Bolesnica je operisana i dalje podvrgnuta psihijatrijskom lečenju. **Zaključak.** Diferencijalno dijagnostički, trihobezoar trebalo bi uzeti u obzir, naročito kod mladih žena sa bolovima u trbuhu, povraćanjem, palpabilnom epigastričnom masom i psihičkim poremećajem. Najveći broj trihobezoara zahteva hiruški tretman, a bolesnici dugotrajno psihijatrijsko lečenje i praćenje.

Ključne reči:
bezoari; trihotilomanija; gastrointestinalne noplazme; hirurgija, digestivni sistem, procedure; psihoterapija; lečenje, ishod.

Introduction

Trichobezoars are foreign bodies, concrements, composed of hair, which commonly occur in the stomach, but can extend through pylorus into duodenum and lower parts of the small intestine. They are almost always combined with trichotillomania and trichotillophagia or other psychiatric disorders. Trichotillomania belongs to the group of obsessive-compulsive disorders [1]. It occurs almost exclusively in girls and younger women [2].

Human hair is resistant to digestion. Over time, continual ingestion of hair, together with food and mucus, leads to trichobezoar formation. The most common presenting symptoms of trichobezoar include palpable abdominal mass, vomiting and noticeable hair loss. It should be suspected in young women suffering from trichotillomania (pulling hair) and trichotillophagia (swallowing hair) [3].

Continual ingestion of hair leads to the enlargement of trichobezoars with possible complications such as erosion, gastric ulcer, perforation of the stomach and small intestine,

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intussusceptions, enteropathy with protein loss, pancreatitis, and even lethal outcome [4, 5].

Rapunzel syndrome is an uncommon presentation of trichobezoar, involving strands of swallowed hair extending as a tail through the small intestine, beyond the stomach [6].

Case report

A 19-year-old female patient was admitted to the Clinic for Gastroenterology and Hepatology of the Clinical Centre Niš, with stomach pain, heartburn, nausea, weight loss and vomiting. These symptoms began two months prior to admission and worsened over time.

The patient had no history of prior diseases. Family medical history showed mother's death from lung tumor.

The patient's father described his daughter as moody after her mother's death, with the habit of pulling hair.

After clinical inspection, hair loss and evident asymmetry in epigastric region of the abdomen were detected.

Abdominal palpation revealed a hard, tender, well-defined mass of aproximately 10 × 5 cm in the epigastric region, extending into the right upper quadrant.

Laboratory findings revealed hypochromic anemia with hemoglobin levels of 116 g/L, hematocrit 34.7%, iron 1.5 μmol/L, reactive thrombocytosis (407×10^9/L) and hypoproteinemia of 65 g/L. There was no electrolyte disturbance and liver functions, serum amylase, urea and creatinin were normal.

Plain abdominal radiography showed a certain amount of gas and intestinal content in the colon, whereas chest X-ray was normal.

Abdominal echosonography was done using a Siemens Acuson X 300, with multi frequency abdominal probe from 2 to 5 MHz.

Abdominal echosonography showed a homogeneous, echogenic mass, about 10 cm in diameter, below the pancreas. The ultrasonography of the liver, gallbladder, pancreas and spleen were normal.

Endoscopy was performed by using a Pentax video gastroscope. Endoscopy revealed a tumor mass in the stomach made up of hair, food residues and mucus completely filling the stomach, extending through the pylorus and blocking passage of the endoscope (Figure 1). Endoscopically, extraction was considered inappropriate due to the size of trichobezoar.

Computed tomography (CT) scan (Figure 2) showed a non-homogeneous, oval and large mass with a hazy outline that filled the entire stomach and the first part of duodenum. There were air pockets and the mass showed no contrast staining. It was surrounded by a thin rim of contrast material.

A psychiatrist was consulted and he claimed that a patient was apsychotic, with prominent depressive symptomatology, followed by a high level of anxiety, starting after her mother death.The psychiatrist recommended futher psychiatric tretment.

The patient was transferred to the Surgical Clinic, where she was operated.

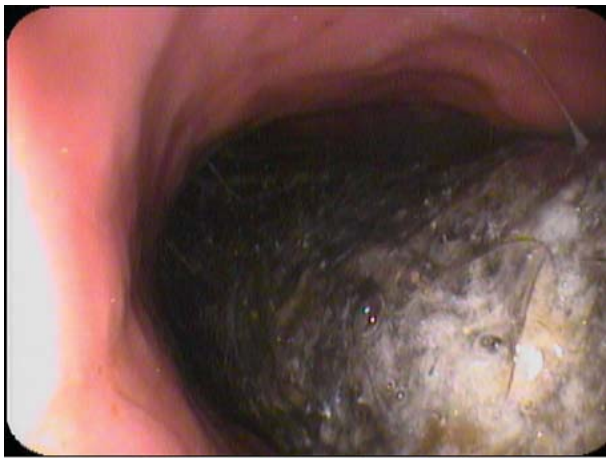

Fig. 1 – Endoscopy revealed a tumor mass made up of hair in the stomach

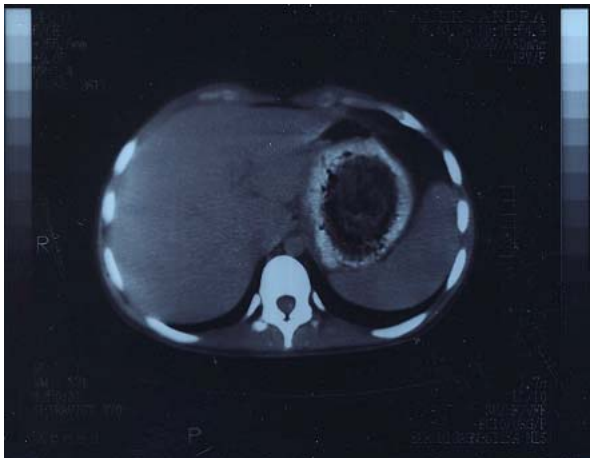

Fig. 2 – Computed tomography (CT) scan showed a non-homogenous oval and ladge mass with a luzy outline that filled the entire stomach and the first part of duodenum

An exploratory laparotomy through an upper midline abdominal incision was performed. Gastrotomy was done and trichobezoar was extracted (Figure 3). A trichobezoar completely filled the stomach and the first part of the duodenum.

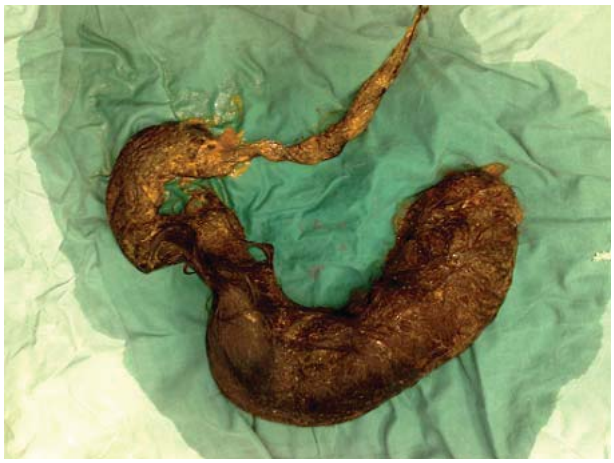

Fig. 3 – A gastrotomy was done and a trichehobezoar was extracted

The patient was discharged with no recurrence of the symptoms, referred to the Psychiatry Department for psychiatric treatment.

Discussion

Bezoars are concrements composed of hair, animal or plant fibres, minerals, medicaments etc., accumulating in gastrointestinal tract, most often in the stomach and rarely in the small intestine. Bezoars composed of hair or hair-like fibres are called trichobezoars.

Trichobezoars, unlike other bezoar types, most frequently occur in patients with psychiatric disorders, trichotillomania and trichotillophagia [7]. They usually appear with signs and symptoms due to a mass in the stomach and may rarely extend to the small bowel as a tail (Rapunzel syndrome) [8].

Trichotillomania is a behavioral disorder which implies compulsive hair pulling [2]. Hair is commonly pulled out from the scalp but also eyelashes, eyebrows, pubic region or some other body parts. Trichotillomania can lead to alopecia. This disorder begins in the earliest childhood or adolescence [7, 9].

Five to 18% of patients who suffer from trichotillomania develop trichotillophagia (swallowing hair), which leads to potentially serious complication, trichobezoar formation [10]. Approximately 37.5% of patients suffering from trichotillophagia will form trichobezoar [11].

Rapunzel syndrome is a rare form of trichobezoar, first described by Vaughan in 1968, as a tail-like extension of gastric trichobezoar into the small intestine. In 1999, Dalshaug reported 11 cases of Rapunzel syndrome, whereas in a recent literature review in 2007 only 24 cases were found [12].

For a long time trichobezoar can be asymptomatic or be manifested by epigastric anxiety (80%), abdominal pain (70%), nausea and vomiting (38%), asthenia with weight loss, diarrhea or obstipation (33%). The first manifestations of bezoars are sometimes gastrointestinal complications such as: ulceration bleeding, mechanic intestinal obstruction, perforation of the stomach or small intestine with peritonitis or subphrenic abscess, digestive fistula, acute pancreatitis or cholestasis due to obstruction of Vater's ampulla in Rapunzel syndrome [13]. The most common complication is intestinal obstruction [2]. Perforation and peritonitis result in death in 30% of cases [14].

An abdominal mass in the epigastrium is the most common sign [12]. In our case, the size of abdominal mass led to asymmetry of the abdomen and was observed during examination. Laboratory findings confirm hypoproteinemia and hypochromic anemia as the most common manifestations of malabsorption syndrome [15].

