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SADRŽAJ/CONTENTS

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TREND INCIDENCIJE I MORTALITETA OD KARCINOMA USANA, USTA, ŽDRELA I DRUGE LOKALIZACIJE U CENTRALNOJ SRBIJI U PERIODU OD 1999. DO 2020. GODINE

TREND OF INCIDENCE AND MORTALITY RATE OF OTHER AND ILL-DEFINED SITES OF LIP, ORAL CAVITY AND PHARYNX CANCER IN CENTRAL SERBIA FROM 1999 TO 2020

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Sažetak

Uvod: *Smrtnost izazvana karcinomom je visoka u razvijenim zemljama i u zemljama u razvoju, a očekuje se i da će trend oboljevanja rasti širom sveta, posebno u zemljama sa slabijim ekonomskim razvojem, gde živi oko 82% svetske populacije.*
Cilj *ovog istraživanja bio je da se predstave i procene trendovi incidencije, stope mortaliteta i MIR malignih neoplazmi drugih i nedefinisanih lokalizacija karcinoma usne, usne duplje i ždrela u centralnoj Srbiji od 1999. do 2020. godine.*
Materijal i metode: *Studija zasnovana na registru rađena je na osnovu podataka iz javno dostupnog Statističkog godišnjaka Instituta za javno zdravlje Srbije – Incidencija i mortalitet u centralnoj Srbiji, od 1999. do 2020. godine. Za izračunavanje trenda i godišnje procentualne promene (APC) korišćene su stope incidencije i mortaliteta sa odgovarajućim intervalima poverenja od 95%.*
Rezultati: *U centralnoj Srbiji je od 1999. do 2020. godine registrovano ukupno 558 slučajeva (436 kod muškaraca i 122 kod žena) drugih i nedefinisanih lokalizacija karcinoma usne, usne duplje i ždrela. Gruba stopa (CR) i starosno standardizovana stopa (ASR-V) incidencije kod muškaraca su porasle (p < 0,001, za oba) tokom perioda studije, sa APC od 4,8% i 9,0%, respektivno. Gruba stopa (CR) i starosno standardizovana stopa (ASR-V) mortaliteta kod muškaraca su se smanjile (p < 0,001, za oba) tokom perioda istraživanja, sa APC od -7,5%, -7,2%, respektivno. Smanjenje stope mortaliteta je praćeno padom MIR-a između 2001. i 2020. godine, sa APC od -5,6 (p < 0,001).*
Zaključak: *Naši rezultati pokazuju da je incidencija drugih i loše definisanih mesta raka usne, usne duplje i ždrela u centralnoj Srbiji porasla tokom perioda istraživanja. Stopa mortaliteta i MIR za ovaj karcinom smanjili su se tokom 22 godine.*

Ključne reči: *loše definisana mesta raka usne, usne duplje i ždrela; stopa incidencije; stopa mortaliteta; registar raka; trendovi*

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Abstract

Introduction*:Cancer is causing death in countries with more or less economic development, and it is expected that the burden will grow worldwide, especially in countries with less developed populations, where about 82% of the global population lives.*
The aim *of this study was to present and estimate trends in incidence, mortality rate and MIR of malignant neoplasm of otherand ill-defined sites of lip, oral cavity and pharynx cancer in Central Serbia from 1999 to 2020.*
Material and methods:*The registry-based study was conducted using the data from the publically accessible Yearbooks of the Institute of Public Health of Serbia: Incidence and Mortality in Central Serbia, from 1999 to 2020. Joinpoint regression was used to determine the trend and annual percentage change (APC) of the incidence and mortality rate with corresponding 95% confidence intervals.*
Results: *A total number of 558 cases (436men and 122women) of other and ill-defined lip, oral cavity and pharynx cancer sites registered in Central Serbia from 1999 to 2020.*
The crude rate (CR) and age-standardized rate (ASR-W) of incidence in males increased (p<0.001, for both) during the study period with APC of 4.8% and 9.0%, respectively. The crude rate (CR) and age-standardized rate (ASR-W) of mortality in males decreased (p<0.001, for both) during the study period with APC of -7.5%, and -7.2%, respectively. The mortality rate decrease was followed by the decline in MIR between 2001 and 2020 with anAPC of -5.6 (p<0.001).
Conclusions: *Our results reveal that the incidence of other and ill-defined lip, oral cavity and pharynx cancer sites in Central Serbia increased through the study period. The mortality rate and MIR for this cancer decreased during 22 years.*

Key words: *ill-defined sites of lip, oral cavity and pharynx cancer; incidence rate, mortality rate, cancer registry, trends*

Uvod

Smrtnost izazvana karcinomom je visoka u razvijenim zemljama i u zemljama u razvoju, a očekuje se i da će trend oboljevanja rasti širom sveta, posebno u zemljama sa slabijim ekonomskim razvojem, gde živi oko 82% svetske populacije. Usvajanje stilova života za koje se pokazalo da povećavaju rizik od karcinoma, uključujući pušenje, lošu ishranu i fizičku neaktivnost, povećalo je opterećenje oboljevanjem od karcinoma u slabije razvijenim zemljama[1]. Oboljevanje od orofacijalnih karcinoma jeste jedan od glavnih javnozdravstvenih problema na globalnom nivou. U 2012. godini karcinom usne duplje i orofarinksa bio je šesti najčešći karcinom među muškarcima u Evropi (standardizovana stopa – ASR: 18,8/100.000), dok je među ženama rangiran na 16. mestu (ASR: 4,9/100.000) (EUCAN)[2]. U 2012. godini procenjeno je 300.400 novih slučajeva oralnih karcinoma (uključujući i karcinom usne) i 144.540 smrtnih slučajeva širom sveta. Najveće stope javljaju se u Maleziji, Južnoj i Centralnoj Aziji i Centralnoj i Istočnoj Evropi, dok su najniže u Zapadnoj Africi i Istočnoj Aziji[1].

Ipak, u poslednjih nekoliko decenija incidencija oralnog karcinoma značajno je smanjena kod oba pola u Aziji, Severnoj Americi i Australiji, kao i u Južnoj i Zapadnoj Evropi[3]. Pušenje, konzumiranje alkohola i HPV infekcija glavni su faktori rizika za oralni karcinom; pritom, kombinacija konzumiranja cigareta i alkohola pokazuje sinergističke efekte[4]. Doprinos faktora rizika opterećenju od oboljevanja karcinoma razlikuje se u različitim regionima sveta[5]. Procenjuje se da pušenje ima doprinos u skoro tri četvrtine smrtnih slučajeva od karcinoma oralne regije (uključujući ždrelo) u zemljama sa visokim ekonomskim razvojem, odnosno u 37% smrtnih slučajeva u zemljama sa niskim i srednjim ekonomskim razvojem. Konzumiranje alkohola utiče približno na jednu trećinu smrtnih slučajeva u razvijenim zemljama i na jednu sedminu smrtnih slučajeva u nisko i srednje razvijenim zemljama[6]. Utvrđeno je da je učestalost novih slučajeva veća ukoliko se konzumiraju duvan i alkohol zajedno, što ukazuje na multiplikovanje efekata ova dva faktora rizika kao karcinogena oralne šupljine / ždrela[7]. Učestalost konzumiranja duvana porasla je u mnogim zemljama Istočne i Severne Evrope, kao i među ženama u Južnoj i Zapadnoj Evropi[3]. Ovi podaci su u suprotnosti sa trendom opadanja u svim uzrastima, primećenom kod muškaraca i žena u mnogim drugim razvijenim zemljama, u kojima je

Introduction

Cancer is causing death in countries with more or less economic development, and it is expected that the burden will grow worldwide, especially in countries with less developed populations, where about 82% of the global population lives. Adopting a lifestyle that has been shown to increase the risk of cancer, including smoking, eating poorly, and physical inactivity, has increased the burden of cancer in less developed economies[1]. Orofacial cancer is one of the major concerns when it comes to public health on a global scale. In 2012, cancers of the oral cavity and oropharynx were the sixth-most common cancer among men in Europe (Ages standardized rate (ASR): 18.8/100000] while in the case of women, they were ranked 16th (ASR: 4.9/100 000) (EUCAN)[2]. In 2012, there were estimated 300,400 new cases of oral cancer and 144,540 deaths worldwide (including cancer of the lip). The highest rates occur in Melanesian, South Central Asia, and Central and East Europe, while the lowest rates are in West Africa and East Asia[1].

In the past few decades, the incidence of oral cancer has significantly decreased among male and female patients in Asia, Northern America, and Australia, as well as between male and female patients in southern and Western Europe, respectively[3]. Smoking, alcohol consumption, and infection by HPV are the main risk factors for oral cancer, and the combination of cigarettes and alcohol has synergistic effects[4]. The contribution of all of these risks to burden differs in different regions of the world[5]. Smoking is estimated as contributing to almost three-quarters of deaths from oral cancer (including the pharynx) in countries with high incomes and as contributing to 37% of death in countries with low and middle incomes, while alcohol accounts for approximately one-third of deaths, and one-seventh of deaths, respectively[6]. The association between tobacco and alcohol is stronger among smokers than non-smokers, indicating an over-multiplication effect of smoking and alcohol on oral/pharynx carcinogens[7]. The rate of tobacco consumption has increased in many countries of Eastern and Northern Europe, as well as among women in Southern and Western Europe[3]. This contrasts to the decreasing trend in all ages, which has been observed in males as well as females of many other developed countries where the epidemic of tobacco began earlier and was declining.

epidemija duvana počela ranije i trenutno opada. Dodatno, stope incidencije oralnih karcinoma povezanih sa HPV infekcijom (npr. orofilaksa, krajnici i dno jezika) u nekim zemljama su povećane, što, delimično, može biti posledica promena u oralnom seksualnom ponašanju[8].

Nekoliko faktora može uticati na promenu trenda mortaliteta – promena u prevalenciji izloženosti ključnim faktorima rizika za datu bolest, dostupnost dijagnostike i rane dijagnoze i pristup ranoj dijagnozi[7,9]. U tom kontekstu, u Srbiji su uočene značajne varijacije u poslednjih trideset godina. Prethodna istraživanja analizirala su trend mortaliteta od karcinoma orofarinksa (OPC) u Srbiji[10,11]. Međutim, nedostaju ažurirana istraživanja o trendovima incidencije i mortaliteta od karcinoma usana, usta, ždrela i druge lokalizacije u centralnoj Srbiji (idLOP). U okviru analize trenda oboljevanja i smrtnosti od nekog karcinoma, preporučljivo je paralelno proceniti preživljavanje. U tu svrhu može se koristiti i analizirati odnos mortalitet–incidencija (MIR)[12]. Stoga je cilj ove studije bio da se prezentuju i procene trendovi incidencije, stope mortaliteta i MIR karcinoma usana, usta, ždrela i druge lokalizacije u centralnoj Srbiji od 1999. do 2020. godine.

Cilj ovog istraživanja bio je da se predstave i procene trendovi incidencije, stope morta-liteta i MIR malignih neoplazmi drugih i nedefinisanih lokalizacija karcinoma usne, usne duplje i ždrela u centralnoj Srbiji od 1999. do 2020. godine.

Materijal i metode

U ovom istraživanju korišćeni su podaci dobijeni iz javno dostupnog registra kancera. Incidencija i mortalitet od raka u centralnoj Srbiji, koji je Institut za javno zdravlje Srbije objavio za period od 1999. do 2020. godine; tu su incidencija i mortalitet prikazani prema polu i starosnoj strukturi i prema dijagnozi. Standardizovane stope incidencije i mortaliteta izračunate su na osnovu ovih podataka za oba pola. Karcinom usana, usta, ždrela i druge (idLOP) lokalizacije kodiran je prema Međunarodnoj klasifikaciji bolesti – deseta revizija (MKB-10) – kao C14. Odnos mortaliteta i incidecnije (MIR) dobijen je deljenjem stope mortaliteta i incidencije i deljenjem standardizovane stope mortaliteta i standardizovane stope incidencije za svaku godinu. Za analizu trenda korišćena je Joinpoint regresiona analiza, pri čemu se izračunavala godišnja procentualna promena (APC) incidencije, mortaliteta i MIR-a sa 95% intervalom poverenja (95% CI).

However, in some countries, the incidence rates of oral cancers related to the HPV infection (e.g., orophylaxis, tonsils, and the base of tongue) have increased, which may be partly due to the changes in the oral sexual behaviour[8]. Several factors may affect the trend in mortality rates such as the change in prevalence of the exposure to key risk factors for the disease, availability of diagnostics and early diagnosis, and the access to early diagnosis[7;9]. In the context of Serbia, significant variations have been observed in the context of the last decade of the twenty-first century.

Previous literature has reported trends in oropharyngeal cancer (OPC) mortality in Serbia[10,11]. However, there is a lack of updated research on the incidence and mortality trends of other and ill-defined sites in the lip, oral cavity and pharynx in Central Serbia (idLOP). It is recommendable to estimate survival together with incidence and mortality. For that purpose, it can be used and analyzed mortality-incidence ratio (MIR)[12]. Therefore, the aim of this study was to present and estimate trends in incidence, mortality rate and MIR of malignant neoplasm of other and ill-defined sites in the lip, oral in Central Serbia from 1999 to 2020.

The aim of this study was to present and estimate trends in incidence, mortality rate and MIR of malignant neoplasm of other and ill-defined sites of lip, oral cavity and pharynx cancerin Central Serbia from 1999 to 2020.

Material and methods

Publicly available Yearbooks of the Institute of Public Health of Serbia: Incidence and Mortality in Central Serbia, from 1999 to 2020, were used to extract data for the registry-based study. Extracted data consisted of the incidence and mortality rates aggregated and stratified by gender, 5-year age groups, and diagnosis. Malignant neoplasm of other and ill-defined sites in the lip, oral cavity, and pharynx(idLOP) was coded according to the tenth Revision of the International Classification of Disease (code C14)[13]. Mortality to incidence ratio (MIR) was calculated as a ratio of the crude mortality rate and crude incidence rate for each year. Joinpoint regression analysis calculated the trend and the annual percentage change (APC) of the incidence and mortality rate with corresponding 95% confidence intervals (95%CI). The optimal number of joinpoints was identified using the Monte Carlo permutation method. For trend analyses, the Joinpoint Regression Program version 4.1.0 was used (available at

Optimalan broj prelomnih tačaka dobijen je metodom Monte Karlo permutacije. Za analizu trenda korišćen je programski paket Joinpoint Regression Program, verzija 4.1.0 (dostupan na linku: http://surveil- lance. cancer.gov/joinpoint). Nulta hipoteza testirana je sa pragom značajnosti $p < 0,05$.

Rezultati

U centralnoj Srbiji je u periodu od 1999. do 2020. godine registrovano ukupno 558 novoobolelih slučajeva karcinoma usana, usta, ždrela i druge lokalizacije (436 muškarca i 122 žene) (Tabela 1). Odnos muškaraca prema ženama je 3,6 : 1. Najviše novoobolelih bilo je starosti od 40 do 65 godina – 53,2% kod muškaraca i 46,7% kod žena. Ukupan broj umrlih u periodu obuhvaćenom ispitivanjem iznosio je 480 slučajeva (391 umrli muškarac i 89 umrlih žena) od idLOP-a registrovanih u centralnoj Srbiji od 1999. do 2020. godine (Tabela 2). Najviše umrlih bilo je starosti od 40 do 65 godina – 83,4% kod muškaraca, odnosno 42,7% kod žena.

U Tabeli 3 predstavljena je opšta (CR) i standardizovana stopa incidencije i mortaliteta (ASR-W, prema svetskoj populaciji) od idLOP-a. Najveće CR i ASR-W incidencije kod muškaraca bile su 1999. i 2017. godine (1,4, 0,9, odnosno 0,8), a najniže vrednosti tih stopa bile su 2005. godine (0,3, odnosno 0,1). Kod muškaraca, CR i ASR-W stope mortaliteta bile su najveće 2001. godine (1,2, odnosno 0,7), a najniže 2011. godine (0,3, odnosno 0,2). Kod žena, najveće vrednosti CR i ASR-W incidencije bile su 2012. godine (0,5, odnosno 0,2), a najniže vrednosti tih stopa bile su 2010. i 2011. godine (0,0, odnosno 0,0). Kod žena, vrednosti CR i ASR-W stope mortaliteta bile su veoma niske između 1999. i 2020. godine – u rasponu od 0,0 do 0,3.

Zbog male učestalosti karcinoma kod žena, regresiona analiza urađena je samo za pripadnike muškog pola. Analiza trenda incidencije idLOP-a kod muškaraca pokazala je značajno povećanje trenda između 2001. i 2017. godine, sa APC od 4,8% (95% CI 1,1% – 8,7%; $p < 0,001$). Standardizovana stopa incidencije kod muškaraca pokazala je značajno povećanje trenda između 2005. i 2015. godine, sa APC od 9,0% (95% CI 1,3% – 17,2%; $p < 0,001$) (Grafikon 1). Opšta stopa mortaliteta od idLOP-a kod muškaraca pokazala je statistički značajan trend opadanja vrednosti između 1999. i 2010. godine, sa APC -7,5 (95% CI od -14,3 do -0,2; $p < 0,001$). Standardizovana stopa mortaliteta od idLOP-a kod muškaraca pokazala je značajan trend smanjenja tokom

http: //surveillance.cancer.gov/joinpoint). The trend was considered to be significantly changing when the p-value was below 0.05 ($p < 0.05$).

Results

A total of 558 cases (436 males and 122 females) of other and ill-defined lip, oral cavity and pharynx sites were registered in Central Serbia from 1999 to 2020 (Table 1). The men to women ratio was 3.6:1. Most new cases were aged 40–65 years in males (53.2%) and females (46.7%). The total number of deaths in a specific period was 480 cases (391 deaths in males and 89 deaths in females) of other ill-defined lip, oral cavity and pharynx sites registered in Central Serbia from 1999 to 2020 (Table 2). Most deaths were aged 40-65 in males (83.4%) and in females (42.7%).

Table 3 presents the distribution of idLOPby age and the crude rate of incidence and mortality, the age-standardized incidence and mortality rate (ASR-W; to the world population) and mortality to an incidence rate (MIR) to the specified rates according to the years of observation. The highest CR and ASR-W of incidence in males were in 1999 and 2017 (1.4, 0.9 and 0.8, respectively), and the lowest values of those rates were in 2005 (0.3, 0.1, respectively). In males, the CR and ASR-W of the mortality rate were highest in 2001 (1.2, 0.7, respectively) and lowest in 2011 (0.3, 0.2, respectively). In females, the highest CR and ASR-W of incidence were in 2012 (0.5, 0.2, respectively), and the lowest values of those rates were in 2010 and 2011 (0.0, 0.0, respectively). In females, the CR and ASR-W of mortality rate were very low between 1999–2020, in the range of 0.0–0.3.