Various imaging modalities have been recommended for detection of trichobezoars. Plain abdominal radiography is helpful in the diagnosis of intestine obstruction, but contributes little to the confirmation of trichobezoars. Echosonographic trichobezoar looks like a hyperechogenic mass, with wavy edges. The presence of multiple acoustic interfaces created by trapped air and food limits the ultrasonography of the trichobezoars [16].

Esophagogastroduodenoscopy is a method of choice for diagnosing trichobezoars. The typical colour of trichobezoar at endoscopy is black. It allows the clinician to distinguish between phytobezoars and trichobezoars. This is very important because tretment depends on the nature of a bezoar [17].

CT scan is also very useful in diagnosing trichobezoars. Trichobezoar is presented on CT as well-defined ovoid intraluminal heterogeneous mass, occupying almost the entire lumen. A typical CT finding shows air bubbles trapped within the mass [18]. In the Rapunzel syndrome, CT scans have shown a hypodense lesion in the stomach with a mesh-like pattern. Oral contrast is sparse within the mesh, though prominent around the margins. The presence of a tail in the small intestine is reflected by small areas of hypodensity [16].

Small trichobezoar can be removed endoscopically from the stomach, but they are rare. Previous to removal, trichobezoar first must be fragmented by the bioptic device or by using bezotomes [16]. In most cases fragmentation is not possible due to the size and content, as in the presented patient. Fragments of large trichobezoars can migrate through the pylorus, causing obstruction of distal parts of the small intestine. Extraction of fragmented parts involves a large number of repeated insertions of endoscope, which can lead to esophagitis, ulcerations, even perforation of esophagus [3].

Surgical treatment is indicated in most trichobezoar cases, mostly for their size, but also composition. Nirasawa et al. [19] first described laparoscopic removal of trichobezoars. A successful laparoscopic removal requires significantly longer operation time as compared to conventional laparotomy [3].

Laparotomy is a therapy method of choice, with respect to its success, possibility of careful examination of the whole gastrointestinal tract (stomach and intestines), as well as low level of complications [3].

In prevention of recurrence of trichobezoar, psychiatric treatment of trichotillomania and monitoring of the patient is very important. Common treatment includes medicamental and cognitive behavioral therapy. Selective serotonin reuptake inhibitors are medications with the highest efficacy in the treatment of trichotillomania [2, 20].

Habit-reversal training is an initial behavioral therapy.

Conclusion

Trichobezoar should be differentially diagnostically taken into consideration in younger women with abdominal pain, nausea, vomiting, palpable abdominal mass and psychiatric disorders.

Therapy modalities depend on trichobezoar size and possible complications, but most of the cases demand surgical treatment. Each patient has to be submitted to psychiatric treatment and regular control.

This rare case demonstrates the importance of understanding patients in the context of their life situation.

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CASE REPORT

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Paraganglioma – a cause of hypertension in a young patient

Paragangliom kao uzrok hipertenzije kod mladog bolesnika

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Abstract

Introduction. Collections of neuroendocrine cells dispersed throughout the body are known as paraganglia and the tumor arising from these paraganglia are known as paragangliomas. Paragangliomas located along side the aorta are associated with the pheochromocytoma and they secrete and store catecholamines. **Case report.** We reported a 29-year-old woman with episodes of headache, palpitations, dizziness and sweats, associated with hypertension. Elevated urine catecholamines were consistent with pheochromocytoma. Nuclear magnetic resonance (NMR) was performed and the symptoms were caused by associated mediastinal and retroperitoneal paragangliomas. The tumors were surgically removed. In a 3-year follow-up period the patient had two recidivate lesions, one of them was surgically removed, and for the last one a 6-month follow-up was recommended, because urine cathecholamine level was not significantly elevated and blood pressure was normal. **Conclusion.** Clinical and imaging data of patients with extra adrenal paragangliomas are not specific. Many of them may be asymptomatic even when the lesion is large, but if tumor is functional, diagnosis may be easier. Patients should be initially evaluated by determining catecholamine level, followed by computerized tomography (CT) or NMR to locate the primary lesion. Since there are no definite microscopic criteria for the distinction between benign and malignant tumors, radical excision and prolonged follow-up is necessary.

Key words:
paraganglioma; hypertension; surgical procedures, operative; diagnostic techniques and procedures; histology.

Apstrakt

Uvod. Grupe neuroendokrinih ćelija koje su lokalizovane u različitim delovima tela poznate su kao paraganglije, a tumori poreklom od ovih ćelija su paragangliomi. Paragangliomi lokalizovani duž aorte imaju iste karakteristike kao feohromocitom, tj. luče povećane količine kateholamina. **Prikaz bolesnika.** Prikazana je 29-godišna bolesnica sa povremenim glavoboljama, palpitacijama, mučninama i preznojavanjem praćeni hipertenzijom. Povećan nivo kateholamina u 24-časovnom urinu ukazivao je na postojanje feohromocitoma. Urađena je nuklearna magnetna rezonanca (NMR) toraksa i abdomena i utvrđeno je da su opisani simptomi uzrokovani paragangliomima u posteriornom medijastinumu i retroperitoneumu. Tumorske mase bile su operativno odstranjene. Tokom 3-godišnjeg praćenja, bolesnica je imala dva recidiva, a jedan od njih je hirurški otklonjen. Posle otkrivenog drugog recidiva, krvni pritisak i nivo kateholamina u 24-časovnom urinu bili su u granicama normale, te smo savetovali 6-mesečne redovne kontrole. **Zaključak.** Klinički i radiološki znaci ekstraadrenalnih paraganglioma su nespecifični. Mnogi su asimptomatični, čak i kada se radi o vrlo velikim lezijama, ali ako su funkcionalne, dijagnoza je lakša. Kod takvih bolesnika određuje se nivo kateholamina u urinu i radi se kompjuterizovana tomografija (KT) ili NMR radi lociranja primarne lezije. Kako ne postoji definitivan mikroskopski kriterijum za razdvajanje benignih od maligne lezije, neophodni su radikalna ekscizija i kliničko praćenje operisanih bolesnika.

Ključne reči:
paragangliom; hipertenzija; hirurgija, operativne procedure; dijagnostičke tehnike i procedure; histologija.

Introduction

Collections of neuroendocrine cells dispersed throughout the body are known as paraganglia and tumors arising from these paraganglia are known as paragangliomas [1]. The paraganglia based on their anatomic distribution can be divided into three groups: branchiomeric, intravagal and aorticosympathetic [2]. The branchiomeric and intravagal paraganglia are associated with the parasympathetic nervous system and are located close to the major arteries and cranial nerves of the head and neck.

Aorticosympathetic paragangliomas or extra-adrenal pheochromocytomas are located along side of the aorta and are associated with the sympathetic nervous system. They secrete and store catecholamines. Symptoms such as hypertension, flushing, sweating, headache, diaphoresis, anxiety, tachycardia

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or palpitations are symptoms reported in patients with increased catecholamine secretion in functional tumors [3].

Computerized tomography (CT) scans or magnetic resonance imaging (MRI) are very useful, but diagnoses of paragangliomas can only be made with careful histological and immunohistochemical evaluation [4]. Histologically, it is well circumscribed neoplasm composed of epithelioid cells with eosinophilic cytoplasm arranged in a group and peripherally surrounded by more spindle shaped cells. Immunohistochemical stains on the paraffin tissue specimen, including chromogranin, synaptophysin, and S100, confirm the neuroendocrine origin of this neoplasm.

Twenty-four-hour urine collections in our patient showed marked elevation of norepinephrine, light elevation of epinephrine and normal level of dopamine.

The first thoracic and abdominal MRI scan demonstrated a 30.7 × 23.6 × 15 mm mass in the right paravertebral region in the level of costotransversal articulation of Th10, with heterogeneous increased intensity on T2 weighted images, which suggested necrosis and cystic degeneration of lesion. The second lesion was 18 × 12.8 mm, with homogeneous high intensivity on T2 weighted images behind the right renal vein and laterally from the inferior vena cava (Figures 1 and 2).

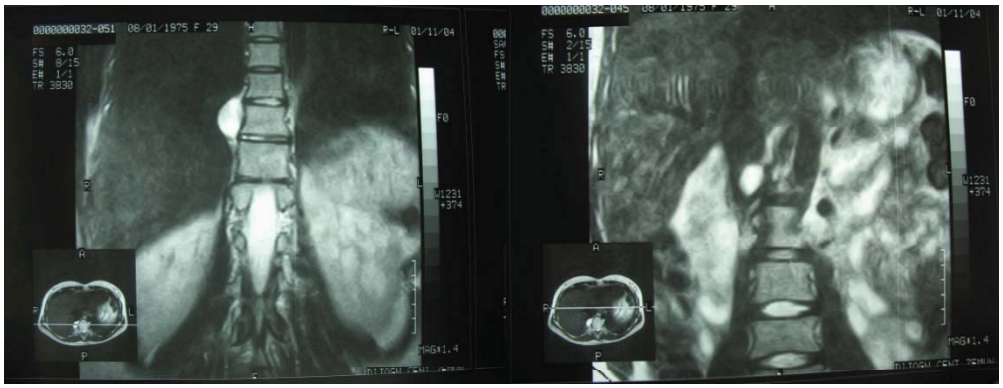

Fig. 1 – Thoracic magnetic resonance image (MRI) demonstrated lesion in the right paravertebral region in the level of Th 10 vertebra. Abdominal MRI demonstrated lesion behind the right renal vein, laterally from the *v. cava inferior*

The treatment of choice for paragangliomas is a complete surgical resection followed by a prolonged follow-up. This may be done by 6-month ultrasound and one-year CT or MRI examinations [5].

Case report

We described a 29-year-old woman presented with a 5-month history of headache, palpitations, dizziness, sweats, associated with hypertension (160/120 mm Hg), before any examinations.

Routine laboratory tests recommended before initiating therapy, which included urinalysis, blood glucose, hematocrit, creatinine, calcium and lipoprotein profile, were normal. Holter electrocardiographic monitoring revealed inverted T wave in D1, aVL, V4-V6 leads, which attended hypertension period.

Heart, thyroid and abdominal ultrasound, renal artery doppler and ophthalmology examination were made to exclude coarctation of the aorta, thyroid and parathyroid disease, renovascular hypertension, and the above tests were normal.

Pheochromocytoma should be suspected in patients with paroxysms of hypertension accompanied by headache, palpitations, pallor perspiration and 24-hour urinary metanephrine and normetanephrine is screening diagnostic test for this disease. This involves obtaining a special urine container, which has a small amount of preservative from a medical laboratory and filling it with one entire day's worth of urine. The test is somewhat inconvenient but well worth the trouble due to its reliability and unrivaled specificity.

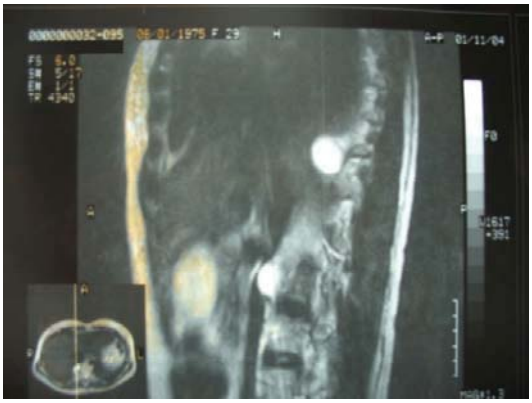

Fig. 2 – Toracoabdominal magnetic resonance (MR) scan demonstrated paravertebral paragangliomas

Elevated urinary catecholamines and MRI scan were consistent with an aorticosympathetic paraganglia in the right paravertebral space.

Preoperative management – all patients with pheochromocytoma and paraganglioma undergoing surgery should receive preoperative medical management to minimize operative and postoperative complications. The main goal of preoperative management is to normalize blood pressure, heart rate and protect a patient from the effects of high levels of circulating catecholamines during surgery, which may cause hypertensive crises and arrhythmias. Preoperative management in this case included α-adrenergic antagonists, β-adrenergic antagonists, calcium channel blockers and catecholamine synthesis inhibitors.

The thoracic lesion was surgically removed without complications, and four months later an abdominal mass was removed, too. The characteristic of tumors were the same, they were incapsulated, without capsular invasion, solid formed, with abundant vascularisations, composed of epithelioid cells, with eosinophilic cytoplasm, surrounded with stromal septa. Immunohistochemistry showed strong positive staining of vimentin, S-100 protein, chromogranin, synaptophysin, thus the diagnosis of paraganglioma was confirmed (Figures 3 and 4).

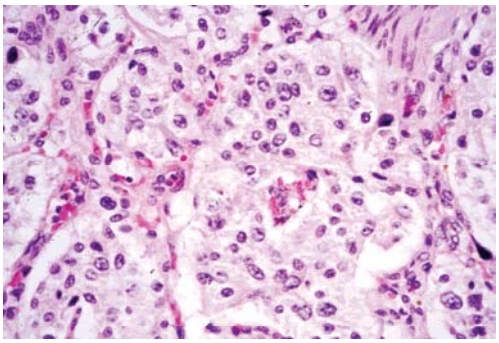

Fig. 3 – A patohistologic finding demonstrated epithelioid cells, with eosinophilic cytoplasm, surrounded with stromal septa (HE ×45)

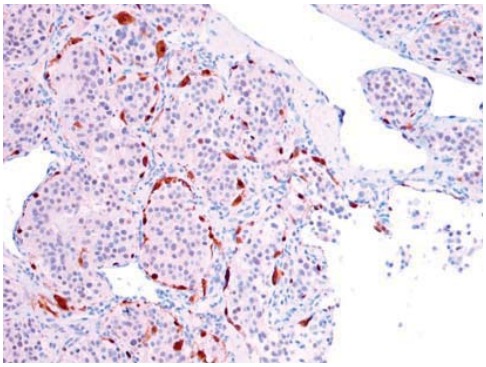

Fig. 4 – Immunohistochemistry – the presence of peripheral S100-positive cells, typical for paragangliomas (S100 ×65)

In one-year follow-up period, hypertension was persistent and in 24-hour urine collections catecholamines level was higher than normal. Functional imaging with metaiodobenzylguanidine was done and the result was normal, focal lesion was not reviewed.

It has been proposed that all patients diagnosed with a pheochromocytoma or paraganglioma should consider genetic testing to early identificate a hereditary syndrome and early screening for other associated tumors and eventual identification of family members who are at risk. Many cases of familial paraganglioma are caused by mutations in the succinate dehydrogenase (succinate: ubiquinone oxidoreductase) subunit gene SDHD.

Genetic testing showed that the patient was negative for a succinate dehydrogenase (SDH) subunit B mutation.

Multislice abdominal CT scan demonstrated inhomogeneously enhancing a soft-tissue mass of 20.8 mm located in the right paravertebral area, in front of the anterior crus of adrenal gland, behind the inferior vena cava (Figure 5). After the third surgical intervention, histopatological characteristics of the tumour indicated paragangliomas. Postoperatively, the patient was normotensive and exhibited catecholamine levels within the normal range.

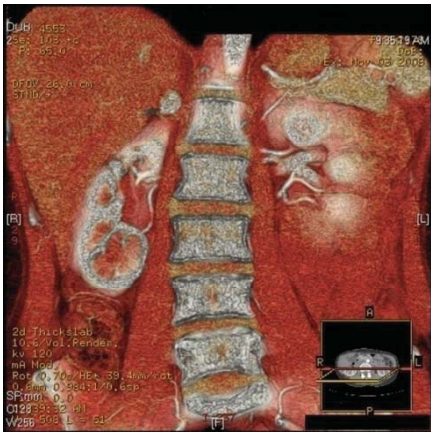

Fig. 5 – Multislice computed tomography (CT) demonstrated a soft-tissue mass a 20.8 mm located in the right paravertebral area

Follow-up in six months was recommended. After 18 months MRI scan demonstrated 16 × 15 mm recidivate tumour in the right retroperitoneal area in front of the anterior crus of the adrenal gland, behind surgical clips. Abdominal ultrasound demonstrated 14 mm hypoechoic lesion in the position of the right adrenal gland (Figure 6). However, catecholamine level was not significantly increased and blood pressure was normal.

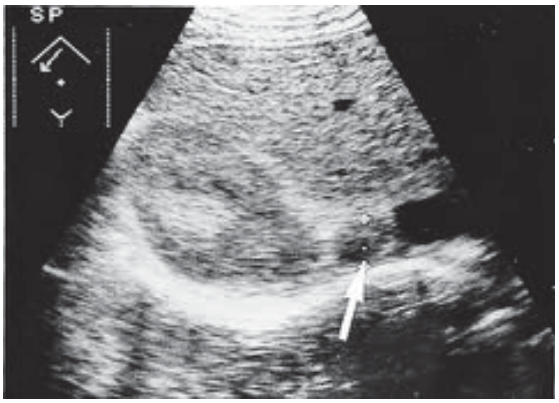

Fig. 6 – Ultrasound showed a hypoehoic mass in the positin of the right adrenal gland

Ultrasound and catecholamine level in 6 mounths and CT scans or NMR per year were recommended.

Discussion

Paragangliomas are extra-adrenal pheochromocytomas that arise from chromaffin cells in the sympathetic (localized in the retroperitoneum and the thorax) or parasympathetic (next to the aortic arch, neck, and skull base) neural paraganglial. They account for 10% of adult pheochromocytomas [1].

About 70% of sympathetic paragangliomas are intraabdominal, usually found in the perinephric and paraaortic spaces. The remaining 30% are located in the chest [5]. Associated toracal and abdominal paragangliomas, such as in the presented case, are very rare.

Extraadrenal paragangliomas affect patients in the 2nd or 3rd decade of life [6]. It has been reported that 10%–40% of extra-adrenal paragangliomas are malignant [7]. Distant metastasis is the only reliable criteria for confirming malignancy. Local tissue invasion or pathological evidence of nuclear pleomorphism or mitotic activity do not necessarily imply malignancy [8].

Functioning extra-adrenal paragangliomas represent more than 10% of all pheochromocytomas [9]. Functional paragangliomas secrete norepinephrine and normetanephrine and account for 30–60% of tumors [10]. If secretory tumor is present, patients undergo paroxysmal episodic hypertension, as well as the typical triad of symptoms associated with pheochromocytomas: palpitations, headache and profuse sweating. The nonsecretory type most commonly presents as abdominal pain or mass [11] and a large proportion of these tumors are incidentally discovered in normotensive patients during imaging evaluation for other reasons [12].

The diagnosis is usually established with high urine catecholamine metabolites, VMA and metanephrine levels [11]. The imaging modality of choice for primary tumor evaluation and staging is CT of the thorax, abdomen and pelvis.

On CT, retroperitoneal paraganglioma appears as a hypervascular mass. Areas of intralesional hemorrhage and necrosis can be frequently seen as the tumor enlarges. They are commonly located in the para-aortic region, and they may be confused with other retroperitoneal tumors, especially pancreatic tumors [13]. MRI is more sensitive than CT in detecting extra-adrenal tumors. Scintigraphy with 123-I labelled MIBG offers superior specificity than CT and MRI imaging [14]. Genetic disorders involving mutations within the succinate dehydrogenase B and D units (SDHB, SDHD) and the von Hippel-Lindau (VHL) gene places an increased risk in the development of extra-adrenal paragangliomas and adrenal pheochromocytomas [15].