Joinpoint regression analysis was performed only in males due to small rates in females. Joinpoint analysis of the crude incidence rate of idLOPin males showed a significantly increasing trend between 2001 and 2017 with APC4.8% (95%CI 1.1–8.7%, $p<0.001$). The age-standardized incidence rate in males showed a significantly increasing trend between 2005 and 2015, with APC 9.0% (95%CI 1.3 – 17.2%, $p<0.001$) (Figure 1). Crude mortality ratesof LOPnsin males showed asignificantly decreasing trend between 1999 and 2010with APC -7.5 (95%CI -14.3 - -0.2, $p<0.001$). The age-standardized mortality rate of idLOP in males showed a significantly decreasing trend during the period from 1999 to 2010 with APC -7.2% (95%CI -13.7 - -0.1, $p<0.001$) (Figure 2).

perioda od 1999. do 2010. godine, sa APC -7,2% (95% CI od -13,7 do -0,1; p < 0,001) (Grafikon 2). MIR je kod muškaraca pokazao značajan trend opadanja u periodu između 2001. i 2020. godine (APC -5,6, 95% CI od -9,2 do -1,8; p < 0,001) (Grafikon 3)

The MIR in males showed a significantly downward trend between 2001 and 2020 (APC -5.6, 95%CI -9.2 – -1.8, p<0.001) (Figure 3).

Tabela 1. Broj novoregistovanih pacijenata obolelih od nespecifičnog karcinoma usana, usta i farinksa podeljen na osnovu pola i starosti i odnos obolelih muškaraca i žena u centralnoj Srbiji od 1999. do 2020. godine

Table 1. Total number of new cases of other ill-defined sites of lip, oral cavity and pharynx cancer by age and gender, and M/F ratio in Central Serbia, between 1999-2020.

Period	Males				Females				M/F ratio
	Total	< 40	40-65	65+	Total	< 40	40-65	65+	
2020	31	0	9	22	11	1	2	8	2.8
2019	22	1	7	14	6	0	0	6	3.7
2018	16	0	7	9	7	0	2	5	2.3
2017	49	0	27	22	11	0	8	3	4.5
2016	32	0	19	13	6	0	3	3	5.3
2015	31	2	15	14	4	2	2	0	7.8
2014	15	0	8	7	7	0	4	3	2.1
2013	17	0	10	7	4	0	1	3	4.3
2012	18	0	9	9	13	0	7	6	1.4
2011	10	1	6	3	4	0	1	3	2.5
2010	13	0	6	7	1	0	1	0	13.0
2009	17	0	10	7	9	0	7	2	1.9
2008	12	0	4	8	6	0	3	3	2.0
2007	14	0	8	6	2	0	1	1	7.0
2006	18	0	11	7	2	1	0	1	9.0
2005	7	0	1	6	1	0	1	0	7.0
2004	18	1	15	2	5	0	3	2	3.6
2003	10	0	4	6	5	2	3	0	2.0
2002	12	0	8	4	2	1	1	0	6.0
2001	10	1	7	2	9	0	4	5	1.1
2000	27	0	15	12	2	0	1	1	13.5
1999	37	0	26	11	5	0	2	3	7.4
Total	436	6	232	198	122	7	57	58	3.6

Tabela 2. Broj pacijenata umrlih od nespecifičnog karcinoma usana, usta i farinksa podeljen na osnovu pola i starosti i odnos obolelih muškaraca i žena u centralnoj Srbiji od 1999. do 2020. Godine

Table 2. Total number of deaths of other ill-defined sites of lip, oral cavity and pharynx cancer by age and gender, and M/F ratio in Central Serbia, between 1999-2020

Period	Males				Females				M/F ratio
	Total	< 40	40–65	65+	Total	< 40	40–65	65+	
2020	19	0	11	8	5	0	1	4	3.8
2019	12	0	6	6	0	0	0	0	-
2018	13	0	4	9	4	0	1	3	3.3
2017	26	0	14	12	3	0	1	2	8.7
2016	31	0	18	13	4	0	2	2	7.8
2015	21	0	14	7	2	0	3	0	10.5
2014	14	0	10	4	2	0	2	0	7.0
2013	9	0	8	1	3	0	1	2	3.0
2012	11	0	3	8	5	0	2	3	2.2
2011	9	0	4	5	6	0	1	5	1.5

2010	9	0	6	3	3	0	1	2	3.0
2009	9	0	5	4	0	0	0	0	-
2008	14	0	5	9	6	0	2	4	2.3
2007	19	0	9	10	6	1	0	5	3.2
2006	28	0	15	13	7	0	3	4	4.0
2005	16	0	12	4	2	1	1	0	8.0
2004	22	3	11	8	6	0	4	2	3.7
2003	18	0	10	8	3	0	1	2	6.0
2002	16	0	7	9	4	0	3	1	4.0
2001	31	0	17	14	9	1	3	5	3.4
2000	30	0	13	17	2	0	1	1	15.0
1999	14	1	9	4	7	1	5	1	2.0
Total	391	4	211	176	89	4	38	48	4.4

Tabela 3. Broj novoregistovanih pacijenata, stopa incidencije i mortaliteta i standardizovana stopa incidecnije i mortaliteta nespecifičnog karcinoma usana, usta i farinksa u Centralnoj Srbiji od 1999 do 2020.godine

Table 3. Crude rate, ASR-W of incidence and mortality and mortality to incidence ratio of other ill-defined sites of lip, oral cavity and pharynx cancer, by gender in Central Serbia from 1999-2020

	Males						**Females**					
Period	Incidence		Mortality		MIR of CR	MIR of ASR	Incidence		Mortality		MIR of CR	MIR of ASR
	CR	ASR-W	CR	ASR-W			CR	ASR-W	CR	ASR-W		
2020	0.9	0.4	0.6	0.3	0.67	0.75	0.3	0.1	0.1	0.0	0.33	0.00
2019	0.7	0.3	0.4	0.2	0.57	0.67	0.2	0.0	0.0	0.0	0.00	
2018	0.5	0.2	0.4	0.2	0.80	1.00	0.2	0.1	0.1	0.0	0.50	0.00
2017	1.4	0.8	0.8	0.4	0.57	0.50	0.3	0.2	0.1	0.0	0.33	0.00
2016	0.9	0.5	0.9	0.5	1.00	1.00	0.2	0.1	0.1	0.0	0.50	0.00
2015	1.2	0.7	0.8	0.5	0.67	0.71	0.1	0.1	0.1	0.0	1.00	0.00
2014	0.6	0.3	0.5	0.3	0.83	1.00	0.3	0.1	0.1	0.1	0.33	1.00
2013	0.7	0.4	0.4	0.2	0.57	0.50	0.1	0.1	0.1	0.0	1.00	0.00
2012	0.7	0.4	0.4	0.3	0.57	0.75	0.5	0.2	0.2	0.1	0.40	0.50
2011	0.4	0.3	0.3	0.2	0.75	0.67	0.1	0.1	0.2	0.1	2.00	1.00
2010	0.5	0.3	0.3	0.2	0.60	0.67	0.0	0.0	0.1	0		
2009	0.7	0.4	0.3	0.2	0.43	0.50	0.3	0.2	0.0	0.0	0.00	0.00
2008	0.5	0.3	0.5	0.3	1.00	1.00	0.2	0.1	0.2	0.1	1.00	1.00
2007	0.5	0.3	0.7	0.4	1.40	1.33	0.1	0.0	0.2	0.1	2.00	
2006	0.7	0.4	1.1	0.6	1.57	1.50	0.1	0.0	0.3	0.1	3.00	
2005	0.3	0.1	0.6	0.4	2.00	4.00	0.0	0.0	0.1	0.1		
2004	0.7	0.5	0.8	0.5	1.14	1.00	0.2	0.1	0.2	0.1	1.00	1.00
2003	0.4	0.2	0.7	0.4	1.75	2.00	0.2	0.2	0.2	0.0	1.00	0.00
2002	0.5	0.3	0.6	0.3	1.20	1.00	0.1	0.1	0.1	0.1	1.00	1.00
2001	0.4	0.3	1.2	0.7	3.00	2.33	0.3	0.2	0.3	0.2	1.00	1.00
2000	1	0.6	1.1	0.7	1.10	1.17	0.1	0.0	0.1	0.0	1.00	
1999	1.4	0.9	0.5	0.4	0.36	0.44	0.2	0.1	0.2	0.2	1.00	2.00

CR – crude rate ASR-W – the age-standardized rate

Tabela 3. Analiza trenda incidencije i mortaliteta nespecifičnog karcinoma usana, usta i farinksa u Centralnoj Srbiji u periodu od 1999 do 2020.godine
Table 3. Joinpoint analysis of the trend in the crude rate, ASR-W of incidence and mortality rate and MIR of other and ill-defined sites of lip, oral cavity and pharynx cancer, by gender in Central Serbia from 1999-2020

	Period	APC	95%CI	p
Incidence - Crude rate	1999-2001	-49.0	-78.2-19.7	0.100
	2001-2017	4.8*	1.1-8.7	<0.001
	2017-2020	-5.9	-38.6-44.1	0.800
Incidence - ASR -W	1999-2001	-41.3	-73.5-30.1	0.200
	2001-2005	-8.6	-38.6-36	0.600
	2005-2015	9.0*	1.3-17.2	<0.001
	2015-2018	-15.8	-61.9-86.5	0.600
	2018-2020	8.2	-51.1-139.6	0.800
Mortality - Crude rate	1999-2010	-7.5*	-14.3--0.2	<0.001
	2010-2020	4.3	-4.5-13.9	0.300
Mortality - ASR -W	1999-2010	-7.2*	-13.7--0.1	<0.001
	2010-2020	1.7	-6.6-10.6	0.700
MIR male	1999-2001	84.1	-51-591.8	0.300
	2001-2020	-5.6*	-9.2--1.8	<0.001

* indicates that the Annual Percent Change (APC) is significantly different from zero at the alpha =0.05 level, 95%CI – 95% confidence interval, trend for incidence, and mortality rate for females wasn't calculated

Diskusija

Naša studija utvrdila je da je stopa incidencije idLOP-a kod muškaraca u Srbiji povećana u periodu od 2005. do 2015. godine. Smrtnost od LOPns-a kod muškaraca pokazala je opadajući trend između 1999. i 2010. godine. Pored toga, ovaj trend prati i pad MIR-a kod muškaraca između 2001. i 2020. godine. U periodu obuhvaćenom istraživanjem, incidencija i stope mortaliteta kod žena bile su veoma niske i stabilne. Rezultati povećanja stope incidencije koherentni su i sa podacima zbirno objavljenim za karcinome ždrela (C09–C10, C12–C14) u Beogradu od 1999. do 2010. godine[11]. Ako se trend incidencije uporedi sa svetskim trendom incidencije orofaringealnog karcinoma, mogu se uočiti slični obrasci[14]. U ovoj studiji[14] oktriveno je da su slučajevi orofaringealnig karcinoma česti u razvijenim zemljama, među pripadnicima oba pola i među mlađom populacijom (starost manja od 60 godina). Literatura iz većine zemalja širom sveta pokazuje da je stopa oralnog karcinoma najmanje dva puta veća kod muškaraca nego kod žena starosti od 15 do 19 godina[15-19], što je i našom studijom za idLOP potvrđeno. Naši rezultati pokazuju da je ovaj karcinom bio čest kod muškaraca starijih od 40 godina, kao i da je, u proseku, polovina pacijenata imala između 40 i 65 godina.

Discussion

The temporal trend of incidence rates of idLOP in males in Serbia increased during the period of 2005–2015. The mortality of LOPns in males showed a decreasing trend between 1999 and 2010. In addition, this trend is followed by the decline of MIR in males between 2001 and 2020. In the study period, the incidence and mortality rates in females were very low and stable. The significantly increased incidence rate results are also coherent with the data published for pharyngeal cancers (C09-C10, C12-C14) in Belgrade from 1999 to 2010[11]. If we compare the incidence trend with the worldwide trend in the incidence of oropharyngeal cancer similar patterns can be noticed[14]. This study [14] revealed that OPC cases are common in developed countries, among both genders and in younger populations (age < 60 years). The literature from most countries worldwide demonstrates that the rate of oral cancer is at least twice as high in males than in females[15-19], as we confirmed in our study for the idLOP. This cancer was common in males over 40 years, and on average half of the patients were between 40-65 years. This observation suggests that sex and age should be taken into consideration as factors increasing the risk of developing idLOP.

Ovakvi nalazi treba da ukažu na to da se pol i starost razmatraju kao faktori koji povećavaju rizik od razvoja idLOP-a.

Nedavno istraživanje u Srbiji pokazalo je da je stopa mortaliteta od orofacijalnih karcinoma u našoj zemlji u sedamnaesto-godišnjoj analizi trenda stabilna[10]. Naši ažurirani podaci za idLOP pokazuju da su stope mortaliteta u opadanju između 1999. i 2010. godine. Slični rezultati prijavljeni su za istu MKB-10 dijagnozu u Brazilu za slični period praćenja, između 2002. i 2013. godine[20], i u SAD-u, za period između 1999. i 2020. godine[18]. Na smanjenje mortaliteta od karcinoma delom bi moglo uticati poboljšanje u definisanju specifičnih lokalizacija karcinoma ove regije. Smanjenje stope smrtnosti od idLOP-a, karcinoma koje je, kako se smatra, teško klinički ispitati, može biti posledica poboljšanog pristupa zdravstvenim ustanoyama i naprednim hirurškim metodama.

Životni stilovi su društveno strukturirani, a procene sugerišu na to da bi se gotovo 70% slučajeva karcinoma moglo izbeći zahvaljujući promenama u načinu života, koje se tiču pušenja, alkohola, ishrane i seksualnog ponašanja[21]. Nacionalni profil faktora rizika za orofacijalne karcinome, kojima pripada i idLOP, uključuje prekomerno pušenje, konzumaciju alkohola i visoku prevalenciju HPV infekcija. Srbija se još uvek smatra državom sa veoma visokom stopom pušenja[22], a efekti u smanjenju pušenja još nisu procenjeni[23]. Takođe, studije su pokazale da našu zemlju karakteriše prekomerna konzumacija alkohola u različitim populacijama[24-26].

Među mogućim faktorima rizika za nastanak karcinoma orofacijalne regije nalaze se HPV infekcije[27], kojima se poslednjih godina posvećuje posebna pažnja. Sa HPV infekcijom[28] se takođe povezuje predilekciona mesta na usni, usnoj duplji i ždrelu. Podaci iz novijih istraživanja pokazuju da u Srbiji postoji generalno visoka prevalencija HPV infekcije, kao i visoka prevalencija HPV-a, 16/18 kod žena sa zdravom kožom i normalnom citologijom u cervikalnoj šupljini[29,30], što ukazuje na to da bi HPV vakcinacija mogla biti primarna preventivna strategija u smanjenju karcinoma ove regije. Međutim, ona u našoj zemlji za sada nije deo obaveznog nacionalnog programa imunizacije[31]. Sve navedeno vezano za faktore rizika upotpunjuje sliku Srbije kao zemlje sa visokom učestalosti faktora rizika od pojave orofacijalnog karcinoma. Primena preventivnih mera sa ciljem smanjenja faktora rizika svakako može dati kumulativni efekat; ipak, efekti ovih mera ispoljavaju se tek nakon dugotrajnog perioda primene.

A recent analysis in Serbia showed that the mortality rate of orofacial cancers in our country in the 17-year trend analysis is stable [10]. Our study shows that mortality rates have been declining between 1999 and 2010. Similar results were reported for the same ICD-10 code in Brazil for a similar period, between 2002–2013[20] and in the US between 1999–2020[18]. The decline in this cancer group could also be affected by the improvement in defining the specific location of the death cause. The reduction in mortality rate in these cases, which are considered difficult to examine clinically, may be due to the increased access to healthcare facilities and advanced surgical methods.

Lifestyles are socially structured, and estimates suggest that nearly 70% of cases could be avoided through lifestyle changes such as smoking, alcohol, diet, and sexual behaviour[21]. National risk factors profilefor OPCcancers include excessive smoking, alcohol consumption and high HPV prevalence. Serbia is still considered to have an exceptionally high smoking rate[22], and the effects of tobacco control[23] haven't been estimated yet. Studies reported that our country is characterized by excessive alcohol consumption in different populations[24-26].

In the group of possible risk factors for OPC cancers, special attention was drawn to HPV infection[27]. Other and ill-defined sites in the lip, oral cavity,and pharynx[28] cancers are associated with HPV infection. Recent data show that, in Serbia, there is a high prevalence of HPV infection in general and 16/18 women with healthy skin and normal cytology in the cervical cavity[29]. These findings are consistent with the latest research[30]. Therefore, HPV vaccination can be a primary prevention strategy in reducing OPC generally, but in our country, this vaccine is not part of the mandatory national immunization program[31]. The facts mentioned above complete Serbia's image of a country with high levels of risk factors for OPC generally. However, these preventive measures may be able to alter or reduce the rates only for a long time since carcinogen factors have cumulative effects and a long-time delay. Also, considering the association between the impact of HPV immunization and the reduction of oropharyngeal cancer, estimation of lung cancer trends should be included.

The idLOP cancer is specific because the ICD-10 code C14 can be classified as oropharyngeal cancer (C14.0 and C14.2), but also includes overlapping lesions of lip, oral cavity, and pharynx.

Efekte imunizacije HPV vakcinom treba dodatno analizirati uz procenu trenda karcinoma pluća.