The differential diagnosis of spinal paraganglioma includes metastases, multiple myeloma and other highly vascular tumors. Differentiation of paragangliomas from these tumors is frequently not possible on MRI and CT, because of considerable overlap in their imaging findings [1]. Thus, histopathological findings are the only adequate diagnosis for paragangliomas.

Surgical excision remains the mainstay of treatment. Since there are no definite microscopic criteria for the distinction between benign and malignant tumors, radical excision is the treatment of choice and prolonged follow-up is necessary.

Conclusion

Clinical and imaging data of patients with extra adrenal paragangliomas are not specific. Many of them may be asymptomatic even when the lesion is large, but if tumor is functional, diagnosis may be easier. Patients should be initially evaluated by determining catecholamine level, followed by CT or MRI to locate the primary lesion. Since there are no definite microscopic criteria for the distinction between benign and malignant tumors, radical excision and prolonged follow-up is necessary.

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CASE REPORT

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Mitral valve endocarditis during brucellosis relapse

Endokarditis mitralnog zaliska u toku recidiva bruceloze

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Abstract

Introduction. Endocarditis is the most common cardiovascular manifestation of brucellosis with high mortality rate. Brucella is less accesable to antibiotic (but not for all) and relapse can occur after a various period of clinical latency. **Case report.** A 55-year-old farmer was diagnozed with acute systemic *Brucella* infection in May 2008 and treated with antibiotic therapy in regional hospital for two months and for three months after discharge. He began to feel myalgia, arthralgia, malaise, shortness of breath, abdominal pain, vomiting, diarrhoea and lost weight eight months after initial symptoms occured. Because symptoms progressed he was admitted to our hospital in February 2009. Based on a combination of epidemiological, clinical data (on admission he was catchetic, adynamic, dyspneic, hypotensive 80/50 mmHg, fever up to 39.5^{0}C), positive serological Wright test for brucellosis (1 : 5,120), and echocardiographic examination findings, the diagnosis of very severe relapse of brucellosis with mitral valve endocarditis, complicated with perforation of anterior mitral leaflet, severe mitral regurgitation and pulmonary hypertension was established. He was treated with a combined triple antibiotic therapy (vancomycin, ciprofloxacin and gentamicin, and swiched to regimen with doxycycline, gentamicin and imipenem, replacing gentamicin by rifampicin) for 4 weeks and for the next 2 weeks was receiving trimetoprime/sulfamethoxazole and rifampicin. The patients' condition was improved and he was operated. The diagnosis of infective endocarditis was confirmed intraoperatively. Mitral valve replacement was performed, and combined triple antibiotic treatment (amikacin + ciprofloxacin + cefazolin, for 2 weeks and cephazolin + doxycycline + rifampicin, for 2 weeks) was continued, following with two antibiotics (doxycycline + rifampicin) for 5 months. The patient completely recovered without any signs of infection 30 months postoperatively. **Conclusion.** A combined antibiotic therapy and surgery reduce complications and mortality associated with *Brucella* endocarditis and improve quality of patients' life.

Key words:
brucellosis; endocarditis; mitral valve prolapse; recurrence; anti-bacterial agents; surgical procedures, operative; treatment outcome.

Apstrakt

Uvod. Endokarditis je najčešća kardiovaskularna manifestacija bruceloze i ima visoku stopu mortaliteta. *Brucella* je intracelularni patogen, što je čini slabije dostupnom za antibiotike (mada ne za sve), pa se relaps može javiti posle različito dugog klinički latentnog perioda. **Prikaz bolesnika.** Poljoprovredniku, starom 55 godina, postavljena je dijagnoza bruceloze u regionalnoj bolnici u maju 2008. i lečen je antibioticima dva meseca, kao i dva meseca posle otpusta. Međutim, osam meseci posle pojave inicijalnih simptoma bolesnik je osetio bolove u mišićima i kostima, slabost, otežano disanje, bolove u trbuhu, mučninu, povraćao je i imao dijareju, kao i smanjenje telesne mase. Zbog pogoršanja simptoma primljen je u februaru 2009. u kardiološku kliniku. Na osnovu kombinovanih epidemioloških, kliničkih podataka (na prijemu kahektičan, adinamičan, dispnoičan, hipotenzivan 80/50 mmHg, febrilan do 39,5^{0}C), pozitivnog Wright-ovog serološkog testa za brucelozu (1 : 5 120) i ehokardiografskog nalaza, postavljena je dijagnoza veoma teškog recidiva bruceloze sa endokarditisom mitralnog zaliska, komplikovanog perforacijom prednjeg mitralnog zaliska, teškom mitralnom regurgitacijom i plućnom hipertenzijom. Bolesnik je lečen trojnom antibiotskom terapijom (vankomicin, ciprofloksacin i gentamicin, promenjeni u režim sa kombinacijom doksiciklin, gentamicin i imipenem, uz kasniju zamenu gentamicina rifampicinom) tokom četiri nedelje, a sledeće dve nedelje kombinacijom trimetoprim/sulfametoksazol i rifampicin. Stanje bolesnika bilo je bolje, pa je operisan. Mitralni zalistak je zamenjen i nastav-

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ljeno je sa kombinovanom trojnom antibiotskom terapijom (amikacin + ciprofloksacin + cefazolin, dve nedelje i cefazolin + doksiciklin + rifampicin, 2 nedelje), uz kasniju primenu dvojne antibiotske terapije (doksicikline + rifampicin) tokom 5 meseci. Bolesnik se oporavio 30 meseci posle operacije, bez ikakvih znakova infekcije. **Zaključak.** Kombinacija antibiotskog i hirurškog lečenja može smanjiti komplikacije i mortalitet koji prati brucelozni endokarditis i, takođe, može poboljšati kvalitet života bolesnika.

Ključne reči:
bruceloza; endokarditis; zalistak, mitralni prolaps; recidiv; antibiotici; hirurgija, operativne procedure; lečenje, ishod.

Introduction

Brucellosis affects more than 500,000 people worldwide each year, and this makes it the most frequent zoonosis [1]. Brucellosis may appear in four different forms, namely, acute, subacute, chronic, and relapse [2]. Even with the appropriate treatment, the incidence of brucellosis relapse remains high, ranging from 5% to 40% of patients in the largest series reported to date [3, 4].

Brucella infection may involve any organ or tissue in the body. Organ involvement can be assigned as focal or complication. Endocarditis is the most common presentation of cardiovascular involvement, which is reported in less than 2% of patients with brucellosis [2, 5–7].

We presented a patient with *Brucella* endocarditis, as a complication of *Brucella* relapse infection, who was successfully treated by medical and surgical therapy.

Case report

A 55-year old farmer from the Republic of Srpska, entity of Bosnia and Herzegovina was admitted in the regional hospital in May 2008 with the symptoms of acute systemic *Brucella* infection. Epidemiological history revealed that the patient came from the village where *Brucella* infection was present from time to time. In addition, he was a cattleman by vocation and consumed unpasteurized milk products of his private production. During June and July 2008, the patient was treated in the regional hospital with ceftriaxone 4 g/day and metronidazole 1,500 mg/day until the diagnosis of brucellosis was made and then with doxycycline 200 mg/day and gentamicin 160 mg/day. When the patient went home, he was receiving doxycycline 100 mg/day for 3 months. All that time, the patient underwent regular controls and felt well. During that period the patient did not return to his job, *ie* he did not have contact with animals, and there was no other case of *Brucella* infection in his village. But, again in December 2008, he began to feel myalgia, arthralgia, malaise, shortness of breath, abdominal pain, vomiting, and diarrhoea, began to lose weight and was treating with symptomatic therapy. As symptoms prograded he was admitted to the regional hospital in January 2009. Ten days afterwords, on February 10, 2009 he was transferred to our division with symptoms of fever up to 39.5°C, chills, sweating, fatigue, shortness of breath, loss of appetite, vomiting, diarrhea, weight loss, intermittent myalgia and headache.

On admission the patient was cachectic, pale, adynamic, dyspneic, hypotensive (80/50 mmHg) and febrile. Heart auscultation revealed regular rhythm, S3 heart sound and 4/6 holosystolic murmur on the apex. Abdomen palpation revealed painful epigastric region.

Laboratory blood tests showed erythrocyte sedimentation rate 64 mm/h (normal </= 20 mm/h), C-reactive protein 61 mg/mL (normal range <4 mg/L), hemoglobin 99 g/L (normal range 130–180 g/L), red blood cells 3.4 × 10^{12}/L (normal range 4.15–4.90 × 10^{12}/L), serum iron levels 3.4 μmol/L (11–29 μmol/L), platelets 77 × 10^{9}/L (normal range 130–400 × 10^{9}/L), aspartate aminotransferase 55 IU/L (normal range 0–35 U/L) and serum creatinine 134 μmol/L (normal value < 133 μmol/L). Blood cultures were negative despite prolonged (3 weeks) incubation. The suspicion of brucellosis was verified with positive Wright sero-reaction, 1 : 5,120 (positive 1 : 320).

Electrocardiography showed sinus rhythm, left atrial enlargement, incomplete right bundle branch block, while chest X-ray revealed cardiomegaly and enhanced opacity of the pulmonary vasculature. Transthoracic echocardiography showed mitral valve prolapse with the rupture of *chordae tendineae* of the anterior mitral leaflet, oscillating vegetation (21 × 13 mm) on that leaflet, calcification on the posterior mitral annulus and severe mitral regurgitation, enlargement of the left atrium (49 mm) and left ventricle end diastolic dimension (60 mm) with normal systolic left ventricular function (ejection fraction 62%; normal range 60%–70%), and moderate tricuspid regurgitation. Pulmonary artery systolic pressure was 70 mmHg normal pulmonary artery systolic pressure at rest is 18 to 25 mmHg (Figure 1).

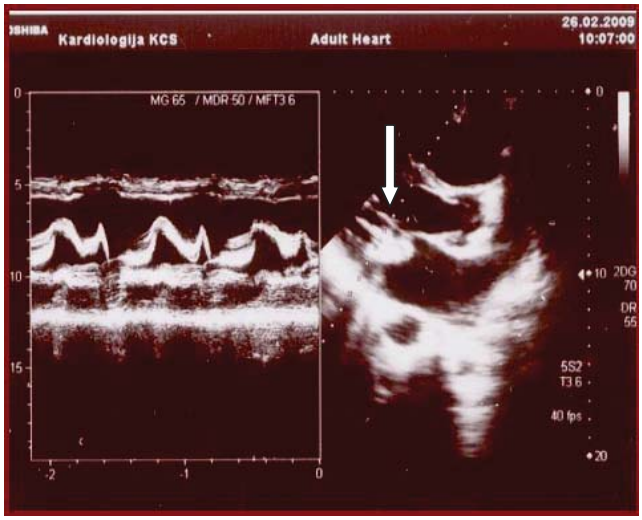
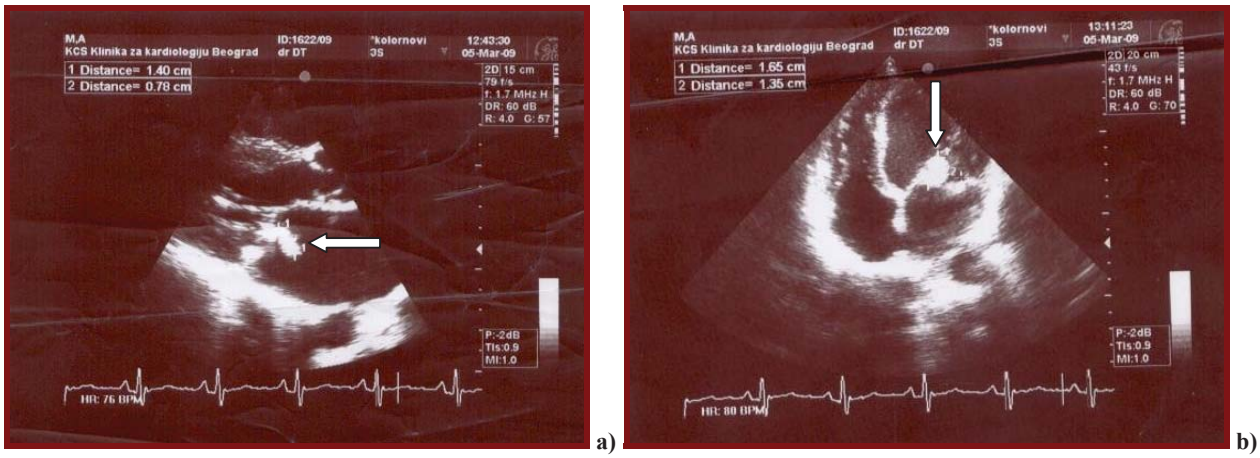


Fig. 1 – M and 2-D echocardiogram, parasternal long axis view presenting the huge vegetation (arrow) attached to anterior mitral leaflet (during medical therapy)

At the beginning of hospitalization the patient was treated with vancomycin 1,000 mg/day, ciprofloxacin 200 mg/day and gentamicin 80 mg/day. When the suspicion to *Brucella* infection was verified, the patient was immediately swiched to triple antibiotic regimen including doxycycline 200 mg/day, gentamicin 80 mg/day and imipenem 1,500 mg/day and after 2 weeks gentamicin was replaced by rifampicin 600 mg/day. This therapy was administrated for 4 weeks and then for the next 2 weeks, the patient was receiving trimetoprime/sulfamethoxazole 960 mg/day and rifampicin 600 mg/day.

After 4 weeks of antibiotic and symptomatic therapy, the patient's condition was significantly improved, he was not febrile any more, the laboratory tests were much better, but echocardiography still showed huge, mobile mitral valve vegetation (Figures 2a and 2b) and perforation of the anterior mitral leaflet. Heart catheterization confirmed pulmonary hypertension. Selective coronarography which is routinely performed in patients older than 40 years of age undergoing, besides coronary revascularization, any other form of heart surgery, failed to show significant coronary artery stenosis. Computed tomography which is also routinely performed in patients with infective endocarditis in preoperative evaluation before the heart operation showed small old multiple cerebral infarctions. On the 29th of March 2009, when general condition was tolerable, the patient was operated on. The diagnosis of the infective endocarditis was confirmed intraoperatively (Figures 3a and 3b). Mitral valve replacement was performed, using the No. 27 mm St. Jude bileaflet prosthetic valve. Histopathologic examination revealed the signs of infective endocarditis, and cultures from the valve were negative. Antibiotic treatment was continued four weeks after the operation with three antibiotics: amikacin 1000 mg/day, ciprofloxacin 400 mg/day and cefazolin 2 g/day for 2 weeks parenteraly, followed by cephazolin 2 g/day, doxycycline 200 mg/day and rifampicin 600 mg/day for another 2 weeks. Postoperative period was complication-free. During the following 5 months, the patient was treated orally with doxycycline 200 mg/day and rifampicin 600 mg/day. Clinical follow-up was done on regular basis. In September 2011, 30 months after the operation, the patient felt well, completely recovered and without any signs of infection.



a) b)

Fig. 2 – Reapeted two-D echocardiogram, parasternal long axis (a) and apical 4 chamber view (b) with huge still present vegetation (arrows) attached to anterior mitral leaflet and rupture of the *chordae tendineae*

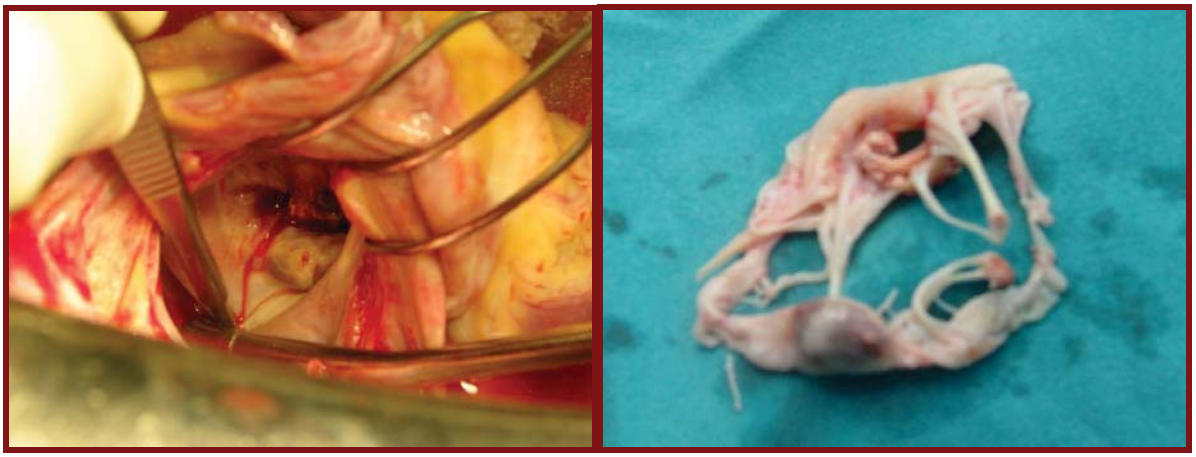


Fig. 3 – Intraoperative finding: a) vegetation on the anterior mitral leaflet with perforation of the leaflet; b) vegetation on the mitral valve after extraction

Discussion

Brucellosis is a ubiquitous zoonosis, endemic in Mediterranean basin, Arabian Peninsula, South Asia, Central and South America. It is present in the Balkan region as well [8–10].

The primary transmission route of brucellosis is by the ingestion of unpasteurized dairy products in endemic countries. It is systemic disease which may affect almost every organ or tissue in the body. Organ involvement can be assigned as focal involvement or complication. The most common affected systems are the locomotor, gastrointestinal, genitourinary and hematologic. Cardiovascular complications are rare, occurring in 0.7% to 2.3% of patients in large studies [4–6, 11]. Despite treatment including several antibiotic regimens, the relapse is estimated to occur in 5%–40% [3, 4], even up to 50% with a single drug regimens [12], of patients with acute brucellosis in the following year, depending on antibiotic use, duration of treatment, and drug combination. In the literature, the highest rate of relapses is with osteoarticular manifestation. In the biggest reported series of patients with brucellosis there was no patient with relapse involving the cardiovascular system [4].

We present our experience in the treatment of rare form of relapse of brucellosis associated with mitral valve endocarditis successfully treated both medically and surgically.

Our patient had the first attack of illness in May 2008. It is well known that most brucellosis infections present in spring and summer months [2, 6, 13]. Although he was treated for few months, the illness recurred in December 2008. *Brucella* is an intracellular pathogen, which makes it immune to defense mechanisms of the host by phagocytes and polymorphonuclear leucocytes. After surviving intracellular defense mechanisms it stays in reticuloendothelial system [14]. Because of this relapse can occur after a various period of clinical latency. Our patient, despite a prolonged antibiotic therapy, had very severe relapse with mitral valve endocarditis complicated with perforation of anterior mitral leaflet. These complications are rarely described in literature [15, 16]. The diagnosis of brucellosis was based on combination of epidemiological, clinical data and positive serologic reactions.

Endocarditis is a rare and very severe complication of brucellosis, with high mortality rate [9]. The left side of the heart is usually affected, predominantly the aortic valve (75%), less common (8.3%) mitral valve [17, 18]. *Brucella* is slowly destructive organism, with marked tendency to tissue ulceration [15, 17]. Vegetations in *Brucella* endocarditis are large, carrying the significant risk of embolization, and difficulty in eradicating with medical therapy alone [18].