Ovaj tip karcinoma, označen prema MKB-10 kao C14, može se klasfikovati dvojako, kao karcinom orofaringsa (C14.0 i C14.2), ali takođe uključuje uznapredovale lezije usne, usne duplje i ždrela. Prijavljene stope incidencije za ovaj karcinom do 2007. godine bile su manje od stopa mortaliteta, što može ukazati na nedostatke u Nacionalnom registru karcinoma, jer je MIR za idLOP bio veći od 1. Ovaj pokazatelj može se višestruko analizirati. MIR se najpre može koristiti za procenu preživljavanja kod pacijenata sa idLOP-om[12]. Prema našim podacima, MIR za idLOP se kontinuirano smanjivao sa 2,33 u 2001. godini na 0,67 i 0,75 u 2019. i 2020. godini, s vrhuncem vrednosti od 4,00 u 2005. godini. Moguće je da je smanjenje od 5,6% u MIR-u idLOP-a pokazatelj boljeg preživljavanja ovog raka tokom dvadesetak godina. Glavni razlozi povećanja stope preživljavanja verovatno su opsežniji programi preventivnih pregleda i rano otkrivanje bolesti, kao i unapređenje znanja i stavova o strategijama u smanjenju preventibilnih faktora rizika i povećanje kvaliteta zdravstvene zaštite, koja se pruža pacijentima sa orofacijalnim karcinomima. Drugo, ukoliko sagledavamo vrednosti MIR-a u odnosu na vrednosti incidencije ovog tipa karcinoma[32], može se očekivati da je porast incidencije delom posledica poboljšanja kvaliteta Nacionalnog registra karcinoma. Konkretno, analiza nedovoljno definisanih lokalizacija karcinoma jedan je od značajnih pokazatelja kompletnosti Nacionalnog registra karcinoma[33]. Treće, pomenuta MKB-10 šifra klasifikovana je kao garbage dijagnoza sa umerenim uticajem na donošenje odluka javnozdravstvene politike[34]. Preterana upotreba garbage dijagnoza maskira pravi obrazac smrtnosti u jednoj populaciji. Stoga, na osnovu naših nalaza o povećanju stope incidencije idLOP-a i padu mortaliteta i MIR-a moglo bi se zaključiti da je prevalencija faktora rizika za orofacijalne karcinome visoka u našoj zemlji, da postoje određenja poboljšanja u kompletnosti registra karcinoma, kao i u popunjavanju potvrda o smrti tokom 22 godine.

Ograničenja studije

Postoji nekoliko mogućih ograničenja ove studije. Strategije prevencije raka proizlaze iz epidemioloških podataka; zato je vrlo važna procena kvaliteta registra raka.

Until 2007, the reported incidence rates were less than the mortality rates, meaning there were many gaps in the cancer registry, and diagnosis was delayed. The period before 2007 was characterized by the MIR of idLOP higher than 1. This indicator can be analyzed manifold. Firstly, the MIR can be used to indicate survival in idLOP patients[12]. According to our findings, the overall trend of idLOP MIR continuously decreased from 2.33 in 2001 to 0.67 and 0.75 in 2019 and 2020, with a peak in 2005 (4.00). Hopefully, the 5.6% reduction in MIR of idLOPis an indicator of improved survival from this cancer over 20 years. The main reasons for the increase in survival rates are probably more extensive screening programs and early detection of diseases, as well as the promotion of knowledge and attitudes about strategies in the reduction of modifiable risk factors and the promotion of improved care for patients with oral cancers. Secondly, if the incidence is related to the MIR of idLOP[32], we might expect a rise in incidence to be a consequence of improving cancer registry completeness. Particularly, the analysis of the ill-defined cancer site is a significant indicator of the completeness of the cancer registry[33]. Thirdly, this ICD-10 code is classified as garbage code with a medium impact on policy-making[34]. Excessive use of garbage codes masks the true mortality pattern. Therefore, according toour findings of an increase in the incidence rate of idLOP and a decline in mortality and MIR, it might be summarized that risk factors for orofacial cancers persist, but the completeness of the cancer registry and quality of death certificates improved over 22 years.

Limitations of the study

There are several possible limitations to this study. Strategies for cancer prevention are derived from the epidemiological data. Therefore, the level of quality of the cancer register is important. The quality of the cause of death data in Serbia has been rated moderately by the World Health Organization [35]. Also, moderate quality of death data can be assumed based on the percentage of unknown and ill-defined cancer deaths in our country[36]. The anatomical definition of cancer in this sector is usually not the same among studies, which makes comparisons of incidence, mortality, or survival challenging.

Svetska zdravstvena organizacija procenila je kvalitet podataka o uzrocima smrti u Srbiji kao umeren[35]. Takođe, umeren kvalitet naših mortalitetnih podataka može se potvrditi na osnovu udela nedovoljno definisanih stanja u ukupnom mortalitetu[36], te podatke dobijene iz registra treba analizirati sa određenom rezervom. Sem toga, anatomska klasifikacija karcinoma ove regije je heterogena u studijama, pa je poređenje rezultata vrlo izazovno.

Zaključak

Orofaringealni karcinomi mogu se u velikoj meri sprečiti kontrolom faktora rizika povezanih sa zdravim stilovima života. Analiza trenda stopa incidencije i mortaliteta od karcinoma od ključnog je značaja za epidemiološki nadzor karcinoma. Stope incidencije idLOP-a pokazale su porast, koji prate smanjena stopa smrtnosti i MIR-a u Srbiji između 1999. i 2020. godine. Ovi nalazi ukazuju na moguće poboljšanje kompletnosti i kvaliteta registra karcinoma. S druge strane, zemlje u razvoju prolaze transformaciju od zaraznih bolesti ka nezaraznim bolestima, što potencijalno upućuje na to da se deo porasta incidencije ovih karcinoma može pripisati i ovoj transformaciji[37]. Posledično, povećanje stope incidencije ukazuje na visoku prevalenciju faktora rizika, uglavnom pušenja i konzumiranja alkohola, što sugeriše na to da postoji potreba za kreiranjem nacionalne javnozdravstvene strategije sa ciljem smanjenja upotrebe alkohola i duvana.

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Conclusion

OPC cancers can be highly prevented by controlling the risk factors associated with a healthy lifestyle. Examining cancer incidence and mortality rates is critical for cancer epidemiology and surveillance. The cancer incidence rates for other and ill-defined sites in the lip, oral cavity, and pharynx showed a rise, followed by a decline in mortality rates and MIR in Serbia between 1999 and 2020. These findings imply possible improvement in completeness of cancer registry. On the other hand, developing countries underwent a transformation from infectious illnesses to noncommunicable diseases, potentially indicating that this rise can be attributable to the transition [37]. Subsequently, the high presence of risk factors, mostly smoking and drinking, suggests that public health initiatives should be taken at the national level. Those initiatives should be focused on cost-effective procedures to reduce alcohol and tobacco use.

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ANALIZA LIMFOCITARNOG INFILTRATA KAO PREDIKTIVNOG FAKTORA POJAVE METASTAZA NA VRATU KOD ORALNOG SKVAMOCELULARNOG KARCINOMA

ANALYSIS OF LYMPHOCYTIC INFILTRATE AS A PREDICTIVE FACTOR OF NECK METASTASES IN ORAL SQUAMOUS CELL CARCINOMA

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Sažetak

Uvod: *Karcinom pločasto slojevitog epitela usne duplje – oralni skvamocelularni karcinom (OSCC) – jeste invazivna patološka lezija epitela različitog stepena skvamozne diferencijacije, a odlikuje se ranim i ekstenzivnim metastazama, infiltracijom okolnih anatomskih struktura, pojavom učestalih recidiva i relativno niskom stopom petogodišnjeg preživljavanja, koja je manja od 50%.*
Cilj *ove studije je utvrđivanje korelacije između analize limfocitarnog infiltrata biopsijskih preparata sa patohistološki dokazanim metastazama oralnog skvamocelularnog karcinoma na postoperativnim preparatima disekata vrata.*
Materjali i metode*: Istraživanje je obuhvatilo 42 pacijenta koja su nakon patohistološke verifikacije oralnog skvamocelularnog karcinoma (OSCC) operisana na Odeljenju za maksilofacijalnu hirurgiju Klinike za dentalnu medicinu u Nišu u periodu od 2018. do 2022. godine. Histopatološka analiza podrazumevala je dubinu invazije tumora, histopatološku analizu limfnih nodusa disekata vrata, analizu limfocitarne infiltracije, prisustvo limfovaskularne i perineuralne invazije.*
Rezultati: *Utvrđeno je da se dubina invazije statistički značajno razlikuje u odnosu na stepen limfocitarne infiltracije (p = 0,004). Invazija preko 4 mm prisutna je kod 20,0% pacijenata sa visokom infiltracijom, kod 44,4% pacijenata sa srednjom infiltracijom i kod 85,7% pacijenata sa niskom infiltracijom.*
Zaključak*: Budući da rezultati studije ukazuju na to da analiza limfocitarnog infiltrata može biti pouzdan prediktivni faktor pojava metastaza u limfnim nodusima vrata, dalja istraživanja valja usmeriti ka povezivanju limfocitarne infiltracije i pojedinih biohemijskih i genetskih parametara na osnovu kojih se može stvoriti plan lečenja vrata N0 stadijuma oralnog skvamocelularnog karcinoma.*

Ključne reči: *limfocitarna infiltracija, oralni skvamocelularni karcinom, hirurško lečenje*

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Abstract

Introdudction: *Carcinoma of the stratified squamous epithelium of the oral cavity - oral squamous cell carcinoma (OSCC) is an invasive pathological lesion of the epithelium with varying degrees of squamous differentiation. It is characterized by early and extensive metastases, infiltration of adjacent anatomical structures, frequent recurrences, and a relatively low five-year survival rate of less than 50%.*
The aim *of the study to determine the correlation between the analysis of the lymphocytic infiltrate of biopsy specimens with pathohistologically proven metastases of oral squamous cellular carcinoma on postoperative neck dissection specimens.*
Material and methods: *The study included 42 patients with pathohistologically verified oral squamous cellular carcinoma who underwent surgery at the Department of Maxillofacial Surgery of the Clinic of Ddental medicine in Niš in the period from 2018 to 2022. The histopathological analysis included the depth of tumor invasion, histopathological analysis of the lymph nodes of neck dissections, analysis of lymphocytic infiltration, and presence of lymphovascularand perineural invasion.*
Results: *It was determined that the depth of invasion is statistically significantly different regarding the degree of lymphocytic infiltration (p=0.004). Invasion of over 4mm was present in 20% of patients with high infiltration, 44.4% of patients with medium infiltration, and 85.7% of patients with low infiltration.*
Conclusion: *Given that the results of the study indicate that the analysis of the lymphocytic infiltrate can be a reliable predictive factor of the appearance of metastases in the lymph nodes of the neck, further research should be directed towardas sociating lymphocytic infiltration with certain biochemical and genetic parameters based on which a plan can be created for neck treatment in the N0 stage of oral squamous cellular carcinoma.*

Key words: *lymphocytic infiltration, oral squamous cell carcinoma, surgical treatment*

Uvod

Karcinom pločasto slojevitog epitela usne duplje – oralni skvamocelularni karcinom (OSCC) – jeste invazivna patološka lezija epitela različitog stepena skvamozne diferencijacije, a odlikuje se ranim i ekstenzivnim metastazama, infiltracijom okolnih anatomskih struktura, pojavom učestalih recidiva i relativno niskom stopom petogodišnjeg preživljavanja, koja je manja od 50%[1].

Statistički, OSCC predstavlja najučestaliji maligni tumor glave i vrata[2]. OSCC je šesti karcinom po učestalosti kod muškaraca i deseti kod žena u razvijenim zemljama, dok je po učestalosti treći kod muškaraca, a četvrti kod žena u zemljama u razvoju[3].

Hirurgija predstavlja apsolutno najefikasniji način lečenja OSCC-a. Radikalna ablacija tumora sa zdravom marginom od 4 mm do 10 mm uz limfadenektomju vrata, adekvatnu rekonstrukciju nastalog defekta i postoperativnu onkološku terapiju predstavlja standard u lečenju OSCC-a[4].

Veruje se da je prisustvom limfocita koji infiltriraju tumor (TILs) moguće predvideti odgovor na imunoterapiju, hemioterapiju, samu agresivnost tumora i predvideti pojavu metastaza na vratu[5,6]. Naime, smatra se da prisustvo limfocita u samom tumoru, ali i njegovoj okolini, podržava imunski sistem pojedinca, naročito u aspektu antitumorskog odgovora.

Kvantifikacija limfocita uglavnom je relativno laka u tumorskom tkivu, ali kvalitativni aspekt infiltrata se razlikuje. U sastavu su prisutne ćelije i urođenog i adaptivnog imunskog odgovora i njihov odnos zavisi od tipa tumora, kao i od samog organa u kojem se odvija tumorski proces. Kumulativni podaci na osnovu pretkliničkih i kliničkih studija povezali su većinu leukocita sa dominantnim doprinosom u protumorskom ili antitumorskom odgovoru.

Na osnovu faktora u mišjim modelima identifikovani su leukociti mijeloidne loze, i to makrofagi, dendritske i supresorne ćelije. U tom kontekstu, antitumorske T-ćelije, koje migriraju u ovu sredinu, mogu biti aktivisane ili suprimirane. Imajući u vidu značaj unakrsnog ćelijskog odgovora u tumorskom tkivu, pod dejstvom T-limfocita makrofagi mogu biti polarizovani u pravcu M2 (protumorogeni fenotip) ili M1 (antitumorski fenotip)[7,8].

Introduction

Carcinoma of the stratified squamous epithelium of the oral cavity - oral squamous cell carcinoma (OSCC) is an invasive pathological lesion of the epithelium with varying degrees of squamous differentiation. It is characterized by early and extensive metastases, infiltration of adjacent anatomical structures, frequent recurrences, and a relatively low five-year survival rate of less than 50% [1].

Statistically, OSCC is the most common malignant tumor of the head and neck region[2]. OSCC is the sixth most common carcinoma in men and the tenth most common in women in developed countries, i.e., the third and the fourth most common carcinoma in men and women, respectively, in developing countries[3].

Surgery is undoubtedly the most effective way of treating OSCC. Radical tumor ablation with a healthy margin of 4–10 mm, along with lymphadenectomy of the neck, adequate reconstruction of the resulting defect, and postoperative oncological therapy is considered standard in the treatment of OSCC[4].

It is believed that the presence of tumor-infiltrating lymphocytes (TILs) can predict the response to immuno- and/or chemotherapy, the aggressiveness of the tumor, as well as the appearance of metastases in the neck[5,6]. Namely, it is considered that the presence of lymphocytes not only in the tumor but also in its surroundings supports the individual's immune system, especially in the aspect of anti-tumor response.

The quantification of lymphocytes in tumor tissue is generally rather easy. However, the qualitative aspect of the infiltrate differs. The composition includes cells of both the innate and adaptive immune response, and their ratio depends on the type of tumor, as well as on the organ itself in which the tumor process develops. Cumulative data from preclinical and clinical studies have associated most leukocytes with a dominant contribution in the pro-or antitumor response.

Based on their factors,the myeloid line age leukocytes, namely macrophages, dendritic and suppressor cells, were identified in mouse models. In this context, anti-tumor T cells, which migrate into this environment, can be activated or suppressed. Considering the importance of the cross-cellular response in tumor tissue, macrophages can be polarized under the influence of T lymphocytes in the direction of M2 (pro-tumorigenic phenotype) or M1 (antitumor phenotype)[7,8].

Kliničke studije sugerišu adaptivni imunski odgovor posredovan T-limfocitima i B-limfocitima, koji obezbeđuje adekvatan antitumorski imunitet. Ekstenzivna infiltracija CD8+ T-limfocitima u visokom stepenu povezana je sa preživljavanjem i dobrim odgovorom na terapiju[9-11]. Prisustvo CD4+ regulatornih T-limfocita (Treg) povezano je i sa dobrim i sa lošim ishodom[12-14]. Među ostalim subpopulacijama CD4+ T-limfocita, prisustvo Th1 ćelija (glavni ćelijski izvor interferona-γ) povezano je sa povoljnim kliničkim ishodom[15], dok je prisustvo Th2 ćelija povezano sa smanjenim antitumorskim odgovorom[16]. Th 17 ćelije, odgovorne ćelije za proinflamatornu citokinsku familiju interleukina[17], imaju promenljive efekte u zavisnosti od ostalog citokinskog miljea. Ovo može biti objašnjeno mestom nastanka i samim tipom tumora[18].

Cilj ove studije jeste da se utvrdi korelacija između analize limfocitarnog infiltrata biopsijskih preparata sa patohistološki dokazanim metastazama OSCC-a na postoperativnim preparatima disekata vrata.

Materijal i metode

Istraživanjem su obuhvaćena 42 pacijenta koja su nakon patohistološke verifikacije OSCC-a operisana na Odeljenju za maksilofacijalnu hirurgiju Klinike za dentalnu medicinu u Nišu u periodu od 2018. do 2022. godine.

Iz studije su isključeni pacijenti sa recidivantim tumorskim procesom, pacijenti sa patohistološki potvrđenim nalazom OSCC-a i prisutnim udaljenim sekundarnim depozitima, pacijenti kojima je intervencija u opštoj endotrahealnoj anesteziji (OETA) bila kontraindikovana zbog komorbiditeta, kao i pacijenti koji su zbog inicijalno inoperabilnog tumorskog procesa bili primarno onkološki tretirani i prevedeni u operabilno stanje.

Analizirani su anamnestički podaci (porodična i lična anamneza), period od prvih subjektivnih tegoba do operativnog zahvata i loše navike. Valja napomenuti da je porodična anamneza zabeležena kao pozitivna isključivo u prvoj liniji srodstva.

Analiza kliničkog nalaza podrazumevala je preciznu anatomsku lokaciju tumora, veličinu tumora, prisustvo uvećanih limfnih nodusa vrata, kao i TNM klasifikaciju.

Histopatološka analiza podrazumevala je dubinu invazije tumora (DOI), histopatološku analizu limfnih nodusa disekata vrata, analizu limfocitarne infiltracije i prisustvo limfo-vaskularne (LVI) i perineuralne invazije (PNI).

Clinical studies suggest an adaptive immune response mediated by T and B lymphocytes, which provides adequate antitumor immunity. Extensive infiltration of CD8+ T lymphocytes is highly associated with survival and good response to therapy[9-11]. The presence of CD4+ regulatory T lymphocytes (Treg) is linked with both good and poor outcome[12-14]. Among other CD4+ T lymphocyte subpopulations, the presence of Th1 cells (the main cellular source of interferon-γ) is associated with a favourable clinical outcome[15], whereas the presence of Th2 cells is associated with a reduced antitumor response[16]. Th17 cells, i.e., cells responsible for the pro-inflammatory cytokine family of interleukins[17], have variable effects depending on the rest of the cytokine milieu. This can be explained by the place of origin and type of thetumor[18].

The aim *of* the study was to determine the correlation between the analysis of the lymphocytic infiltrate of biopsy specimens with pathohistologically proven metastases of OSCCon postoperative neck dissection specimens.

Material and methods

The study included 42 patients with pathohistologically verified OSCC who had undergone surgery at the Department of Maxillofacial Surgery of the Dental Medicine Clinic in Niš in the period from 2018 to 2022.

The study excluded patients with a recurrent tumor process, patients with pathohistologically confirmed OSCC and remote secondary deposits, patients in whom surgery under general endotracheal anaesthesia (GETA) had been contraindicated due to comorbidities, as well as patients who, due to an initially inoperable tumor process,received oncological treatment that brought them into operable condition.