The treatment of human brucellosis continues to pose a problem. The best therapeutic approach to *Brucella* endocarditis involves a combination of medical and surgical treatment. It is reported in literature that only these two treatments together successfully eradicate infection as *Brucella* can produce very destructive lesions when it is nested in the valvular endocardium [17, 18]. Antibiotic treatment alone is considered ineffective by most authors [19–21] although there are sporadic cases successfully treated with only medical therapy [22, 23]. This is attributed to the intracellular localization of *Brucella*, the site that is relatively inaccessible to antibiotics [24]. Even if symptoms improved and subsided with antibiotics, surgery would be still necessary because of the embolic potential of residual vegetation or to relieve valvular obstruction. Literature has reported confronting theories regarding the proper timing of surgical procedure of the affected valve in patients with diagnosed *Brucella* endocarditis. Although some authors implicate the necessity of surgical treatment as early as possible even during the antimicrobial therapy, others suggest that it is better to postpone the surgical valve replacement after the antimicrobial treatment [25, 26]. The duration of antimicrobial therapy after valve replacement remains a bit disputable. Treatment periods that have been reported by different authors vary from 2–13 months [26, 27]. The decision to discontinue antimicrobial therapy could be determined on patient-to-patient basis, after a thorough clinical observation and evidence of negative IgA antibodies, normal CRP, and reduction of Wright seroreaction titers below 1/64. A patient also must be symptom-free. In our case, the patient was administered 6 month-postoperative antimicrobial treatment in order to eradicate *Brucella*. Justification for such postulation was confirmed in our case where patient was *Brucella*-free, symptom-free, and without cardiac complications after 30 months of a follow-up period.

Conclusion

Cardiac involvement in human brucellosis is extremely rare, especially in relapse, but should not be overlooked, since it is a major mortality cause in brucellosis infection. The success of *Brucella* endocarditis treatment depends on timely and complete medical and epidemiological evaluation, which leads to adequate medicamentous and surgical treatment of a patient. This approach reduces complications and mortality associated with *Brucella* endocarditis and improves patients' quality of life.

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I S T O R I J A M E D I C I N E

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Srpski lekari – književnici 19. veka

Serbian physicians – writers of 19th century

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Ključne reči:
istorija, 19-ti vek; lekari; pisanje; literatura; srbija.

Key words:
history, 19th century; physicians; writing; literature; serbia.

Uvod

Danas, u vreme savremene tehnologije, naučnog napretka i istraživačkih dostignuća, sa oduševljenjem prihvatamo otkrića iz oblasti medicine do kojih su došli vredni timovi stručnjaka. Ljudska misao, međutim, ne može a da ne odleti čitav vek i više unazad, a savremeni lekar da se ne zapita ko su bili prvi srpski lekari, začetnici zdravstva na ovim prostorima. U traganju za njima kroz medicinsku literaturu, pojavljuje se zlatna nit umetnosti koja vodi do lekara književnika, koji su zahvaljujući svome posebnom daru, hipokratski nastrojeni, nalazili lek kako za telo tako i za dušu.

Pored srpskih lekara književnika 19. veka, kao što su dr Vladan Đorđević i dr Mihailo-Radmio Lazarević, visoko mesto u istoriji zdravstva i srpske književnosti, kao i opšte kulture, imaju dr Jovan Stejić, dr Laza K. Lazarević i dr Jovan Jovanović Zmaj.

Budući da su u to vreme lekari bili najobrazovaniji intelektualci, pored medicinskih poruka koje su nosila njihova književna dela, isticala se i vaspitna uloga namenjena mladim generacijama.

Dr Jovan Stejić, začetnik lekarske profesije u Srbiji i književnik

U vreme vladavine kneza Miloša Obrenovića Srbija je bila veoma zdravstveno neprosvećena, pa je postala praksa da srpska vlada aktivno pomaže i stipendira školovanje domaćih lekara na evropskim univerzitetima. I sam knez Miloš je izdržavao nekoliko pitomaca na studijama u Beču, od kojih se, nažalost, zbog smrti od tuberkuloze ni jedan nije vratio u Srbiju [1].

Kao prvi školovani lekar u Srbiji navodi se Konstantin Aleksandridi, koji je radio kao lični knežev lekar od 1819. do 1821. kada, po zapisima Vuka Karadžića, napušta zemlju zbog sukoba sa knezom. Posle dr Vita Romita iz Napulja u Srbiju stiže dr Jovan Stejić (slika 1), rođen 1803. u Aradu, a koji je po doktoriranju u Beču 1829, kao prvi lekar Srbin, Prečanin, došao svom dobrotvoru Jevremu Obrenoviću. Ubrzo postaje lični lekar kneza Miloša, ali uz tu funkciju obavljao je i posao vaspitača kneževih sinova sve do 1830 [1, 2].

Sl. 1 – Jovan Stejić (1803–1853)

U tadašnjoj Srbiji lekarima se nije verovalo, svaka nova ideja je sa sumnjom prihvatana, a plate lekara bile su niske. Bez obzira na sve prethodno navedeno, dr Stejić postaje utemeljivač organizovane građanske zdravstvene službe. On uspeva da u Srbiju donese moderne i napredne ideje po uzoru na zdravstvo zemlje u kojoj je studirao. Uvodi srpsku medicinsku terminologiju, a prevodi i dopunjava delo čuvenog nemačkog lekara dr Hristofora Vilhelma Huferlanda „Makroviotika ili nauka o produženju života čovečeskog“, čime na naše prostore donosi osnove makrobiotike. Njegov naučni rad objavljen 1827. daje slikovit prikaz uzroka i posledica alkoholizma, kao i načina lečenja alkoholičara [2, 3].

Prva štampana knjiga u prvoj srpskoj štampariji u Beogradu bila je Stejićeva knjiga „Sabor taštine i nauke“ iz 1831. Između ostalog, zabeleženo je i to da je prvi kaput u

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Srbiji 1829. poneo baš dr Stejić koga je tada detaljno opisao izvesni putopisac.

Zbog neslaganja sa knezom Milošem, kao i mnogi njegovi sledbenici, napustio je Srbiju, u koju se vratio tek 1840. kada je sa dr Karlom Pacekom osnovao Srpski građanski sanitet. Potom, 1845, postavljen je za sekretara „Državnog sovjeta“ i na tom položaju zadržao se sve do svoje smrti 1853 [2, 4].

Dr Stejić je objavio prvu „Antropologiju ili nauku o čoveku“ na srpskom jeziku 1850. Značajnim se smatra i Stejićev književni i umetnički rad. Kako su mu uzor bile Kantove ideje, propovedao je moralnost, skromnost i marljivost, kao i osećanje dužnosti. Navodio je da je osnova svega obrazovanje i služio se novim pravopisom Vuka Karadžića, zbog čega je i napustio službu kod kneza Miloša. Napisao je kritiku Vukovog prevoda „Novog zaveta“ i bio je jedan od osnivača Društva srpske slovesnosti. Još davne 1828. u Beču je izdavao „Zabavu za razum i srce [2].

Dr Jovan Stejić je ostao zapamćen kao utemeljivač lekarske profesije u Srbiji. U mnogo čemu prvi, dr Stejić je svojim književnim radom pokušao da ukaže na osnove moralnih vrednosti i na neprikosnovenu „jasnu i mirnu savest“ i time postavio osnove lekarske etike.

Dr Laza K. Lazarević – narodni lekar, pisac, naučnik i poznavalac ljudske psihe

Posmatrajući život i delo lekara i književnika dr Laze Lazarevića, nailazimo na impozantnu činjenicu da je u svome kratkom veku, nešto više od 39 godina, ostavio nemerljivo kulturno i stručno nasleđe. Poštovan i kao pisac i kao doktor, plemenit i osećajan, davao je maksimum svoje delatnosti, zauzevši time počasno mesto u istoriji književnosti i medicine.

Laza Lazarević (slika 2), rođen je 13. maja 1851. u Šapcu i sa samo devet godina, izgubivši oca, ostaje sa majkom i svoje tri sestre. Živeći u patrijarhalnoj porodici, uz majku

Sl. 2 – Laza K. Lazarević (1851–1891)

koja se radeći žrtvovala za njega i sestre, on biva jako privržen familiji, formira kult srpske majke i postaje poštovalac tradicionalnosti. Tako će se Laza kroz celi svoj život kao i u svojim pripovetkama, vraćati kući i porodici kao nečem neprikosnovenom i zaštitničkom, utočištu za koga se treba boriti i, vrlo često, platiti visoku cenu [4, 5].

Pravni fakultet Velike škole završio je 1871. a naredne godine, posle nanovo odobrene stipendije, odlazi u Berlin gde studira medicinu. Tokom studija u Berlinu, pohađao je predavanja na Filozofskom fakultetu, gde se i susreo sa čuvenim slavistom našeg porekla Vatroslaw-om von Jagitschom. Studije, međutim, prekida dva puta u periodu 1876–1878. kada u Srpsko-turskom ratu radi kao lekarski pomoćnik i biva odlikovan srebrnom medaljom [6].

Kao rezervni major u Nišu, 1885, organizovao je vojnu bolnicu sa 1 800 kreveta i sa svega šest lekara lečio preko 3 000 ranjenika.

Dr Vladan Đorđević pisao je o vojnoj bolnici i Lazinom radu „koji mi sa zasukanim rukama do lakata i krvavom keceljom pokaza sobu gde sam imao prenoćiti, a on se vrati na posao...tužan i nesrećan“ [7].

Godine 1879. završio je studije medicine i stekao naučno zvanje Doktora medicinskih nauka i hirurgije odbranivši disertaciju pod nazivom „Uticaj žive na tkiva zečeva“. Lazinu disertaciju, što je bila izuzetna retkost, štampali su u udžbeniku Analitičke hemije 1879. Navedenim radom dr Lazarević se našao uz same utemeljivače toksikologije, ali to je samo početak njegove naučne delatnosti [8, 9].

Kada se vratio u Beograd, počinju da ga poštuju i kao lekara i kao pisca. Dobio je mesto lekara Beogradskog okruga, a potom je postavljen za prvog lekara Opšte državne bolnice. Lazarević je osnovao prvu laboratoriju u Varoškoj bolnici i postao šef Internog odeljenja, kao izvrsni kliničar. Oženio se sestrom svoga druga Koste Hristića, Poleksijom, i sa njom dobio četvoro dece. Laza će imati tu nesreću da sopstvenim bacilom tuberkuloze zarazi svoja dva sina i izgubi ih zbog tuberkuloznoog meningitisa. No, i pored sopstvene bolesti i nesreće, on napreduje u radu i daje doprinos kako medicini, tako i književnosti [4, 10].

Jedini je naš pisac koji je stekao večnu slavu sa objavljenih samo devet pripovedaka. Iako je bio pisac realizma, postavio je temelje srpske psihološke pripovetke i može se nazvati njenim tvorcem, a tome je, u prvom redu, doprinelo njegovo poznavanje psihijatrije kroz lekarsku praksu [11].

Književnim radom Laza se bavio još u gimnaziji, kao trinaestogodišnjak, ali od toga, nažalost, ništa nije sačuvano. Udaja Lazine sestre Milke za Milorada Popovića Šapčanina, koji je bio državni činovnik i književnik u Beogradu, samo devet godina stariji od Laze, omogućilo mu je dalje školovanje na Velikoj školi. Pored toga što je imao stan i hranu, Lazarević je došao u kontakt sa visokim beogradskim intelektualcima, kao i sa obiljem knjiga Šapčaninove biblioteke. Zahvaljujući svome zetu, Laza je razvio ogromnu ljubav prema književnosti i knjizi uopšte.

Objavio je osam pripovedaka, a pripovetku „Švabica“ objavljuju tek sedam godina nakon njegove smrti. Za ovu pripovetku smatra se da je bila autobiografska, a još osam pripovedaka je ostalo nedovršeno. Nazvan je „Turgenjevim srpske pripovetke“. Zbog zasluga iz oblasti književnosti, 1888. izabran je za člana Srpske akademije nauka. Naredne godine postaje lični lekar kralja Milana i sanitetski potpukovnik [5, 10].

Visokomoralna, dostojanstvena i stabilna Lazarevićeva ličnost odavala je iskusnog psihologa i u isto vreme skromnog mladića sa sela koji je u svakoj prilici pomagao siromašnima, ne naplaćujući im svoje usluge već, naprotiv, vrlo često plaćajući sam njihove troškove [5, 6].

Kao poznati humanista, bez obzira što u toku svojih studija od skromne stipendije nije imao ni za osnovne potrebe, pa se često zaduživao, skromno i bez ikakve naknade, pomagao je siromašnim bolesnicima. Tako iz pisanja dr Vladana Đorđevića saznajemo da je Laza znao da „onako slab" i nežnoga zdravlja, obilazi svoje siromašne bolesnike dva puta dnevno, „kao i svoje najbogatije bolesnike" i to po čitavu godinu dana, kao u slučaju jedne učiteljice, udovice sa mnogo nezbrinute dece. A po njenoj smrti, „Lazarević vadi iz džepa sve što je imao novaca pri sebi" i daje decu na staranje jednom pouzdanom čoveku [12].

Pod uticajem predavanja dr Josifa Pančića, dr Lazarević počinje da se interesuje za naučni rad. Studiozan u svemu, on se zalaže za higijenu, vakcinaciju, zdravstvenu prosvećenost, a u isto vreme 1881. osniva prvo odeljenje za gerijatriju u zakupljenoj kući pod nazivom „Odsek za lečenje staraca". Za vreme svog lekarskog staža od jedanaest godina uspeo je da objavi ukupno 78 radova iz raznih oblasti medicine i to: neurologije, ginekologije, interne medicine, hirurgije, infektologije, urologije, epidemiologije, toksikologije, javnog zdravstva, oftalmologije i sudske medicine [9].

Godine 1880, dakle čitavu godinu dana pre prezentacije neurološkog znaka od strane Forsta, Lasegueovog učenika, dr Lazarević u svome radu „*Ischias postica Cotunnii*" opisuje znak koji se sastoji u pojavi bola u toku podizanja zahvaćene noge, bez fleksije kolena, dok je bolesnik opružen na leđima. U današnjoj literaturi za istovetni opis koriste se i Lasegue-ov znak i „Lazarevićev znak" [8].

Američki neurolog svetskog glasa dr Wartenberg je nazvao znak „Lazarević-Lasegue" i dao naučnu prednost dr Lazareviću od skoro 10 godina. I kao što je Lazarević mislio da snovi govore jezikom podsvesti, na granici našeg i, za sada nama još uvek nepoznatog, drugog sveta, stigao je, zauvek obavijen mističnošću, da u grešci od dvadesetak minuta predvidi svoju smrt 10. januara 1891. u Beogradu [6, 8], gde se danas nalazi njegova spomen-kuća.

Da li je dr Lazarević bio veći lekar, naučnik, praktičar ili pripovedač teško je odgovoriti. Biće da su oba dela njegove ličnosti dostigla svoje delimično ispunjenje, jer može samo da se zamisli dokle bi njegov napredni duh dospeo da ga bolest nije u tome sprečila. Jedno je sigurno „narod ga je pozlatio".

Dr Jovan Jovanović Zmaj – rodoljub, lekar i pesnik dečje duše

Smatran istaknutim pesnikom srpskog romantizma i prvim piscem dečje poezije, dr Jovan Jovanović, savesni i predani lekar i satiričar, ostao je zauvek poznat kao čika Jova Zmaj. Put kroz njegovu biografiju vodi nas kroz lekarsku praksu, do tragedije osećajne duše koja je do svog ovozemaljskog kraja pevala, a i dalje peva za svu decu.

Jovan Jovanović Zmaj (slika 3) rođen je 24. novembra 1833. u Sremskoj Kamenici, u advokatskoj građanskoj poro-

Sl. 3 – Jovan Jovanović Zmaj (1833–1904)

dici. U Novom Sadu je završio osnovnu školu i upisao gimnaziju, ali je nju pohađao i u Hakšu i Požunu, da bi po završetku iste upisao prava u Pešti. Studirao je u Pragu i Beču, gde je upoznao Branka Radičevića, koji će mu postati poetski uzor. Njegovo poznanstvo sa Đurom Jakšićem, takođe, ostavlja traga na njegovo stvaralaštvo [13]. Ipak, najveći uticaj na njegovu poeziju imaće poznanstvo, ljubav, a kasnije i brak, sa Ružom Ličanin, koju upoznaje po završetku studija 1860, kada se zapošljava u novosadskom magistratu. Ostvaren i srećan kao porodičan čovek, dr Jovanović stvara „Đulića", nazvane po supruzi, čije ime na turskom jeste „*Gul*", tj. ruža [14]. Prvi časopis koji uređuje jeste „Javor", kao i list satiričara „Komarac", a 1864. i „Zmaj", nazvan tako jer je 3. maja 1848. po julijanskom kalendaru održana Majska skupština. Od tada Jovanović postaje Zmaj [15].

U Pešti je jedno vreme radio kao nadzornik „Tekelijanuma" i u „Matici srpskoj", a istovremeno je studirao i medicinu. Lekarskim poslom počinje da se bavi od 1870. u Novom Sadu [14, 15]. Njegova sreća na privatnom i poslovnom planu biva narušena ličnom katastrofom, gubi jedno za drugim svu decu i najzad suprugu. Tako nastaju "Đulići uveoci". Suprugu Ružu nakratko je nadživela poslednja kćerka Smiljka, ali je Zmaj i nju izgubio. Sa udovicom Marijom Kostić imao je kćerku Anku i poćerku Mariju i, nažalost, sve umiru pre njega. Pored ove zbirke objavljuje i zbirke pesama „Pevanija", „Snohvatice" i „Devesilje", pozorišni komad „Šaran", a bavi se i prevođenjem Petefija, Getea, Ljermontova [15, 16].

Zmaj, rodoljub i satiričar, iako predstavljen kao romantičar, posedovao je realističan i kristalno jasan duh. Ono o čemu je pisao jeste stvarno, razumljivo, zdravo, a o svojim pesmama Zmaj šalje veliku rodoljubivu poruku svom narodu. Osećajan i obrazovan, pametan i nežan, sa ogromnom tugom u srcu zbog sopstvene nesreće, Zmaj postaje „Čika Jova", jer peva srpskoj deci i za srpsku decu. Budući lekar i etičar, Zmaj pribegava jednom moćnom lekovitom oružju (učinku), a to je dečja poezija vaspitnog karaktera, ali i izuzetne književne vrednosti [16]. On širi ideje higijene i dezinfekcije, postavlja osnove epidemiologije, sve vreme negujući nežna dečja osećanja. Kao dečji psiholog, peva deci o onome što vole, savetuje ih, razume, ponekad kudi i ulazi u tančine dečjeg sveta. U tome je nenadmašan [14, 15]. Lekar u njemu istrajavao je u principu da je najpreče

pomoći bolesniku, pa je siromašne od početka lečio besplatno. Besplatno je vodio sanitarni nadzor u školama, a u saradnji sa desetak svojih kolega osnovao je prvu ambulantu u Srbiji. Za vreme lekarskog staža u Beču od 1880. do 1889. omogućuje lečenje Srba kod austrijskih specijalista [13–15].