The analysis included anamnestic data (family and personal medical history), the period between first symptoms and surgery, as well as bad habits. It should be noted that the family history was recorded as positive in the first line of kinship exclusively.

The analysis of clinical findings included the exact anatomical location of the tumor, the size of the tumor, the presence of enlarged neck lymph nodes, and the TNM classification.

The histopathological analysis included the depth of tumor invasion (DOI), histopathological analysis of the lymph nodes of neck dissections, analysis of lymphocytic infiltration, and presence of lymphovascular (LVI) and perineural invasion (PNI).

Statistička obrada podataka

Podaci su prikazani u vidu apsolutnih i relativnih brojeva. Poređenje kategorijskih obeležja između grupa vršeno je Hi kvadrat testom i Fišerovim testom egzaktne verovatnoće. Hipoteza je testirana, a prag značajnosti postavljen je na $p < 0,05$. Statistička obrada podataka vršena je u programskom paketu EPI INFO v 7.2.2.6.

Rezultati

U Tabeli 1 prikazane su demografske i kliničke karakteristike ispitivane populacije, te su predstavljene u odnosu na limofocitarnu infiltraciju.

Većina pacijenata bila je starosti od 50 do 60 godina (45,2%) i muškog pola (59,5%). Polovina pacijenata (52,4%) imala je dubinu invazije > 4 mm. Perineuralne invazije bile su prisutne kod 40,5% pacijenata. Limfovaskularne invazije bile su prisutne kod 52,4% pacijenata. Distribucija lokalizacije promena je sledeća: jezik kod 40,5% pacijenata, jezik i pod usta kod 19,0% pacijenata, sluzokoža obraza kod 11,9% pacijenata, pod usta kod 11,9% pacijenata, alveolarni nastavak kod 9,5% pacijenata, tvrdo nepce kod 7,1% pacijenata. Prisutni su sledeći stadijumi bolesti u ispitivanoj populaciji: stadijum I kod 28,6% pacijenata, stadijum II kod 28,6% pacijenata, stadijum III kod 23,8% pacijenata i stadijum IV kod 19,0% pacijenata.

Utvrđeno je da se starost i pol ne razlikuju statistički značajno u odnosu na stepen limfocitarne infiltracije ($p = 0,991$, odnosno $p = 0,303$). Dubina invazije statistički se značajno razlikuje u odnosu stepena limfocitarne infiltracije ($p = 0,004$) (Grafikon 1). Invazija preko 4 mm prisutna je kod 20,0% pacijenata sa visokom infiltracijom, 44,4% pacijenata sa srednjom infiltracijom i 85,7% pacijenata sa niskom infiltracijom. Učestalost perineuralne invazije, lokalizacija i stadijum bolesti ne razlikuju se statistički značajno u odnosu na stepen limfocitne infiltracije ($p = 0,882$, $p = 0,390$, odnosno $p = 0,085$).

U ispitivanoj populaciji metastaze su prisutne kod 27 pacijenata (64,3%). Utvrđeno je da starost i pol nisu statistički značajno povezani sa prisustvom metastaza ($p = 0,466$, odnosno $p = 0,923$) (Tabela 2). Dubina invazije statistički je značajno povezana sa prisustvom metastaza ($p = 0,045$). Metastaze su prisutne kod 70,4% pacijenata sa dubinom invazije > 4 mm.

Statistical data processing

Data are presented in the form of absolute and relative numbers. The comparison of categorical characteristics between groups was performed using the Chi-square test and Fisher's exact probability test. The hypothesis was tested with a significance threshold of $p<0.05$. Statistical data processing was performed in EPI INFO v 7.2.2.6 software pack.

Results

Table 1 shows the demographic and clinical characteristics of the studied population in relation to lymphocytic infiltration.

Most patients were 50–60 years old (45.2%) and of male sex (59.5%). Half of the patients (52.4%) had a depth of invasion >4 mm. Perineural invasions were present in 40.5% of the patients. Lymphovascular invasions were present in 52.4% of the patients. The distribution of the localization of changes wasthe following: tongue (40.5%), tongue and floor of the oral cavity(19.0%), buccal mucosa(11.9%),floor of the oral cavity(11.9%), alveolar process (9.5%), and hard palate (7.1%). The following disease stages werepresent in the studied population: stage I(28.6%), stage II (28.6%), stage III (23.8%), and stage IV (19.0%).

The study revealed that age and gender did not differ statistically significantly regarding the degree of lymphocytic infiltration ($p=0.991$ and $p=0.303$, respectively). The depth of invasion was statistically significantly differentregarding the degree of lymphocytic infiltration ($p=0.004$) (Graph1). Invasion ofover 4mm was present in 20% of patients with high infiltration, 44.4% of patients with medium infiltration, and 85.7% of patients with low infiltration. The frequency of perineural invasion, localization and stage of the disease did not differ statistically significantly regarding the degree of lymphocytic infiltration ($p=0.882$, $p=0.390$, $p=0.085$, respectively).

In the studied population, metastases were present in 27 patients (64.3%). It was found that age and gender were not statistically significantly associated with the presence of metastases ($p=0.466$ and $p=0.923$, respectively) (Table 2), unlike the depth of invasion ($p=0.045$). Metastases were present in 70.4% of patients with the depth of invasion >4mm.

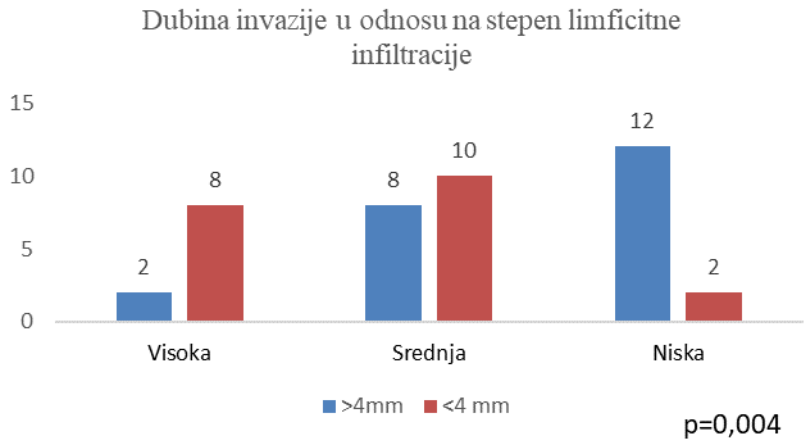
Perineuralane invazije, limfovaskularne invazije i lokalizacija ne razlikuju se statistički značajno u odnosu na prisustvo metastaza (p =1,000, p = 0,263, odnosno p = 0,980). Stadijum bolesti statistički se značajno razlikuje u odnosu na prisustvo metastaza (p < 0,001). Metastaze su prisutne kod 11,1% pacijenata sa stadijumom 1; 18,5% pacijenata sa stadijumom 2; 25,9% pacijenata sa stadijumom 3 i 44,4% pacijenata sa stadijumom 4.

Perineural invasions, lymphovascular invasions, and localization did not differ statistically significantly regarding the presence of metastases (p=1.000, p=0.263, p=0.980, respectively). The stage of the disease was statistically significantly different in relation to the presence of metastases (p<0.001). Metastases were present in 11.1% of patients with stage I, 18.5% of patients with stage II, 25.9% of patients with stage III, and 44.4% of patients with stage IV.

Tabela 1. Kliničke i demografske karakteristike u odnosu na stepen limfocitne infiltracije
Table 1. Clinical and demographic characteristics in relation to the degree of lymphocytic infiltration

Karakteristika / Characteristic	Ukupno / Total		Limfocitarna infiltracija / Lymphocytic infiltration						p[1]
			Visoka High		Srednja Medium		Niska Low		
	n	%	n	%	n	%	n	%	
Starost Age									
< 50	16	38.1	4	40.0	7	38.9	5	35.7	0.991
50-60	19	45.2	4	40.0	8	44.4	7	50.0	
> 70	7	16.7	2	20.0	3	16.7	2	14.3	
Pol Sex									
Muški Male	25	59.5	8	80.0	10	55.6	7	50.0	0.303
Ženski Female	17	40.5	2	20.0	8	44.4	7	50.0	
Dubina invazije Depth of invasion									
> 4mm	22	52.4	2	20.0	8	44.4	12	85.7	0.004
< 4 mm	20	47.6	8	80.0	10	55.6	2	14.3	
Perineuralaneinvazije Perineural invasion									
Da / Yes	17	40.5	4	40.0	8	44.4	5	35.7	0.882
Ne / No	25	59.5	6	60.0	10	55.6	9	64.3	
Limfovaskularneinvazije Lymphovascular invasion									
Da / Yes	22	52.4	2	20.0	10	55.6	10	71.4	0.042
Ne / No	20	47.6	8	80.0	8	44.4	4	28.6	
Lokalizacija Localization									
Jezik Tongue	17	40.5	4	40.0	8	44.4	5	35.7	0.390[a]
Jezik i pod usta Tongue and floor of oral cavity	8	19.0	2	20.0	3	16.7	3	21.4	
Sluzokoža obraza Buccal mucosa	5	11.9	0	0.0	4	22.2	1	7.1	
Pod usta Floor of oral cavity	5	11.9	1	10.0	3	16.7	1	7.1	
Alveolarni nastavak Alveolar process	4	9.5	1	10.0	0	0.0	3	21.4	
Tvrdo nepce Hard palate	3	7.1	2	20.0	0	0.0	1	7.1	
Stadijum Stage									
I	12	28.6	6	60.0	4	22.2	2	14.3	0.085[a]
II	12	28.6	2	20.0	7	38.9	3	21.4	
III	10	23.8	2	20.0	5	27.8	3	21.4	
IV	8	19.0	0	0.0	2	11.1	6	42.9	

[1] Hi-kvadrat test, a Fišherov test egzaktne verovatnoće
[1] Chi-square test, a Fisher's exact probability test



Grafikon 1. Dubina invazije u odnosu na stepen limfocitne infiltracije
Graph 1. The depth of invasion regarding the degree of lymphocytic infiltration

Tabela 2. Kliničke i demografske karakteristike u odnosu na prisustvo metastaza
Table 2. Clinical and demographic characteristics regarding the presence of metastases

Karakteristika / Characteristic	Prisustvo metastaza / Metastases				p[1]
	Prisutne / Existent		Odsutne / Non-existent		
	n	%	n	%	
Starost Age					
< 50	8	29.6	7	46.7	0.466
50-60	14	51.9	5	33.3	
> 70	5	18.5	3	20.0	
Pol Sex					
Muški Male	18	66.7	9	60.0	0.923
Ženski Female	9	33.3	6	40.0	
Dubina invazije Depth of invasion					
>4mm	19	70.4	5	33.3	0.045
<4 mm	8	29.6	10	66.7	
Perineuralaneinvazije Perineural invasion					
Da Yes	12	44.4	6	40.0	1.000
Ne No	15	55.6	9	60.0	
Limfovaskularneinvazije Lymphovascular invasion					
Da Yes	19	70.4	7	46.7	0.263
Ne No	8	29.6	8	53.3	
Lokalizacija Localisation					
Jezik Tongue	10	37.0	5	33.3	0.980 [a]
Jezik i pod usta Tongue and floor of oral cavity	5	18.5	3	20.0	
Sluzokoža obraza Buccal mucosa	4	14.8	2	13.3	
Pod usta Floor of oral cavity	5	18.5	2	13.3	
Alveolarni nastavak Alveolar process	2	7.4	2	13.3	
Tvrdo nepce Hard palate	1	3.7	1	6.7	
Stadijum Stage					
I	3	11.1	8	53.3	<0.001 [a]
II	5	18.5	6	40.0	
III	7	25.9	1	6.7	
IV	12	44.4	0	0.0	

[1] Hi-kvadrat test, a Fišherov test egzaktne verovatnoće
[1] Chi-square test, a Fisher's exact probability test

Diskusija

Limfogena diseminacija u regionalne limfne noduse vrata predstavlja glavni način metastaziranja OSCC-a, a takođe i bitan faktor u definitivnoj prognozi bolesti. Broj i veličina uvećanih metastatskih limfonodusa, prisustvo ekstrakapsularne ekstenzije i angažovanje kaudalnih regija vrata direktno utiču na prognozu bolesti[19]. Uvidom u dostupnu literaturu, utvrđeno je da 50% pacijenata sa OPK-om ima patohistološki potvrđene metastaze u regionalnim limfnim nodusima vrata. Takođe, potvrđeno je da u 5,3% slučajeva prisustvo uvećanih limfonodusa na vratu predstavlja prvi znak prisustva OSCC-a u usnoj duplji[20]. Definitivna prognoza pacijenata sa OSCC-om i metastazama u regionalnim limfnim nodusima vrata znatno je gora, dok je verovatnoća pojave udaljenih metastaza kod pomenute grupe daleko veća[21].

DOI predstavlja jedan od važnijih prognostičkih parametara pojave metastaza na vratu kod OSCC-a. U mnogobrojnim analizama DOI predstavlja nezavisni prognostički faktor koji je povezan sa veličinom tumora, naročito kod pacijenata sa T1–T2 stadijumom[22]. Istraživanje koje je obuhvatilo 161 pacijenata sa OPK-om i kliničkim N0 nalazom na vratu ukazalo je na postojanje korelacije između DOI i pojave metastaza u regionalnim limfnim nodusima vrata[23]. Antonio lo Casto i sar.[24] prikazuju rezultate kojima se dokazuje da je DOI najpouzdaniji prognostički parametar OPK-a u stadijumu T1–T2. Granična vrednost DOI u literaturi varira od 1,5 mm do 10 mm u različitim studijama, tako da je za signifikantnu srednju vrenost preuzeta vrednost od 4 mm, koja predstavlja apsolutnu indikaciju za sprovođenje selektivnih disekscija vrata[25]. Rezultati naše studije pokazuju korelaciju između DOI i prisustva metastaza u limfnim nodusima disekata vrata.

LVI i PNI su po mnogobrojnim autorima, takođe, bitan prognostički faktor povezan sa kliničkim karakteristikama OSCC-a. Teorijski, pojam vaskularne invazije podrazumeva da je određeni broj tumorskih ćelija prodro u lumen krvnog suda i predstavlja prvi korak u metastaziranju. PNI može biti izolovana ili u sklopu LVI. Wu i sar.[26] su grupu od 171 pacijenta sa planocelularnim karcinomom jezika stadijuma T1–T2 podelili u dve grupe u zavisnosti od prisustva ili odsustva LVI i PNI. Uočena je statistički značajna pojava metastaza na vratu i veća pojava recidiva u grupi pacijenata kod kojih su LVI i PVI bili pozitivni.

Discussion

Lymphatic dissemination in the regional lymph nodes of the neck is the main way of OSCC metastasizing and an important factor in the definite prognosis of the disease. The number and size of enlarged metastatic lymph nodes, the presence of extracapsular extension, and the involvement of caudal regions of the neck directly affect the prognosis of the disease [19]. Data from the available literature reveal that 50% of patients with OSCC have pathohistologically confirmed metastases in the regional lymph nodes of the neck. Based on the findings in 5.3% of cases, it was also confirmed thatthe presence of enlarged lymph nodes in the neck region is the first sign of OSCC in the oral cavity[20]. Patients with OSCC have a poor prognosis of the appearance of metastases in the regional lymph nodes of the neck, whereas the probability of the occurrence of distant metastases in these patients is much higher[21].

DOI represents one of the most important prognostic parameters for the appearance of neck metastases in OSCC. In numerous analyses, DOI is an independent prognostic factor that is associated with tumor size, especially in patients with T1–T2 stage[22]. A study that included 161 patients with OSCC and clinical N0 findings in the neck indicated a correlation between DOI andmetastases in the regional lymph nodes of the neck[23]. Antonio lo Casto et al.[24] presented results proving that DOI is the most reliable prognostic parameter of OSCC in stages T1–T2. In literature, DOI values vary from 1.5 to 10 mm in different studies. Thus, a mean value of 4 mm was taken as significant, and it represents an absolute indication for performing selective neck dissections[25]. The results of our study show a correlation between DOI and the presence of metastases in the lymph nodes of neck dissection specimens.

LVI and PNI are also considered important prognostic factors associated with the clinical characteristics of OSCC. Theoretically, the concept of vascular invasion implies that a certain number of tumor cells have penetrated the lumen of a blood vessel, which represents the first step in metastasizing. PNI can be isolated or part of LVI. Wu et al.[26] divided a group of 171 patients with T1-T2 squamous cell carcinoma of the tongue into two groups depending on the presence or absence of LVI and PNI. A statistically significant occurrence of metastases in the neck and a higher incidence of recurrence was observed in the group of patients in whom LVI and PVI were positive.

Yeh i sar.[27] u studiji, koja je obuhvatila 253 pacijenta sa OSCC-om u ranom stadijumu, konstatuju postojanje većeg procenta pojave recidivantnih metastatskih promena na vratu kod pacijenata kod kojih su LVI i PNI bili pozitivni. Rezultati naše studije ne ukazuju na postojanje statistčke značajnosti između LVI i PVI i pojave metastaza u limfnim nodusima vrata. Ovakav rezultat pravdamo malim brojem pacijenata sa pozitivnim LVI i PVI koji su uključeni u studiju, budući da je velik broj pacijenata sa OPK-om bio isključen iz studije.

Kvantifikacija, kvalifikacija i lokacija TILS-a predstavljaju signifikantne prognostičke faktore kod pacijenata sa karcinomom dojke, digestivnog trakta, limfoma i želuca, ali su takođe u koleraciji sa odgovorom na onkološku terapiju i prognozom. Kod OPK-a, tumorska infiltracija antigenprezentujućim ćelijama, npr. makrofagima, Langerhansovim ćelijama i CD1 pozitivnim dendritičnim ćelijama, povezana je sa ponašanjem tumora i preživljavanjem pacijenata. Pojava CD4 limfocita u infiltratu predstavlja povoljan prognostički znak, za razliku od infiltracije makrofagima, koja je povezana sa pojavom metastaza u regionalnim limfnim nodusima vrata[28]. Pojava CD68 pozitivnih makrofaga predstavlja loš prognostički znak i povezuje se sa pojavom metastaza u regionalnim limfnim nodusima vrata[29]. Rezultati naše studije pokazuju korelaciju gustine limfocitarnog infiltrata i pojave metastaza u limfnim nodusima vrata, kao i korelaciju pomenutog parametra sa DOI.

Zaključak

U našoj studiji su prikazani preliminarni rezultati, koji ukazuju na povezanost limfocita koji infiltriraju tumor i kliničkih karakteristika OSCC-a. Rezultati studije ukazuju na to da analiza limfocitarnog infiltrata može biti pouzdan prediktivni faktor pojava metastaza u limfnim nodusima vrata. Dalja istraživanja valja usmeriti ka povezivanju limfocitarne infiltracije i pojedinih biohemijskih parametara i genetskih promena, na osnovu kojih se može stvoriti plan lečenja vrata N0 stadijuma OPK-a, za koji još uvek u hirurgiji glave i vrata ne postoji jasno decidirani stav.

Zahvalnica: Nema

Sukob interesa: Nema

In a study that included 253 patients with OSCC in the early stage, Yehet al.[27] suggested a higher percentage of recurrent metastatic changes in the neck in patients in whom LVI and PNI were positive. The results of our study do not indicate the existence of statistical significance between LVI and PVI and the occurrence of metastases in the lymph nodes of the neck. This result is justified by the small number of patients with positive LVI and PVI included in the study, given that many patients with OSCC were excluded from the study.

The quantification, qualification, and location of TILs is a significant prognostic factor in patients with carcinoma of the breast, digestive tract, and lymphoma, but it is also in correlation with the response to oncological therapy and prognosis. In OSCC, tumor infiltration by antigen-presenting cells such as macrophages, Langerhans cells, and CD1-positive dendritic cells is associated with tumor behaviour and patient survival. The appearance of CD4 lymphocytes in the infiltrate is a favourable prognostic sign, unlike infiltration by macrophages which is associated with the appearance of metastases in the regional lymph nodes of the neck[28]. The appearance of CD68-positive macrophages is a bad prognostic sign and is associated with metastases in the regional lymph nodes of the neck[29]. The results of our study show a correlation between the density of the lymphocytic infiltrate and the occurrence of metastases in the lymph nodes of the neck, as well as a correlation of the mentioned parameter with DOI.

Conclusion

The preliminary results of our study indicate a relationship between tumor-infiltrating lymphocytes and the clinical characteristics of OSCC. The results of the study suggest that the analysis of the lymphocytic infiltrate can be a reliable predictive factor for the appearance of metastases in the lymph nodes of the neck. Further research should be directed towards associating lymphocytic infiltration with certain biochemical parameters and genetic changes based on which a plan can be created for neck treatment in the N0 stage of OSCC, for which there is still no clearly defined viewpoint in head and neck surgery.

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Conflict of Interest:Nil

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ISPITIVANJE KORELACIJE NIVOA GUBITKA ALVEOLARNE KOSTI U INTERDENTALNOM I INTERRADIKULARNOM PROSTORU PRIMENOM RADIOGRAFSKE ANALIZE

EXAMINATION OF CORRELATION OF LEVELS OF ALVEOLAR BONE LOSS IN INTERDENTAL AND INTERRADICULAR SPACE USING RADIOGRAPHIC ANALYSIS

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Sažetak

Uvod: *Jedna od posledica prisustva parodontopatije jeste i gubitak alveolarne kosti u interdentalnom i interradikularnom prostoru. Gubitak koštanog tkiva veoma je bitan za procenu težine oboljenja i primenu terapijskih procedura.*
Cilj: *Cilj je bio da se odrede i uporede gubitak interdentalne i interradikularne alveolarne kosti primenom radiografske analize.*
Materijal i metode: *Ispitivano je 100 pacijenata, starosti od 40 do 60 godina, sa hroničnom parodontopatijom, uz zahvaćenost furkacija III i IV stepena kod mandibularnih molara. Nakon ortopantomografskog snimanja urađena su morfološka merenja mezijalnog i distalnog interdentalnog gubitka kosti, kao i merenja interradikularnog prostora, a zatim je analizirana njihova međusobna veza.*
Rezultati: *Srednja vrednost mezijalnog interdentalnog gubitka kosti bila je 5,90 mm ± 2,4 mm, a srednja vrednost distalnog 6,1 mm ± 6,1 mm; srednja vrednost interradikularnog gubitka kosti bila je 3,55 mm ± 5,1 mm. Korelacija između interradikularnog i interdentalnog gubitka kosti bila je statistički značajna ($p < 0,001$). Veća korelacija bila je prisutna kod ispitanika starijih od 50 godina, nego kod mlađih ispitanika. Što se tiče pola, nije uočena statistički značajna razlika između ispitivanih nivoa kostiju. Zapažen je interradikularni gubitak kostiju od 0,8 mm i više kod ispitanika kod kojih je gubitak kostiju na interdentalnom području bio najmanje 3,7 mm.*
Zaključak: *Rezultati istraživanja pokazuju da postoji međusobna veza između gubtika nivoa alveolarne kosti u interdentalnom i interradikularnom prostoru molara kod hronične parodontopatije, pa interdentalni i interradikularni gubitak kosti može poslužiti kao osnova za dodatno ispitivanje u okviru postavljanja dijagnoze oboljenja. Potrebna su dodatna istraživanja koja bi uključila i primenu trodimenzionalne radiografije za određivanje težine oboljenja i terapijskih procedura.*

Ključne reči: *parodontopatija, furkacije zuba, gubitak alveolarne kosti, dijagnoza, terapija*

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Abstract

Introduction: *One of the consequences of the presence of periodontitis is the loss of alveolar bone in the interdental and interradicular space. Bone loss is very important for assessing the severity of the disease and applying therapeutic procedures.* ***Aim:*** *The objective was to determine and compare the loss of interdental and interradicular alveolar bone using radiographic analysis.*
Material and methods*: 100 patients, aged 40 to 60 years, with chronic periodontitis and involvement of grade III and IV furcations in mandibular molars were examined. After orthopantomographic imaging, morphological measurements of mesial and distal interdental bone loss were performed, as well as the measurements of interradicular space. Then, their interrelationship was analyzed.*
Results: *The mean value of mesial interdental bone loss was 5.90 ± 2.4mm, and the mean value of distal was 6.1 ± 6.1mm, while the mean value of interradicular bone loss was 3.55 ± 5.1mm. The correlation between interradicular and interdental bone loss was statistically significant ($p<0.001$). A higher correlation was present in respondents older than 50 years compared to younger respondents. Regarding gender, no statistically significant difference was observed between the examined bone levels. Interradicular bone loss of 0.8 mm and more was observed in subjects with bone loss in the interdental area of at least 3.7 mm.*
Conclusion: *The results show that there is a correlation between the loss of alveolar bone levels in the interdental and interradicular space of the molars in chronic periodontitis, so interdental and interradicular bone loss can be used as an additional test in diagnosing the disease. Additional research is needed, which would include the use of three-dimensional radiography to determine the severity of the disease and therapeutic procedures.*

Key words: *periodontitis, tooth furcation, alveolar bone loss, diagnosis, therapy*

Uvod

Parodontalno oboljenje jedno je od najčešćih oboljenja kod ljudi, a odlikuje se prisustvom inflamacije i destrukcijom parodontalnog tkiva[1,2]. Parodontalno oboljenje karakterišu periodi egzacerbacije bolesti, u kojima se potporne strukture zuba uništavaju pod dejstvom endotoksina raznih parodonto-patogena, praćeni vremenskim periodima latencije[3]. Progresija parodontopatije izaziva gubitak vezivnog tkiva, gubitak alveolarne kosti i, posledično, labavljenje i migraciju zuba.

Izraz „zahvaćenost furkacija" odnosi se na destrukciju bifurkacijskih i trifurkacijskih prostora višekorenskih zuba parodontalnim oboljenjem[2]. Prostori furkacije predstavljaju jedan od najvećih izazova u terapiji parodontalnog oboljenja. U nekoliko retrospektivnih studija o gubitku zuba zabeleženo je da upravo zubi sa furkacijama imaju veći mortalitet i kompromitovanu prognozu po pitanju terapije od drugih zuba[4,5]. Razlog destrukcije parodonta može biti horizontalni gubitak kostiju ili kosa resorpcija sa pojavom infrakoštanih defekata – tada furkacijski prostori postaju mesto akumulacije oralnog biofilma i detritusa[2,6]. Budući da su ulazi u furkacijski prostor često premali za tretman odgovarajućim instrumentima ili pravilnu kućnu oralnu higijenu[7], maksilarni i mandibularni višekoreni zubi su u većem riziku od bržeg gubitka, uz kompromitovanu dugoročnu prognozu bolesti[8]. Stoga, defekti u furkacijama predstavljaju značajan problem u terapiji parodontopatije[9], što nalaže ranu dijagnozu i lečenje.

U većini slučajeva dijagnoza parodontalnog oboljenja uglavnom zavisi od kliničkih znakova i simptoma. Ipak, za pružanje informacija o vrsti, obimu i težini parodontopatije klinički pregled nekada nije dovoljan[10]. Postoji nekoliko nedostataka u kliničkom pregledu koji mogu negativno uticati na postavljanje dijagnoze parodontopatije: prisustvo i stepen zapaljenja, konzistencija gingivnog tkiva, pritisak primenjen prilikom sondiranja, tip, veličina i oblik sonde, lokacija i ugao prilikom sondiranja itd[11-14]. U slučajevima gubitka kostiju, radiografski pregled može se koristiti kao dodatna dijagnostička metoda[10,15-16].

Međutim, konvencionalnom radio-grafskom procenom ne može se tačno odrediti količina gubitka kostiju. Digitalno merenje, tj. radio-vizuelna grafika (RVG) može poboljšati

Introduction

Periodontal disease is one of the most common diseases in humans, and is characterized by the presence of inflam-mation and destruction of periodontal tissue[1,2]. Periodontal disease is characterized by periods of exacerbation of the disease, in which the supporting structures of the teeth are destroyed by endotoxins of various periodontopathogens, which are followed by periods of latency[3]. Progression of periodontitis causes loss of connective tissue, loss of alveolar bone and consequent loosening and migration of teeth.

The term "furcation involvement" refers to the destruction of bifurcation and trifurcation spaces of multi-rooted teeth by periodontal disease[2]. Furcation spaces represent one of the greatest challenges in the treatment of periodontal disease. In several retrospective studies on tooth loss, it has been noted that teeth with furcation's have a higher mortality and compromised prognosis in terms of therapy, compared to other teeth[4,5]. The reason for the destruction of the periodontium can be horizontal bone loss or oblique resorption with the appearance of infraosseous defects. Then the furcation spaces become a place of accumulation of oral biofilm and detritus[2,6]. Entrances to the furcation space are often too small for treatment with appropriate instruments or proper home oral hygiene[7]. Therefore, maxillary and mandibular multi-rooted teeth are at higher risk for faster loss with compromised long-term prognosis[8]. Therefore, defects in furcation's are a significant problem in periodontal therapy[9] which requires early diagnosis and treatment.

In most cases, the diagnosis of periodontal disease mainly depends on the clinical signs and symptoms. However, to provide information on the type, extent and severity of periodontitis, a clinical examination is sometimes not sufficient[10]. There are several shortcomings in a clinical examination that may adversely affect the diagnosis of periodontitis, such as the presence and degree of inflammation, gingival tissue consistency, probing, type, size and shape of probe, location and angle when probing, etc.[11-14]. In cases of bone loss, radiographic examination may be used as an additional diagnostic method[10,15-16].

However, by conventional radio-graphic assessment, the amount of bone loss cannot be accurately determined.

dijagnostičku interpretaciju radiografskih snimaka u smislu tačnosti, mada je pokazano da se validnost linearnih merenja gubitka kostiju ne može poboljšati osnovnim digitalnim manipulacijama[17].

Vivek i sar.[14] tvrde da, čak i uz redovno održavanje oralne higijene, parodontopatija na mestima furkcije napreduje različitom brzinom u odnosu na ostale površine zuba i da pogođena mesta teže većem gubitku nivoa kliničkog pripoja, bez obzira na terapiju koja se pruža. Međutim, mora se nagovestiti da su ovi autori procenjivali podatke samo za promenu dubine kliničkog pripoja na mestu furkacije, bez procenjivanja promena kliničkog pripoja za ostale površine zuba. Kim i sar.[18] u svom stereomikroskopskom istraživanju 34 ekstrahirana molara izveštavaju o tome da su gubitak pripoja i marginalni gingivitis na površinama okrenutim prema furkacijama veći od onih na spoljnim površinama. Postoji veoma mali broj studija koje su upoređivale brzinu gubitka kosti na mestu furkacije i interdentalnog septuma istog zuba. Prag gubitka alveolarne kosti, koji je povezan sa progresijom razaranja parodonta i zahvatanjem interradikularnih prostora, nije u literaturi jasno definisan. Potreba za proučavanjem proističe iz činjenice da treba saznati da li se gubitak interdentalnih septuma može koristiti kao dodatni vodič za sveobuhvatnu dijagnozu parodontalnog oboljenja pomoću RVG .

Cilj ove studije bio je da se radiografskom procenom istraži veza između interradikularne destrukcije kosti i interdentalnog gubitka kostiju kod pacijenata sa hroničnom parodontopatijom.

Materijal i metode

Istraživanje je sprovedeno u Službi za parodontologiju i oralnu medicinu Klinike za dentalnu medicinu u Nišu. U ovo istraživanje uključeno je 100 pacijenata (56 muškarca i 44 žene) starosti od 40 do 60 godina, kojima je dijagnostikovana hronična parodontopatija. Svi pacijenti su informisani o prirodi istraživanja, nakon čega je dobijena i njihova pismena saglasnost.

Kriterijumi za uključivanje u istraživanje bili su:

1. pacijenti koji imaju hroničnu parodontopatiju sa gubitkom pripojnog epitela ≥ 4 mm na 30% ili više mesta;
2. starosna grupa pacijenata od 40 do 60 godina;

Digital measurement, i.e., Radio Visio Graphy (RVG) can improve the diagnostic interpretation of radiographs in terms of accuracy, although it has been shown that the validity of linear bone loss measurements cannot be improved by basic digital manipulations[17].

Vivek et al.[14] claim that, even with regular maintenance of oral hygiene, periodontitis at the sites of furcation progresses at different speed than onother tooth surfaces and that the affected sites tend to lose more levels of clinical adhesion, regardless of the therapy provided. However, it must be suggested that these authors evaluated the data only for the change in the depth of clinical adhesion at the site of furcation, without estimating the changes in clinical adhesion for other tooth surfaces. Kim et al.[18] in his stereomicroscopic examination of 34 extracted molars report that the loss of adhesion and marginal gingivitis on the surfaces facing the furcationsaregreater than thoseon the outer surfaces. There are very few studies that have compared the rate of bone loss at the site of furcation and the interdental septum of the same tooth. The threshold of alveolar bone loss associated with progression of periodontal destruction and interradicular space involvement has not been clearly defined in the literature. There is a need to learn whether the loss of interdental septa can be used as an additional guide for a comprehensive diagnosis of periodontal disease using RVG.

The aim of this study was to investigate the link between interradicular bone destruction and interdental bone loss in a patient with chronic periodontitis.

Material and methods

This study was conducted in the Department of Periodontology and Oral Medicine of the Clinic of Dental Medicine in Niš. This study included 100 patients (56 men and 44 women) aged 40 to 60 who were diagnosed with chronic periodontitis. All patients were informed about the nature of the research, after which their written consent was obtained.

Criteria for inclusion in the study were:

1. patients with chronic periodontitis with loss of adnexal epithelium ≥ 4 mm, that is,of 30% or more;
2. age group of patients from 40 to 60 years;

3. prisustvo mandibularnog 1. i 2. molara;
4. pravilno postavljeni mandibularni molari (bez dijastema, bez teskobe, bez rotacije);
5. pacijenti voljni da daju saglasnost za ovo istraživanje.

Kriterijumi za isključenje iz istraživanja bili su:
1. pacijenti sa sistemskom bolešću;
2. pacijenti koji su bili podvrgnuti parodontalnoj terapiji u poslednjih šest meseci;
3. molari sa spojenim korenima;
4. mandibularni molari bez kontakta sa antagonistom;
5. uslovi koji ometaju kliničku / rendgenografsku procenu, kao što su ortodontska žica, obimni konzervativni radovi, prekomerno prisustvo čvrstih naslaga, zbog čega se ne može se identifikovati gleđno-cementna granica;
6. pacijenti koji su na terapiji lekovima, koji ometaju metabolizam kostiju;
7. trudnice.

Klinički pregled urađen je kod svih ispitanika korišćenjem parodontalnih parametara, i to : a) dubina parodontalnog džepa (DPDž) pomoću Michigan 0 parodontalne sonde; b) nivo pripojnog epitela (NPE) korišćenjem Michigan 0 parodontalne sonde; c) gingivalni indeks po Löe–Silnessu (1963).

Ortopantomografsko snimanje mandibularnih molara urađeno je kod svih ispitanika paralelnom tehnikom (tehnika dugog konusa / tehnika pod pravim uglom) – korišćen je komercijalno dostupan rendgen aparat, uz pravilno pridržavanje standarda zaštite od zračenja i u aseptičnim uslovima. Na ortopantomografskom snimku identifikovani su anatomski detalji, gleđno-cementna granica, horizontalna, vertikalna i interradikularna resorpcija kosti:
• gleđno-cementna granica – alveolarni greben (kod horizontalne destrukcije kosti);
• gleđno-cementna granica – apikalni defekt kosti (kod vertikalne destrukcije kosti);
• furkacijski forniks – interradikularni očuvani nivo kosti – udaljenost od furkacionog forniksa do netaknute interradikularne kosti (interradikularni gubitak kosti).

Zahvaćenost furkacija kod mandibularnih molara procenjivana je pomoću aproksimalne kalibrisane parodontalne sonde, graduisane intervalima od 2 mm (Hu Friedy, Chicago, IL, USA).

3. presence of mandibular 1st and 2nd molars;
4. properly placed mandibular molars (no diastema, no crowding, no rotation); and
5. patients who were willing to consent to this research.

Criteria for exclusion from the study were:
1. patients with systemic disease;
2. patients whohad undergone periodontal therapy in the last 6 months;
3. molars with fused roots;
4. mandibular molars without contact with antagonist;
5. conditions that interfere with clinical/radiographic assessment such as orthodontic wire, extensive conservative work, excessive presence of solid deposits due to which the enamel-cement boundary cannot be identified;
6. patients on therapy with drugs that interfere with bone metabolism; and
7. pregnant women.

Clinical examination was performed in all subjects using periodontal parameters, namely: a) depth of periodontal pocket (DPJ)—using Michigan 0 periodontal probe; b) level of adnexal epithelium (NPE)—using Michigan 0 periodontal probe; and c) gingival index according to Löe and Silness (1963).