Zmaj je radio i kao dramaturg Narodnog pozorišta u Beogradu (od 1878. do 1880), bavio se politikom i podržavao Ujedinjenu omladinu srpsku. Prilikom osnivanja Srpske književne zadruge 1892, Jovan Jovanović Zmaj izabran je za potpredsednika, a nacrtao je i znak Zadruge. Manje je poznato da se Zmaj u časopisima koje je uređivao, pojavljivao pod oko 500 pseudonima zbog nedostatka saradnika, zatim da je izgubio svoju prvu štampanu pesmu „Srpska zora“, a najmanje je poznato da se vrlo uspešno bavio provodadžisanjem. Od 1880, pa sve do smrti 3. juna, 1904, uređuje svoj deci poznati časopis „Neven“. Sremska Kamenica u kojoj je preminuo, nosila je jedno vreme ime Zmajeva Kamenica [16].

Kada ga je očev prijatelj Sima Milutinović Sarajlija blagoslovio željom da postane pesnik, tada dečak Jovan nije ni slutio da će postati jedan od najvećih pesnika XIX veka, pesnika dečje duše. Da li je doktor u njemu predvideo pesnika ili obrnuto ostaće tajna, tek Čika Jova Zmaj je pesmama lečio, vaspitavao, veselio i savetovao decu, a čini to i danas.

Dr Mihailo (Radmio) Lazarević – lekar, književnik i naučni radnik

Veliki doprinos razvoju i unapređenju zdravstvene službe, kao i književnom radu, dao je i poznati lekar i književnik 19. veka, dr Mihailo Radmio Lazarević.

Mihailo Lazarević (slika 4), rođen je 1846. u Beogradu. Završio je medicinu u Beču, da bi, nakon dolaska u Srbiju, počeo da se bavi privatnom praksom i prvi među tadašnjim lekarima posvetio se pedijatriji. Zaposlio se kao garnizonski lekar u Beogradu 1874, a upravljao je i Ratnom bolnicom u manastiru Sv. Roman kod Đunisa u toku srpsko-turskih ratova 1876–1878.

Sl. 4 – Mihailo (Radmio) Lazarević (1846–1899)

Nakon toga postavljen je za komandira Okružnog sanitetskog odeljenja smederevske vojske. Po napuštanju vojne službe 1894. okreće se ponovo svom lekarskom pozivu i nastavlja sa uspešnom lekarskom privatnom praksom. Na unapređenju zdravstvene službe u Srbiji radi intenzivno od 1895. kada je postavljen za načelnika saniteta u Ministarstvu unutrašnjih poslova.

Uporedo sa lekarskim radom, započeo je, a po odlasku u penziju, i nastavio da se bavi i naučnim radom, naročito u oblasti entomologije. Veliki broj radova objavio je u časopisima „Srpski arhiv“ i „Narodno zdravlje“, a uglavnom su se ticali dečijih i infektivnih bolesti, ali i vojnosanitetskih tema. Njegov doprinos književnosti ogleda se u objavljivanju velikog broja poetskih radova koje je pisao pod pseudonimom Radmio-Radmilo. Književnim radom se bavio još od mladićkih dana, kao član Ujedinjene srpske omladine, šezdesetih godina 19. veka.

Manje je poznato da je tri rada o dnevnim leptirima iz okoline Beograda pred kraj 19. veka na srpskom jeziku objavio upravo dr Mihailo Lazarević [17].

Preminuo je 1899. u Beogradu, ostavivši iza sebe bogat opus naučnih radova i dela, kao i poetskih sastava kojima je dao doprinos kako medicini, tako i književnosti 19. veka.

Dr Vladan (Hipokrat) Đorđević – lekar, reformator, književnik i političar

Govoreći o životu i delu dr Vladana Đorđevića, kao ličnosti koja je obeležila 19. vek u Srbiji, kako svojim lekarskim profesionalizmom, tako i plodnim književnim radom, prosto je nemoguće u navođenju njegovih zasluga ne spomenuti bar neke zasluge, jer ih je zaista bilo u velikom broju. Naime, svestran i sistematičan, uporan i u svuda prisutan, obavljao je niz značajnih funkcija tokom svoga života.

Vladan Hipokrat Đorđević (slika 5), rođen je 1844. u Beogradu, nekadašnjoj Gospodskoj, danas Vasinoj ulici. Otac Đorđe, narodni lekar, poreklom iz Epira, oženio se Ma-

Sl. 5 – Vladan (Hipokrat) Đorđević (1844–1930)

rijom iz cincarske porodice Leko, koja se tridesetih godina 19. veka doselila u Beograd i koja je umrla kada je Vladan imao samo sedam godina. Pri krštenju u Sabornoj crkvi, svome kumčetu kir German je nadenuo ime Hipokrat koje je izgleda postalo njegova sudbina, a koje je zbog neprihvatanja u srpskoj sredini i na savet Đure Daničića, po upisivanju na Licej, promenio u Vladan. Ovo je ime izgledalo „narodnije“, a značilo je prevod drugog dela Hipokratovog imena, tj. *kratia* na grčkom vladavina [18].

Po smrti majke odlazi sa ocem u Sarajevo, gde otac otvara apoteku i gde Vladan završava srpsku školu. Potom upisuje

gimnaziju u Beogradu, kada i objavljuje svoje prve radove „Robovi“ i „Sulejman“ kojima stupa u književni svet. Još kao đak bio je pokretač i sekretar Ujedinjene omladine srpske. Popularnost mu donosi roman „Kočina Krajina“, ali, ma koliko da se kreće u književnim krugovima, biva očaran naukom (veliki uticaj na njega imali su prof. Josif Pančić, kao i dr Stevan Mačaj). Odlučuje da studira medicinu i odlazi u Beč. Postaje najbolji student čuvenog hirurga Bilrota, prevodi Harltovu „Anatomiju čovečijeg tela“ i doktorira 1869. Po završenoj specijalizaciji vraća se u Beograd i postaje prvi školovani hirurg u Srbiji, usavršivši svoja znanja i tokom francusko-pruskog rata, kada je radio kao šef Vojne bolnice u Frankfurtu. Đorđević postaje izuzetno cenjen i imućan kao lekar što izaziva veliku zavist i sumnjičenja. Oženivši Paulinu, svoju ljubav iz Beča, uživajući u porodici sa mnogo dece kao uporištu „Đorđević seče skalpelom i jezikom“, pa ga postavljaju za majora i šefa Vojnog saniteta, kao i profesora hirurgije u Vojnoj akademiji. Preuzeo je i ulogu ličnog lekara kneza Milana, kao i učitelja budućeg kralja. Bio je među osnivačima Crvenog krsta Srbije, kao i jedan od osnivača Srpskog lekarskog društva 1872. a pokrenuo je i časopis „Srpski arhiv za celokupno lekarstvo“ 1874 [18, 19].

Objavljuje „Narodnu medicinu u Srba“ 1872. koja već tada skreće pažnju na mladog lekara punog entuzijazma, ukazujući na uticaj narodne medicine na život naroda uopšte. Đorđević govori o bajanju i lekovima „pozajmljenih iz carstva životinja“, o ranama, gde naš narod „dobro poznaje rane od puške i noža“, pa čak i o zapanjujućim uspešnim trepanacijama. Govori detaljno o transplantaciji, „nameštanju“ kostiju ali i o tome kako je narod bio sumnjičav prema školovanim doktorima, a veličao narodne lekare „jer narod vrlo zazire od ljudi koji dođu da ga ispituju za nešto“.

Stečeno znanje iz oblasti hirurgije Đorđević primenjuje u srpsko-turskim ratovima, radivši kao načelnik sanitetske službe moravsko-timočke vojske, a potom i vrhovne komande Srpske vojske. Prvi je upravljao Vojnom bolnicom u Nišu 1878, a postao je i načelnik civilnog saniteta Srbije.

Posle srpsko-bugarskog rata (1885. do 1886) gde je, takođe, radio kao načelnik sanitetske službe, postavljen je za poslanika u Atini, a 1894, radeći kao diplomata u Carigradu, izdejstvovao je mnoge povlastice za Srbiju.

Dr Đorđević je bio dopisni član Srpske kraljevske akademije, kao i predsednik Vlade i inostranih dela do 1900. Ostavku je podneo posle ženidbe kralja Aleksandra i proveo šest meseci u zatvoru 1906. zbog odavanja, kako su ga tada optužili, državnih tajni.

Njegov književni rad sadržavao je više žanrova: romane, drame i pripovetke, ali i istorijske teme, a ističu se: „Istorija srpskog vojnog saniteta“, istorijski roman „Car Dušan“, „Kraj jedne dinastije“, „Uspomene“. Bio je izdavač časopisa „Otadžbina“ od 1875. do 1892 [20, 21].

Veliki reformator, ličnost puna poleta, dr Vladan Đorđević umro je 1930. u Badenu. Ogromno kulturno, stručno i naučno nasleđe koje je ostavio Srbiji zadužilo je savremene lekare i ostavilo pečat srpskog lekara,intelektualca 19. veka.

Zaključak

Doprinos srpskih lekara Jovana Stejića, Laze Lazarevića, Jovana Jovanovića Zmaja, Mihaila Lazarevića i Vladana Đorđevića kulturi i medicini je izuzetan. Uvek na korak ispred svog vremena, bili su začetnici novih ideja iz kojih je proisteklo bogato nasleđe. Na savremenim lekarima je da ga očuvaju i dopune.

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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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Abbreviations and symbols

Use only standard abbreviations. Avoid abbreviations in the title and abstracts. The full term for which an abbreviation stands should precede its first use in the text.

Detailed Instructions are available at the web site:
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