Orthopantomographic imaging of mandibular molars was performed in all subjects bya parallel technique (long cone technique/right angle technique) using a commercially available X-ray machine with proper adherence to radiation protection standards and in aseptic conditions. On the orthopantomographic image, anatomical details, enamel-cement border, horizontal, vertical and interradicular bone resorption were identified:
• cement-enamel junction—alveolar ridge (in horizontal bone destruction)
• cement-enamel junction—apical bone defect (in vertical bone destruction)
• furcation fornix—interradicular preserved bone level—distance from furcation fornix to intact interradicular bone (interradicular bone loss).

Furcation involvement in mandibular molars was assessed using an approximate calibrated periodontal probe, graduated at 2 mm intervals (Hu Friedy, Chicago, IL, USA).

Statistička analiza

Rezultati za svaki parametar za diskretne podatke i prosečne vrednosti (SV ± SD) predstavljeni su u tabelama i slikama. Pearsonovi koeficijenti korelacije izračunati su kako bi se utvrdilo da li postoji povezanost između interdentalnog i interradikularnog gubitka kosti. U svim pomenutim testovima P vrednost manja od 0,05 uzeta je za statistički značajnu. Podaci su analizirani pomoću SPSS paketa (ver. 18.0).

Rezultati

Ovim istraživanjem vršilo se utvrđivanje veze između interdentalnog i interradikularnog gubitka kostiju, sa veličinom uzorka od 100 pacijenata. Muškaraca je bilo 56 (56%), dok je žena bilo 44 (44%). Minimalna starost pacijenta bila je 40 godina, a maksimalna 60 godina. Prosečna starost pacijenta bila je 49,91 godina ± 2,16 godina. Učesnici su deljeni i u dve starosne grupe sa granicom od 50 godina; većina pacijenata bila je u kategoriji mlađih od 50 godina – njih 54 bilo je prosečne starosti od 44,28 godina ± 2,58 godina. (Tabela 1)

Vrednosti minimalnog i maksimalnog mezijalnog interdentalnog gubitka kostiju među uzorcima dobrovoljaca jesu 3,10 mm i 9,50 mm. Izračunata srednja vrednost iznosi 5,90 mm. Vrednosti minimalnog i maksimalnog distalnog interdentalnog gubitka kostiju kod dobrovoljaca jesu 3,53 mm i 9,80 mm. Srednja vrednost distalnog interdentalnog gubitka kosti izračunata je na 6,10 mm. Vrednosti standardne devijacije mezijalnog i distalnog interdentalnog gubitka kostiju jesu 2,4 i 6,10 mm. Navedeno dokazuje da postoji veće odstupanje u distalnom interdentalnom gubitku kostiju u poređenju sa gubitkom mezijalnog interdentalnog gubitka kosti. Zabeležene vrednosti minimalnog i maksimalnog interradikularnog gubitka kosti kod dobrovoljaca jesu 1,34 mm i 10,00 mm. Srednje vrednosti i vrednosti standardnog odstupanja zabeležene su kao 3,55 mm i 5,1 mm.(Tabela 2).

Statistical analysis

The results for each parameter for discrete data and average values (mean ± SD) for each parameter are presented in tables and figures. Pearson's correlation coefficients were calculated to determine if there was an association between interdental and interradicular bone loss. In all of the above tests, a P value less than 0.05 was considered statistically significant. Data were analyzed using the SPSS package (ver. 18.0).

Results

This study was conducted to determine the relationship between interdental and interradicular bone loss, with a sample size of 100 patients. There were 56 (56%) men and 44% women. The minimum age of the patient was 40 years, and the maximum was 60 years. The mean age of the patient was 49.91±2.16. Participants were also divided into two age groups with a limit of 50 years, where most patients were in the category younger than 50 years, 54 of them with an average age of 44.28±2.58 (Table 1).

The values of minimum and maximum mesial interdental bone loss among the volunteer samples were 3.10 mm and 9.50 mm. The mean value calculated is 5.90 mm. The values of minimum and maximum distal interdental bone loss in volunteers are 3.53 mm and 9.80 mm. The mean value of distal interdental bone loss was calculated at 6.10 mm. The values of the standard deviation of mesial and distal interdental bone loss are 2.4 and 6.10. This proves that there is a larger deviation in distal interdental bone loss compared to the loss of mesial interdental bone loss. The values of minimum and maximum interradicular bone loss in volunteers were recorded as 1.34 mm and 10.00 mm. Mean and standard deviation values were recorded as 3.55 and 5.1. (Table 2).

Tabela 1. Polna i starosna struktura učesnika
Table 1. Gender and age structure of participants

Varijabile / Variable	**PD***	
	(n = 100)	**%**
Pol / Gender Muški/Male	56	(56 %)
Ženski/Female	44	(44 %)
Godine / Ages (SV ± SD) / (mean ± SD)	49.91 ± 2.16	
Raspon godina / Range of yrs	40–60	
≤ 50 god / yrs. (n, SV ± SD / n, mean ± SD)	(54) 44.28 ± 2.58	
> 50 god / yrs. (n, SV ± SD / n, mean ± SD)	(46) 55.91 ± 3.64	

*PD - Periodontal disease

Tabela 2. Srednje vrednosti interdentalnog i interradikularnog gubitka kosti
Table 2. Mean values of interdental and interradicular bone loss

Varijabile/Variable	n (broj/number)	SV/mean	SD*	Median	Min.	Max.
Mezijalni interdentalni gubitak kosti / Mesial interdental bone loss	100	5.90	2.4	4.67	3.10	9.50
Distalni interdentalni gubitak kosti / Distal interdental bone loss	100	6.10	6.10	5.58	3.53	9.80
Interradikularni gubitak kosti/ Interradicular bone loss	100	3.55	5.1	3.41	1.34	10.00

*SD – standard deviation

Srednja vrednost mezijalnog interdentalnog gubitka kosti je 5,90 mm ± 2,4 mm, a srednja vrednost distalnog interdentalnog gubitka kostiju 6,10 mm ± 6,10 mm, što sugeriše da je distalni interdentalni gubitak kosti veći od gubitka mezijalnog interdentalnog gubitka kosti. Ipak, razlika između mezijalnog interdentalnog gubitka kosti i distalnog interdentalnog gubitka kosti nije značajna, budući da je p = 0,418 (Tabela 3). Korelacija između mezijalnog interdentalnog gubitka kosti i distalnog interdentalnog gubitka kosti je snažna i ima pozitivan odnos – kao Pearsonova korelacija (r) vrednost je 0,503 (Tabela 3).

Srednja vrednost mezijalnog interdentalnog gubitka kosti jeste 5,90 mm ± 2,4 mm, a srednja vrednost interradikularnog gubitka kosti 3,55 mm ± 5,10 mm; razlika između mezijalnog gubitka kosti i interradikularnog gubitka kosti je značajna, budući da je p < 0,001.

The mean value of mesial interdental bone loss was 5.90±2.4 mm, and the mean value of distal interdental bone loss was 6.10±6.10 mm, suggesting that distal interdental bone loss was higher compared to the loss of mesial interdental bone loss. But the difference between mesial interdental bone loss and distal interdental bone loss was not significant as p=0.418 (Table3).The Pearson correlation (r) value of 0.503 confirmed strong and positive relationship (correlation) between mesial interdental bone loss and distal interdental bone loss (Table3).

The mean value of mesial interdental bone loss was 5.90±2.4 mm, and the mean value of interradicular bone loss was 3.55±5.10 mm, and the difference between mesial bone loss and interradicular bone loss was significant with p<0.001. The correlation between mesial interdental bone loss and interradicular bone loss was moderately positive with Pearson's correlation value (r) of 0.376 (Table3).

Korelacija između gubitka mezijalne interdentalne kosti i interradikularnog gubitka kosti je umereno pozitivna, jer je Pearsonova korelaciona vrednost (r) 0,376 (Tabela 3).

Srednja vrednost distalnog interdentalnog gubitka kosti jeste 6,10 mm ± 6,10 mm, a srednja vrednost interradikularnog gubitka kosti 3,55 mm ± 5,10 mm; razlika između distalnog interdentalnog gubitka kosti i interradikularnog gubitka kosti je značajna, budući je $p < 0,001$. Korelacija između gubitka distalne interdentalne kosti i interradikularnog gubitka kosti je jako pozitivna, jer Pearsonova korelaciona vrednost (r) iznosi 0,405 (Tabela 3).

Zapaženo je da ispitanici stariji od 50 godina imaju veći stepen korelacije za distalni interdentalni i interradikularni gubitak kostiju; mlađi od 50 godina imali su pak veću korelaciju za mezijalni interdentalni i interradikularni gubitak kostiju. Stoga, korelacija između interradikularnog i interdentalnog gubitka kosti kod ispitanika starijih od 50 godina bila je značajna (Tabela 4). Što se tiče pola, kod žena je postojao veći stepen korelacije za mezijalni interdentalni i interradikularni gubitak kostiju, dok su muškarci imali veću korelaciju između distalnog interdentalnog i interradikularnog gubitka kosti. Dakle, kada se u obzir uzme pol, korelacija između interradikularnog i interdentalnog gubitka kosti nije bila značajna (Tabela 4).

The correlation between mesial interdental bone loss and interradicular bone The mean value of distal interdental bone loss was 6.10±6.10 mm, and the mean value of interradicular bone loss was 3.55±5.10 mm, and the difference between distal interdental bone loss and interradicular bone loss was significant as $p<0.001$. ThePearson's correlation value (r) of 0.405 confirmed very positive correlation between distal interdental bone loss and interradicular bone loss (Table3).

It was observed that participants older than 50 years had a higher degree of correlation of distal interdental and interradicular bone loss; younger than 50 years had a higher correlation of mesial interdental and interradicular bone loss. Therefore, the correlation between interradicular and interdental bone loss in subjects older than 50 years was significant (Table 4). Regarding gender, females had a higher degree of correlation for mesial interdental and interradicular bone loss, while males had a higher correlation between distal interdental and interradicular bone loss. Thus, when gender was taken into account, the correlation between interradicular and interdental bone loss was not significant (Table 4).

Tabela 3. Korelacija između interdentalnog i interadikularnog gubitka kosti
Table 3. Correlation between interdental and interadicular bone loss

	n (broj /number)	SV/ mean	SD/ SD	Razlika/ Difference	SD razlike / SD difference	P value	Pirsonova korelacija (r) / Pearsons correlation (r)
Mezijalni interdentalni gubitak kosti / Mesial interdental bone loss	100	5.90	2.4	-0.20	2.389	0.418	0.503
Distalni interdentalni gubitak kosti / Distal interdental bone loss	100	6.10	6.10				
Mezijalni interdentalni gubitak kosti / Mesial interdental bone loss	100	5.90	2.4	2.35	2.426	***< 0.001***	0.376

Interradikularni gubitak kosti / Interadicular bone loss	100	3.55	5.10				
Distalni interdentalni gubitak kosti / Distal interdental bone loss	100	6.10	6.10	2.55	2.777	***< 0.001***	0.405
Interradikularni gubitak kosti / Interadicular bone loss	100	3.55	5.10				

Tabela 4. Korelacija između interdentalnog i interradikularnog gubitka kostiju na osnovu starosti i pola

Table 4. Correlation between interdental and interradicular bone loss based on age and gender

		n (broj/number)	Interdentalni gubitak kosti / Interradicular bone loss	Interradikularni gubitak kosti / Interdental bone loss	p vrednost / p value
Godine/ Ages	≤ 50	46	Mezijalni/ Mesial	r = 0.569	***0.006***
			Distalni/ Distal	r = 0.341	0,121
	> 50	54	Mezijalni/ Mesial	r = 0.297	0.125
			Distalni/ Distal	r = 0.475	***0.011***
Pol/ Gender	Muški/ Male	56	Mezijalni/ Mesial	r = 0.353	0.044
			Distalni/ Distal	r = 0.434	***0,012***
	Ženski/ Female	44	Mezijalni/ Mesial	r = 0.402	***0.110***
			Distalni / Distal	r = 0.362	0.154

Diskusija

Jedna od glavnih posledica parodontopatije jeste destrukcija alveolarne kosti. Oštećenja kostiju oko zuba su specifična i nisu predvidljiva u pogledu oblika, obima i položaja. U većini slučajeva dijagnoza parodontalnog oboljenja uglavnom zavisi od kliničkih nalaza. Međutim, odlučivanje za terapijske procedure vezane za lečenje može se dopuniti radiografskom procenom nivoa i karakteristika defekta alveolarne kosti, koja služi kao dodatak kliničkom pregledu[19].

Discussion

One of the main consequences of periodontitis is the destruction of the alveolar bone. Bone damage around the teeth is specific and unpredictable in terms of shape, extent, and position. In most cases, the diagnosis of periodontal disease mainly depends on clinical findings. However, deciding on therapeutic procedures related to treatment can be supplemented by radiographic assessment of the level and characteristics of the alveolar bone defect, which serves as an adjunct to the clinical examination[19].

Saniranje molara sa zahvaćenim furkacijama predstavlja jedan od glavnih izazova u kliničkoj parodontologiji[20,21]. Zahvaćenost furkacija kod molara rezultira manje povoljnim ishodom parodontalne terapije i povećanim rizikom od gubitka zuba[22,18]. Zbog toga, za adekvatno donošenje odluka neophodna je tačna dijagnoza stepena furkacije, što značajno utiče na lečenje. Parodontolog se oslanja na podatke iz kliničkih pregleda i radiografskih snimaka . Međutim, opšte je pravilo da je gubitak kostiju uvek veći od onog koji se pojavljuje na radiografiji[22]. Prema tome, moguće je da uključenje furkacije bude prisutno bez radiografskih promena[22]

U metodologiji ovog istraživanja, korišćena je ortopantomografija za procenu gubitka kosti radi ispitivanja korelacije interdentalnog i interradikularnog gubitka kosti pomoću RVG, što je bilo slično istraživanjima drugih autora[18,23,24,25,26]. Ortopantomografska tehnika je jednostavna, a merenja se mogu lako izvesti pomoću različitih mehaničkih i digitalnih mernih alata.

Da bi se proverila povezanost interdentalnog i interradikularnog gubitka kostiju u različitim uzrastima, izabrani su volonteri iz dveju različitih starosnih grupa (≤ 50 godina i > 50 godina), s tim što većina pacijenata spada u kategoriju stariju od 50 godina. Kada je reč o polu, napominjemo da se uzorak uglavnom sastoji od muškaraca.

Prosečna starost grupe je 49,91 godina ± 2,16 godina. Kod pacijenata mlađih od 50 godina uočen je veći stepen korelacije za mezijalni interdentalni i interradikularni gubitak kosti, dok stariji od 50 godina imaju veću korelaciju za distalni interdentalni i interradikularni gubitak kostiju. Stoga je korelacija između interradikularnog i interdentalnog gubitka kosti u grupi iznad 50 godina bila značajna. To je u skladu sa studijom čiji su autori Schei O i sar.[27], u kojoj je pokazano da se resorpcija alveolarne kosti povećava sa starenjem. Drugo istraživanje koje je sproveo Hugoson[28] pokazalo je da u starosnim grupama od 40, 50 i 70 godina nijedan ispitanik nije bio bez vidljivih znakova parodontopatije.

Što se tiče pola, uočeno je da je kod žena postojao veći stepen korelacije za mezijalni interdentalni i interradikularni gubitak kostiju, dok su muškarci imali veću korelaciju između distalnog interdentalnog i interradikularnog gubitka kosti.

Restoration of molars with affected furcationsrepresents one of the main challenges in clinical periodontology[20,21]. Furcation involvement in molars results in a less favourable outcome of periodontal therapy and an increased risk of tooth loss [22,18]. Therefore,for adequate decision-making, an adequate diagnosis of the degree of furcation is necessary, which significantly affects the treatment. The periodontist relies on data from clinical examinations and radiographs. However, as a general rule, bone loss is always greater than what appears on radiographs[22]. Therefore, it is possible for furcation involvement to be present without radiographic changes[22].

In the methodology of this research, orthopantomography was used to assess bone loss to examine the correlation of interdental and interradicular bone loss using RVG, which was similar to research by other authors[18,23,24,25,26]. The orthopantomographic technique is simple, and measurements can be easily performed using various mechanical and diTo verify the association between interdental and interradicular bone loss at different ages, volunteers from two different age groups (≤50 years and> 50 years), were selected with most patients falling into the category older than 50 years. In relation to gender, the sample mainly consisted of men.

The mean age of the group was 49.91±2.16 years. In patient younger than 50 years, a higher degree of correlation of mesial interdental and interradicular bone losswas observed, while those older than 50 years had a higher correlation ofdistal interdental and interradicular bone loss. Therefore, the correlation between interradicular and interdental bone loss in the group over 50 years was significant. This is in accordance with the study conducted by Schei O et al.[27] who showed that alveolar bone resorption increases with age. Another study conducted by Hugoson[28] showed that in the age groups of 40, 50 and 70, no subject was without visible signs of periodontitis. Regarding gender, it was observed that females had a higher degree of correlation for mesial interdental and interradicular bone loss, while males had a higher correlation between distal interdental and interradicular bone loss.

Dakle, na osnovu pola, korelacija između interradikularnog i interdentalnog gubitka kosti nije bila značajna. Ovo je podržano longitudinalnom studijom koju su sproveli Rohner i sar.[29] – u njoj starost, pol i profesionalni status ne utiču na godišnju stopu resorpcije alveolarne kosti.

Grover i sar[30] su u svojoj studiji pokazali da su vrednosti u rasponu od 2,40 mm do 10,50 mm za mezijalni, a one u rasponu od 2,90 mm do 12,90 mm za distalni interdentalni gubitak kostiju povezane sa interradikularnim gubitkom kosti u rasponu od 0,80 mm do 9,70 mm; oboje su bili značajno korelirani jedni sa drugima ($p < 0,001$). Rezultati dobijeni u našoj studiji, gde je srednja vrednost mezijalnog interdentalnog gubitka kosti 5,90 mm ± 2,4 mm, a srednja vrednost distalnog interdentalnog gubitka kosti 6,10 mm ± 6,10 mm povezana sa interradikularnim gubitkom kosti u opsegu 3,55 ± 5,10 mm. Korelacija između mezijalnog interdentalnog gubitka kostiju i interradikularnog gubitka kosti je umereno pozitivna, jer Pearsonova korelaciona (r) vrednost iznosi 0,376. Korelacija između distalnog interdentalnog gubitka kosti i interradikularnog gubitka kosti je jako pozitivna, jer Pearsonova korelacija (r) iznosi 0,405.

Rezultati ove studije otkrili su da je najmanji iznos interradikularnog gubitka kosti od oko 0,34 mm i više primećen samo kada je gubitak kostiju na interdentalnom području jednak 2,10 mm ili veći od toga, što je slično rezultatima koje su dobili Popova i sar.[25], sprovevši studiju u cilju istraživanja veze između interradikularnog razaranja kostiju i interdentalnog gubitka kostiju kod pacijenata sa hroničnom parodontopatijom; tu je gubitak kosti u fukcijama sa opsegom od 1 mm i više bio u korelaciji sa interdentalnim gubitkom kostiju iznad 4 mm.

U skladu sa rezultatima ovog istraživanja jeste i istraživanje koje su sproveli Clara S Kim i sar.[18] kako bi utvrdili da li zubi sa zahvaćenim furkacijama vremenom gube značajno više kosti na mestu furkacije u odnosu na interproksimalna mesta istog zuba; pokazalo se da se promena nivoa kosti u toku vremena kreće u proseku 4,22% za interproksimalna mesta i 4,55% za mesta furkacije.

Određivanje interdentalnog gubitka kosti može se koristiti kao skrining alat za otkrivanje bolesti u ranoj fazi, posebno kada se ima u vidu da je lečenje zahvaćenih furkacija u poodmaklom stadijumu složeno, skupo, dugotrajno i zahteva interdisciplinarni pristup.

Thus, based on gender, the correlation between interradicular and interdental bone loss was not significant. This is supported by a longitudinal study conducted by Rohner et al.[29] in which age, gender, and professional status do not affect the annual rate of alveolar bone resorption.

Grover et al. in their study showed that values ranging from 2.40 to 10.50 mm for mesial and those ranging from 2.90 to 12.90 mm for distal interdental bone loss were associated with interradicular bone loss ranging from 0.80–9.70 mm; both were significantly correlated with each other ($p<0.001$). The results obtained in our study, where the mean value of mesial interdental bone loss is 5.90±2.4 mm, and the mean value of distal interdental bone loss is 6.10±6.10 mm are found to be associated with interradicular bone loss in the range of 3.55±5.10 mm. The correlation between mesial interdental bone loss and interradicular bone loss is moderately positive as the Pearson correlation (r) value is 0.376. The correlation between distal interdental bone loss and interradicular bone loss is strongly positive as Pearson's correlation (r) is 0.405.

The results of this study revealed that the lowest amount of interradicular bone loss of about 0.34 mm and more was observed only when the interdental bone loss was 2.10 mm or more, which is similar to the results obtained by Popova et al.25 who conducted a study to investigate the relationship between interradicular bone destruction and interdental bone loss in patients with chronic periodontitisand found thatbone loss in functions measuring1 mm or more was correlated with interdental bone loss above 4 mm.

In accordance with the results of this research, the research conducted by Clara S. Kim et al.18 to determine whether teeth with affected furcations lose significantly more boneover time at the furcation site compared to the interproximal sites of the same tooth; it was shown that the change in bone level over time is on average 4.22% for interproximal sites and 4.55% for furcation sites.

The determination of interdental bone loss can be used as a screening tool to detect the disease at an early stage, especially when it is considered that the treatment of affected furcationsin an advanced stage is complex, expensive, long-term and requires an interdisciplinary approach.

Ova studija pokazala je da je interradikularni gubitak kosti povezan sa napredovanjem destrukcije kosti kod višekorenih zuba pacijenata sa hroničnom parodontopatijom imao značajnu povezanost sa gubitkom kosti u interdentalnom području. Kada je interdentalni gubitak kosti veći od 3,10 mm, istovremeno se javlja i nekoliko milimetara interradikularnog gubitka kosti, te se interdentalni gubitak kosti može smatrati približnim vodičem za otkrivanje ranih koštanih oštećenja u furkacijama kod pacijenata sa hroničnom parodontopatijom. Ovo može zaustaviti napredovanje bolesti i dovesti do poboljšane prognoze za interradikularne regije višekorenih zuba.

Zaključak

Na osnovu rezultata istraživanja može se reći da je interradikularni gubitak kosti kod višekorenih zuba osoba sa hroničnom parodontopatijom u pozitivnoj korelaciji sa mezijalnim i distalnim gubitkom interdentalne kosti. Ova korelacija sugeriše na to da lečenje interdentalne destrukcije kosti različitim modalitetima može sprečiti dalji gubitak kosti u interradikularnom području, u skladu sa dužinom korena i anatomijom same furkacije.

Buduća istraživanja treba da budu fokusirana na primenu CBCT koji koristi kalibrisanu kliničku i 3D radiografiju za utvrđivanje, između ostalog, napredovanja parodontalnog oboljenja na mestima furkacija višekorenih zuba.

Zahvalnica: Nema

Sukob interesa: Nema

This study showed that interradicular bone loss associated with the progression of bone destruction in multi-rooted teeth of patients with chronic periodontitis had a significant association with bone loss in the interdental area. When interdental bone loss is greater than 3.10 mm, several millimetres of interradicular bone loss also occurs and interdental bone loss can be considered an approximate guide for detecting early bone damage in furcationsin patients with chronic periodontitis. This can stop the progression of the disease and can lead to an improved prognosis for the interradicular regions of multi-rooted teeth.

Conclusion

Based on the research results, it can be said that interradicular bone loss in multi-rooted teeth of patients with chronic periodontitis is positively correlated with mesial and distal interdental bone loss. This correlation suggests that the treatment of interdental bone destruction with different modalities can prevent further bone loss in the interradicular area according to the length of the root and the anatomy of the furcation itself.

Future research should focus on the application of CBCT using calibrated clinical and 3D radiography to determine, among other things, the progression of periodontal disease at the furcation sites of multi-rooted teeth.

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Conflict of Interest:Nil

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ASOCIJACIJA FIBROBLASTA POVEZANIH SA KARCINOMOM SA KLINIČKO-PATOLOŠKIM PARAMETRIMA ORALNOG KARCINOMA SKVAMOZNIH ĆELIJA: IMUNOHISTOHEMIJSKA STUDIJA

ASSOCIATION OF CARCINOMA-ASSOCIATED FIBROBLASTS WITH CLINICO-PATHOLOGICAL PARAMETERS OF ORAL SQUAMOUS CELL CARCINOMA: AN IMMUNOHISTOCHEMICAL STUDY

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Sažetak

Uvod: *Fibroblasti povezani sa karcinomom (CAFs) iz tumorske mikrosredine (TMS) imaju važnu ulogu u progresiji, recidivu i lošoj prognozi oralnog karcinoma skvamoznih ćelija (OKSĆ).*
Cilj: *Utvrditi gustinu CAFs-a u tumorskoj stromi (TS) i utvrditi povezanost gustine CAFs-a sa kliničko-patološkim parametrima i relapsom bolesti kod pacijenata sa OKSĆ-om.*
Materijal i metode: *Imunohistohemijsko bojenje uzoraka tkiva iz primarnog OKSĆ-a obavljeno je kod 45 pacijenata operisanih na Univerzitetskoj klinici za maksilofacijalnu hirurgiju u Skoplju, u Severnoj Makedoniji. Za vizuelizaciju CAFs-a korišćeno je mišje primarno monoklonsko antitelo anti-α-SMA. Gustina CAFs-a α-SMA+ grupisana je u četiri stepena, a dobijeni podaci statistički su analizirani.*
Rezultati: *Prisustvo CAFs-a nije utvrđeno u uzorcima tkiva kod svih pacijenata sa OKSĆ. Postoji signifikantna povezanost gustine CAFs-a u primarnom tumoru sa T, N i TNM statusom, (p = 0,0006; p = 0,0255; p = 0,0164). Difference testom utvrđeno je da je samo u slučaju relapsa bolesti u vidu lokalnog recidiva procentualna zastupljenost pacijenata sa prisutnim CAFs-om značajno veća u poređenju sa pacijentima koji nisu imali CAFs (p = 0,0001).*
Zaključak: *Ovi nalazi sugerišu ucešće CAFs-a u agresivnosti tumora i progresiji bolesti, ali nisu dovoljni da bi bili uključeni kao parametar u standardizovani histopatološki nalaz kod OSCC-a.*

Ključne reči: *tumorska mikrosredina (TMS), α-SMA pozitivni CAFs (CAFs α-SMA+), planocelularni karcinom usne šupljine (PKUD)*

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Abstract

Introduction: *Cancer-associated fibroblasts (CAFs) from the tumor microenvironment (TME) play an important role in the progression, recurrence and poor prognosis of OSCC.*
The aim: *To determine the density of CAFs in the tumorstroma (TS) of OSCC, and to determine the association of the density of CAFs with clinico-pathological parameters and disease relapse in patients with OSCC.*
Materials and methods: *Immunohistochemical staining of tissue samples from primary OSCC was performed in 45 patients operated at the University Clinic for Maxillofacial Surgery, in Skopje, North Macedonia. A mouse primary monoclonal antibody: anti-α-SMA was used to visualize CAFs. The density of CAFs α-SMA+ was grouped into 4 grades, and the obtained data were statistically analyzed.*
Results: *The presence of CAFs was not determined in tissue samples from all patients with OSCC. There is a significant association of the density of CAFs in the primary tumor with T, N and TNM-status, respectively (p=0.0006, p=0.0255, p=0.0164). The Difference test determined that only in case of disease relapse in the form of local recurrence, the percentage representation of patients with CAFs present was significantly higher compared to patients who did not have CAFs (p=0.0001).*
Conclusions: *These findings are suggestive of the role of CAFs in disease progression, but are insufficient to be included as a parameter in a standardized histopathological finding.*

Key words: *tumor microenvironment (TME), α-SMA-positive carcinoma associated fibroblasts (CAFs α-SMA+), oral squamous cell carcinoma (OSCC)*

Uvod

Oralni karcinom skvamoznih ćelija (OKSĆ) je malignitet sa veoma visokim mortalitetom[1] i niskom stopom preživljavanja (manje od 50%), prvenstveno zbog relapsa bolesti, lokalnih recidiva i metastaza u udaljenim organima. Biološko ponašanje oralnog OKSĆ-a je nepredvidivo, a varijabilnost progresije tumora motiviše istraživače da se fokusiraju na faktore koji utiču na prognozu ovog malignog oboljenja[2].

Prethodno prihvaćeni model u kojem se progresija oralnog karcinoma zasniva na kumulativnim genetskim promenama oralnog epitela prolazi kroz promene; predlaže se nov model u kojem tumorsko mikrookruženje (TMs) ima značajan doprinos u progresiji karcinoma. Novi model ima prognostički i terapeutski značaj[3].

OKSĆ se sastoji od dveju međusobno zavisnih komponenenti: tumorskih epitelnih ćelija i strome, u kojoj su ove ćelije dispergovane. TME ili tzv. stroma (TS) predstavlja složen sistem sastavljen od ćelijskih i nećelijskih komponenata. Ćelijska komponenta ne sadrži samo maligne ćelije već i ćelije mezenhimskog i hematopoetskog porekla, dok je nećelijska komponenta TMS-a ekstracelularni matriks (ECM). U takvom okruženju, tumorske ćelije reprogramiraju okolne stromalne ćelije za tumorigenezu, progresiju karcinoma i invaziju u okolno tkivo[4].

Podskup fibroblasta pod imenom fibroblasti povezani sa karcinomom (CAF) ima kritičnu ulogu u tumorigenezi, invaziji i progresiji OKSĆ-a, a kroz stimulaciju angiogeneze i rekonstrukciju ECM-a vrši pripreme za metastaze u ranoj fazi bolesti; takođe, promoviše recidiv tumora predviđajući lošu prognozu bolesti[5,6,7].

Unakrsna komunikacija između neoplastičnih i stromalnih ćelija modifikuje diferencijaciju, proliferativni i invazivni kapacitet tumorskih ćelija, stvarajući svojstva povezana sa malignitetom, kao što su otpornost na apoptozu, invazija kroz brže i bolje kretanje kroz ECM i sposobnost metastaza. Interakcije između invazivnih tumorskih ćelija i ECM-a rezultiraju novostvorenim okruženjem, koje je pogodno za rast i metastaze neoplastičnih ćelija[8].

Smatra se da CAF u TS-u potiče od normalnih fibroblasta (NF), ali mehanizam tranzicije NF u CAF u OKSĆ-u još uvek nije potpuno razjašnjen.

Introduction

Oral squamous cell carcinoma (OSCC) is a malignancy with a very high mortality[1] and low survival (less than 50%) due primarily to disease relapse, local recurrences, and distant organ metastasis. The biological behavior of oral SCC is unpredictable, and the variability of tumor progression is a motivation for researchers to focus on factors influencing the prognosis of this malignancy[2].

The previously accepted model in which oral cancer progression is based on cumulative genetic alterations of the oral epithelium is undergoing changes, and a new model is proposed in which the tumor microenvironment (TME) has a significant contribution to cancer progression. The new model has prognostic as well as therapeutic importance[3].

SCC consists of two interdependent components: tumor epithelial cells and stroma, in which they are dispersed. The TME or so-called "stroma" (TS) is a complex system composed of cellular and non-cellular components. The cellular component not only contains the malignant cells, but also contains cells of mesenchymal and hematopoietic origin, while the non-cellular component of the TME is the extracellular matrix (ECM). In such an environment, tumor cells reprogram the surrounding stromal cells for tumorigenesis, cancer progression, and invasion of the surrounding tissue[4].

A subset of fibroblasts called cancer-associated fibroblasts (CAFs) has a critical role in tumorigenesis, invasion and progression of OSCC, and through stimulation of angiogenesis and reconstruction of the ECM makes preparations for metastasis in the early stage of the disease. It also promotes tumor recurrence anticipating a poor disease prognosis[5,6,7].

Cross-communication between neoplastic and stromal cells modifies the differentiation, proliferative and invasive capacity of tumor cells, generating properties associated with malignancy such as resistance to apoptosis, invasion through faster and better movement through the ECM, and the ability to metastasize. Interactions between invading tumor cells and the ECM result in a newly created environment that is convenient to the growth and metastasis of neoplastic cells[8].

CAFs in TS are thought to originate from normal fibroblasts (NFs), but the mechanism of transition of NFs to CAFs in OSCC is still poorly elucidated. Many consider them to arise from NFs in which tumor cells induce epigenetic changes with

Mnogi smatraju da nastaju iz NF-a u kojima tumorske ćelije indukuju epigenetske promene sa posledičnom mutacijom NF u CAF. Međutim, CAF mogu nastati i epitelno-mezenhimskom tranzicijom (EMT) epitelnih ćelija iz matičnih ćelija koštane srži koje su podvrgnute EMT-u ili iz transdiferenciranih ćelija, kao što su adipociti, periciti ili ćelije glatkih mišića, citokini dobijeni iz karcionoma[9]. CAF proizvode nekoliko proteina specifičnih za mezenhim, uključujući alfa-aktin glatkih mišića (α-SMA). α-SMA odražava ekspresiju CAF-a u mezenhimu tumora i najčešći je marker CAF-a[10]. CAF koji su pretežno α-SMA pozitivni fibroblasti (CAFS α-SMA+), koji se nazivaju MF, jedan su od glavnih ćelijskih sastojaka TS-a.

Utvrđivanje stadijuma bolesti kod bolesnika sa OKSĆ-om preduslov je za definisanje hirurškog i onkološkog lečenja, ali i za procenu rizika od relapsa bolesti i procenu ukupnog preživljavanja (UP), i ima ključnu prognostičku vrednost. TNM sistem za stadijum karcinoma zasniva se na proceni veličine primarnog tumora (T), zahvatanju lokalno regionalnih limfnih čvorova sa metastazama (N) i udaljenim metastazama (M), ali TNM klasifikacija uzima u obzir samo anatomsko proširenje bolesti. Ugrađivanjem drugih parametara, kakvi su stepen diferencijacije malignih ćelija (G), limfo-vaskularna invazija (LI/VI) i perineuralna invazija (PnI), u postojeće patološke sisteme stadijuma, poboljšana je stratifikacija rizika za nepovoljne ishode, a samim tim i utvrđivanje optimalnog tretmana. Višestruke karakteristike u histopatološkom izveštaju imaju prognostički značaj[11-15]. Uspostavljanje preciznog sistema koji bi definisao anatomski stadijum uz uključivanje bioloških prognostičkih informacija predstavlja izazov za AJCC/UICC. Objavljivanje osmog izdanja AJCC/UICC 2017. godine dovelo je do velike prekretnice u određivanju patološkog stadijuma OKSĆ-a[16,19]. Preporučuju se dalje modifikacije poslednjeg, osmog izdanja, jer u određivanje stadijuma, za razliku od histopatološke analize, biomarkeri i novine iz molekularnih studija za OKSĆ još nisu ugrađeni[20].

Tradicionalni pristupi u histopatološkoj proceni i dalje se fokusiraju na sam tumor, a ne na interakcije između strome i domaćina. Iako su predloženi multifaktorski sistemi pokušali da naprave poboljšanja, trenutno su istraživanja raka fokusirana na ispitivanje uloge TME u progresiji tumora. Thode i saradnici[21] su na osnovu svojih rezultata predložili ažuriranje ovih sistema uvođenjem karakteristika CAF α-SMA+ u standardizovani histopatološki izveštaj.

consequent mutation of NFs in CAFs. But CAFs can also arise by epithelial-mesenchymal transition (EMT) of epithelial cells, from bone marrow stem cells that have undergone EMT, or from trans-differentiated cells such as adipocytes, pericytes or smooth muscle cells Transdifferentiation of NFs into CAFs is driven by cancer-derived cytokines[9]. CAFs produce several mesenchyme-specific proteins including alpha-smooth muscle actin (α-SMA). α-SMA reflects the expression of CAFs in the tumor mesenchyme and is the most common marker of CAFs[10]. CAFs which are predominantly α-SMA-positive fibroblasts (CAFS α-SMA+) called MFs, are one of the main cellular constituents of TS.

Determining the disease stage of a patient with OSCC is a prerequisite for defining surgical and oncological treatment, but also for assessing the risk of disease relapse and estimating overall survival (OS), and has a key prognostic value. The TNM system for cancer staging is based on an assessment of the size of the primary tumor (T), involvement of locoregional lymph nodes with metastasis (N) and distant metastases (M), but TNM classification only takes into account the anatomic extension of the disease. By incorporating other parameters, including the degree of differentiation of malignant cells (G), lymphovascular invasion (LI/VI) and perineural invasion (PnI) into existing pathological staging systems, the stratification of risks for unfavorable outcomes has been improved and consequently, determining the optimal treatment. Multiple features in the histopathological report have prognostic significance[11-15]. Establishing a precise system that would define anatomic staging while incorporating biological prognostic information is a challenge for the AJCC/UICC. The publication of the 8th edition of the AJCC/UICC in 2017 led to a major milestone in determining the pathologic staging of OSCC[16-19]. Further modifications of the last 8th edition are recommended because in determining the stage, apart from histopathological analysis, biomarkers and novelties from molecular studies for OSCC have not yet been incorporated[20].

Traditional approaches in histo-pathological evaluation still focus on the tumor itself, rather than on the interactions between the stroma and the host. Although proposed multifactorial systems have attempted to make improvements, currently cancer research is focused on examining the role of the TME in tumor progression. Thode et al.[21] based on their results proposed updating these systems by introducing the characteristics of CAFs α-SMA+ in the standardized histopathological report.

Materijal i metode

Uzorci tkiva

Ovo je retrospektivno-prospektivna kontrolisana studija, koja je obuhvatila ukupno 45 pacijenata sa patohistološki potvrđenim primarnim oralnim karcinomom skvamoznih ćelija (OKSĆ) na šest lokacija u usnoj duplji (jezik, dno usta, gingiva mandibularnog i maksilarnog alveolarnog grebena, bukalna sluzokoža, nepčana sluzokoža i retromolarno područje). Pacijenti su operisani na Univerzitetskoj klinici za maksilofacijalnu hirurgiju u Skoplju, u Severnoj Makedoniji, u periodu od 2016. do 2021. godine. Pacijenti koji su primali hemoterapiju i radioterapiju pre operacije nisu bili uključeni u studiju.

Uzorci tkiva primarnog karcinoma podvrgnuti su IHC-u i analizirani su na Institutu za patologiju u okviru Univerzitetskog kliničkog centra „Majka Tereza" u Skoplju. Imunohistohemija je izvedena korišćenjem *Dako EnVision flek* sistema. Primarno mišje monoklonsko antitelo anti-α-SMA korišćeno je za vizuelizaciju CAF-a.

Sprovođenje studije odobrila je Etička komisija Stomatološkog fakulteta „Sv. Kirilo i Metodije" Univerziteta u Skoplju, u Severnoj Makedoniji.

Bodovanje rezultata imunološkog bojenja

Analiza slajdova obavljena je digitalnim svetlosnim mikroskopom Nikon 80.

CAF su viđeni kao veliki fibroblasti u obliku vretena sa izduženim jezgrom, koje izražava α-SMA. Za određivanje gustine CAFs-a koristili smo modifikaciju sistema klasifikacije koji su dali Kellerman i saradnici[6,22] i Fujii i saradnici[23]. Nivoi gustine kategorisani su u četiri grupe:

Ocena 0 (negativno);
Ocena 1.(retko);
Ocena 2 (fokalna);
Ocena 3 (obilno).

Uzorci u kojima nisu identifikovani CAF ili oni sa manje od 1% MF obojenih α-SMA klasifikovani su kao negativni, uzorci koji su pokazali sporadično prisustvo rasutih CAF-a po celoj stromi klasifikovani su kao retki, oni sa žarišnim rasporedom koji se vidi kao nepravilno koncentrisano bojenje kao fokalni[23], dok su uzorci koji su pokazali brojne i gusto raspoređene CAF klasifikovani kao obilni (Figura1).

Material and methods

Tissue samples

This is a retrospective-prospective controlled study, which included a total of 45 patients with pathohistologically confirmed primary oral squamous cell carcinoma (OSCC) at six locations in the oral cavity (tongue, floor of mouth, gingiva of the mandibular and maxillary alveolar ridge, buccal mucosa, palatal mucosa and retromolar area). The patients were operated at the University Clinic for Maxillofacial Surgery in Skopje, North Macedonia in the period of 2016-2021. Patients who received chemotherapy and radiotherapy preoperatively were not included in the study.

Tissue samples from primary cancer underwent IHC and were analyzed at the Institute of Pathology, within the University Clinical Center "Mother Teresa" in Skopje. Immunohistochemistry was performed using Dako EnVision flex system. Primary mouse monoclonal antibody: anti-α-SMA was used for visualization of CAFs.

The conduct of the study was approved by the Ethics Committee at the Faculty of Dentistry, Ss. Cyril and Methodius University in Skopje, North Macedonia.

Scoring of immunostaining results

Analysis of the slides was performed with a Nikon 80 digital light microscope.

CAFs were seen as large spindle-shaped fibroblasts with an elongated nucleus expressing α-SMA. To determine the density of CAFs we used the modification of the classification system of Kellerman et al.[6,22] and Fujii et al.[23]. Density levels were categorized into 4 categories:

- Grade 0 (Negative)
- Grade 1 (Rare)
- Grade 2 (Focal)
- Grade 3 (Abundant)

Samples where no CAFs were identified or less than 1% of MFs stained with α-SMA were classified as negative; samples that showed the sporadic presence of scattered CAFs throughout the stroma were classified as rare; those with a focal arrangement seen as irregular concentrated staining were classified as focal[23]; while samples that showed numerous and densely arranged CAFs were classified as abundant (see Figure 1).

α-SMA immunoreactivity observed in endothelial cells in vessel walls was used as an internal positive control[24], and was not included in the calculation[23].

α-SMA imunoreaktivnost primećena u endotelnim ćelijama u zidovima krvnih sudova korišćena je kao interna pozitivna kontrola [24] i nije uključena u analizu[23].

Patološki stadijum bolesti (pTNM) određen je u skladu sa kriterijumima sedmog izdanja UICC/AJCC sistema za gradaciju tumora iz 2010. godine za oralni skvamocelularni karcinom[25-27]. Diferencijacija tumora klasifikovana je u četiri stepena prema Broderovoj histološkoj klasifikaciji diferencijacije tumorskih ćelija (Broderov stepen deskriptivnog sistema)[12,28] – dobro, umereno, loše, nediferencirani (anaplastični)−karcinomi.

Statistička analiza

Podaci dobijeni tokom istraživanja statistički su obrađeni pomoću softverskog paketa SPSS, verzija 20.0 za *Windows* (SPSS, Čikago, IL, SAD).

Fisherov egzaktni test i Fisher–Freeman–Halton egzaktni test korišćeni su kako bi se utvrdila povezanost između određenih atributivnih dihotomnih podataka. Za poređenje proporcija korišćen je test razlike. Za određivanje statističke značajnosti korišćena je dvostrana analiza sa nivoom značajnosti $p < 0,05$.

Pathological stage of disease (pTNM) was determined according to the 2010 UICC/AJCC Cancer Staging System 7th edition criteria for oral squamous cell carcinoma[25,26,27]. Tumor differentiation was classified into 4 grades: well, moderate, poor, undifferentiated (anaplastic)−carcinomas according to Broder's histological classification of differentiation of tumor cells (Broder's grading descriptive system)[12,28].

Statistical analysis

The data obtained during the research were statistically processed using the SPSS software package, version 20.0 for Windows (SPSS, Chicago, IL, USA).

Fisher exact test and Fisher Freeman Halton Exact test were used to determine the association between certain attributive-dichotomous data. Difference test was used to compare the proportions. A two-sided analysis with a significance level of $p<0.05$ was used to determine statistical significance.

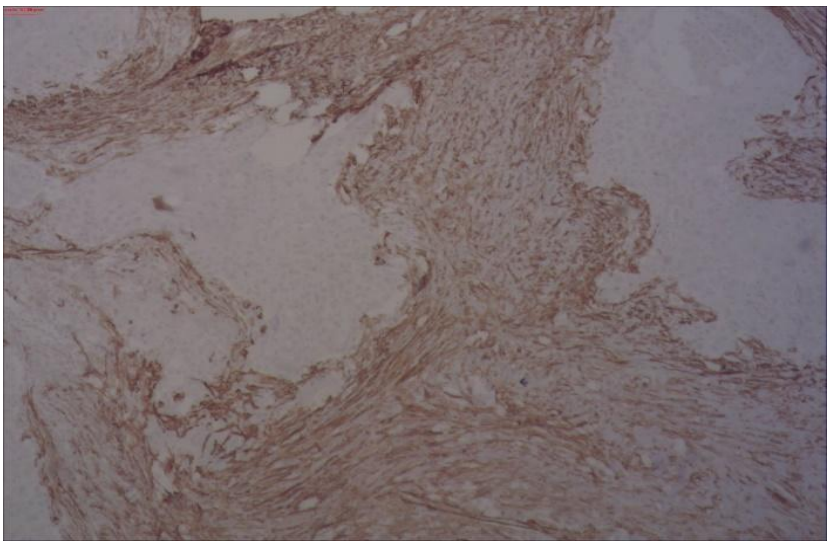

Figura 1. Obilna (Stepen 3) ekspresija α-SMA u tumorskoj stromi OKSĆ-a lokalizovanoj na podu usne duplje pTNM = pT3 pN2b Mk L1 Stadijum IVA

Figure 1. Abundant (Grade 3) expression of α-SMA in tumor stroma of OSCC localized in the floor of the mouth. pTNM=pT3 pN2b Mx L1 Stage IVA

Rezultati

α-SMA pozitivni CAFs (CAFs α-SMA+) utvrđeni su samo u tumorskoj stromi (TS) u 75,5% tumora, dok u 24,4% nisu pronađeni (Tabela 1).

U celom uzorku od 45 pacijenata (100%) *Difference* testom utvrđena je ocena 3 (obilno) kao najzastupljenija; postojala je statistički značajna razlika u zastupljenosti stepena 3 (obilno) u odnosu na ostale stepene gustine CAF-a (Tabela 1).

Nijedan od 45 pacijenata nije imao N3 i G4 stepen diferencijacije malignih epitelnih ćelija.

Fisher–Freeman–Halton egzaktnim testom utvrđena je značajna povezanost T, N, TNM stadijuma sa gustinom CAF-a, odnosno višim T, N, TNM stadijumima (veća tumorska lezija, pozitivni limfni čvorovi na vratu i uznapredovali stadijum bolesti) značajno povezani sa većom gustinom CAF-a, što je potvrđeno i dodatnim grupisanjem T, N i TNM stadijuma u dve kategorije (T1 → T2/ T3 →T4; N0 / N1 → N2 i TNM1 → TNM2/ TNM3 → TNM4), to su mali i veliki tumori, nemaju/imaju metastaze u limfnim čvorovima na vratu i rani/uznapredovali stadijum bolesti (Tabela 2).

Difference testom pokazano je da je procenat pacijenata koji imaju OKSĆ lokalizovan na jeziku sa CAF-om značajno veći od onih kod kojih CAF-a nije bilo. Kod svih pacijenata sa karcinomom dna usne šupljine utvrđeno je prisustvo CAF-a; ta ocena bila je „fokalna" u 12,5% i „obilna" u 87,5% slučajeva. Ni kod jednog od pacijenata sa ovom lokacijom nije primećeno odsustvo CAF-a (Tabela 2).

Nije utvrđena značajna povezanost stepena diferencijacije tumora (G), limfne invazije (LI), perineuralne invazije (PnI) i relapsa bolesti (R) sa gustinom CAFs-a (Fisher–Freeman–Halton egzaktni test) (Tabela 3).

Difference testom utvrđeno je da je samo u slučaju relapsa bolesti u vidu lokalnog recidiva (LR) procentualna zastupljenost pacijenata sa prisutnim CAF-om značajno veća u poređenju sa onima kod kojih CAF nisu pronađeni (Tabela 3).

Results

α-SMA positive CAFs (CAFs α-SMA+) were determined only in the tumor stroma (TS) in 75.5% of tumors, while in 24.4% they were not found (see Table 1).

In the entire sample of 45 patients (100%), the *Difference* test determined the grade 3 (abundant) as most represented percentage, and there was a statistically significant difference in the representation of grade 3 (abundant) in relation to the other degrees of density of CAFs (see Table 1).

None of the 45 patients had N3 and G4-grade of differentiation of the malignant epithelial cells.

Fisher Freeman Halton Exact test determined a significant association of T, N, TNM stage with the density of CAFs, i.e. higher T, N, TNM stages (bigger tumor lesion, positive neck lymph nodes and more advanced stage of the disease) significantly associated with a higher density of CAFs, which was also confirmed by additional grouping of T, N and TNM stage into two categories (T1→T2/ T3→T4; N0 / N1→N2 and TNM1→TNM2/ TNM3→ TNM4), that is small and large tumors, no/have neck lymph node metastases, and early/advanced disease stage (see Table 2).

The *Difference* test showed that the percentage of patients with OSCC localized on the tongue who had CAFs was significantly higher compared to those where CAFs were absent. In all patients with carcinoma of the floor of the mouth, the presence of CAFs was determined, and that grade was "focal" in 12.5% and "abundant" in 87.5%. In none of the patients with this location, the absence of CAFs was determined (see Table 2).

No significant association of the degree of tumor differentiation (G), lymphatic invasion (LI), perineural invasion (PnI) and disease relapse (R) with the density of CAFs was determined (Fisher Freeman Halton Exact test) (seeTable 3).

The *Difference* test determined that only in case of relapse of the disease in the form of local recurrence (LR), the percentage representation of patients with CAFs present was significantly higher compared to those where CAFs were not found (see Table 3).

Tabela 1. Analiza odabranih kliničko-patoloških parametara prema stepenu gustine CAF α-SMA+

Table 1. Analysis of selected clinical-pathological parameters according to degrees of density of CAFs α-SMA+

Parameters	CAFs α-SMA+ grade				p
	CAFs 0 N=11	CAFs 1 N=8	CAFs 2 N=6	CAFs 3 N=20	
T - stage					
T1 (N=12)	9 (75%)	2 (16.67%)	0 (0%)	1 (8.33%)	T1→T4 / N+R→F+A †p=0.0006*
T2 (N=16)	1 (6.25%)	4 (25%)	2 (12.5%)	9 (56.25%)	
T3 (N=8)	0 (0%)	2 (25%)	2 (25%)	4 (50%)	
T4 (N=9)	1 (11.11%)	0 (0%)	2 (22.22%)	6 (66.67%)	
T – stage (groups)					
T1→T2 (N=28)	10 (35.71%)	6 (21.43%)	2 (7.15%)	10 (35.71%)	†p=0.0491*
T3→T4 (N=17)	1 (5.88%)	2 (11.76%)	4 (23.53%)	10 (58.82%)	
N - stage					
N0 (N=31)	10 (32.26%)	6 (19.35%)	1 (3.23%)	14 (45.16%)	N0→N1 / N→A †p=0.0255*
N1 (N=11)	1 (9.09%)	2 (18.18%)	4 (36.36%)	4 (36.36%)	
N2 (N=3)	0 (0%)	0 (0%)	1 (33.33%)	2 (66.67%)	-
N – stage (groups)					
N0 (N=31)	10 (32.26%)	6 (19.35%)	1 (3.23%)	14 (45.16%)	†p=0.0164*
N1→N2 (N=14)	1 (7.14%)	2 (14.29%)	5 (35.71%)	6 (42.86%)	
TNM - stage					
TNM1 (N=10)	8 (80%)	2 (20%)	0 (0%)	0 (0%)	TNM1→TNM4 / N→R+F+A †p=0.00001*
TNM2 (N=12)	1 (8.33%)	4 (33.33%)	0 (0%)	7 (58.33%)	
TNM3 (N=11)	1 (9.09%)	2 (18.18%)	3 (27.27%)	5 (45.45%)	
TNM4 (N=12)	1 (8.33%)	0 (0%)	3 (25%)	8 (66.67%)	
TNM – stage (groups)					
TNM 1→TNM2 (N=22)	9 (40,91%)	6 (27,27%)	0 (0%)	7 (31,82%)	††p=0,0165*
TNM 3→TNM4 (N=23)	2 (8,70%)	2 (8,70%)	6 (26,09%)	13 (56,52%)	
Localisation					
Floor of the mouth (N=8)	0 (0%)	0 (0%)	1 (12.50%)	7 (87.50%)	-
Tongue (N=20)	6 (30%)	5 (25%)	1 (5.00%)	8 (40%)	†††p=0.0125*
Buccal mucosa (N=7)	2 (28.57%)	2 (28.57%)	3 (42.86%)	0 (0%)	†††p=0.1224
Gingival mucosa (N=8)	3 (37.50%)	0 (0%)	1 (12.50)	4 (50%)	†††p=0.3329
Retromolar area (N=1)	0 (0%)	0 (0%)	0 (0%)	1 (100%)	-
Palate (N=1)	0 (0%)	1 (100%)	0 (0%)	0 (0%)	-

T stadijum (veličina tumora); N stadijum (metastaze u cervikalnim limfnim čvorovima); TNM – patološki staging tumor–čvor–metastaza
Negativno + Retko/Fokalno + Obilno = N + R → F + A
† Fisher–Freeman–Halton egzaktni test; † † CAFs: nema/ima – Fisherov egzaktni test; ††† Test razlike (CAF nema/ima), *nivo značajnosti $p < 0,05$
CAFs0 = Negative; CAFs1 =Rare; CAFs2 = Focal; CAFs3 = Abundant
T- stage (tumor size); N- stage (cervical lymph node metastasis);TNM – pathological tumor-node-metastasis staging
Negative+Rare/Focal+Abundant = N+R→F+A
†Fisher Freeman Halton Exact test;† † CAFs : no/have – Fisher exact test ;†††Difference test (CAFs no/have),*significant for $p<0.05$

Tabela 2. Analiza odabranih kliničko-patoloških parametara prema stepenu gustine CAFs α-SMA+

Table 2. Analysis of selected clinical-pathological parameters according to the degree of density of CAFs α-SMA+

Parameters	CAFs α-SMA grade				p
	CAFs 0 N=11	CAFs 1 N=8	CAFs 2 N=6	CAFs 3 N=20	
G - grade					
G1 (N=6)	2 (33.33%)	2 (33.33%)	0 (0%)	2 (33.33%)	G1→G3 / N+R→F+A †p=0.3573
G2 (N=28)	9 (32.14%)	3 (10.71%)	4 (14.29%)	12 (42.86%)	
G3 (N=10)	0 (0%)	3 (30%)	2 (20%)	5 (50%)	
G – grade (groups)					
G1→ G2 (N=34)	11 (32.35%)	5(14.71%)	4 (11.76%)	14 (41.18%)	††p=0.4744
G3 (N=10)	0 (0%)	3 (30%)	2 (20%)	5 (50%)	
LI– Lymphatic invasion					
No invasion (N=28)	9 (32.14%)	6 (21.43%)	3 (10.71%)	10 (35.71%)	†p=0.2609
Have invasion (N=17)	2 (11.76%)	2 (11.76%)	3 (17.65%)	10 (58.82%)	
PnI – Perineural invasion					
No invasion (N=37)	11 (29.73%)	6 (16.22%)	3 (8.11%)	17 (45.95%)	No→Have / N+R→F+A ††p=0.4355
Haveinvasion (N=8)	0 (0%)	2 (25%)	3 (37.50%)	3 (37.50%)	
R - Recurrence					
No (N=17)	3 (17.65%)	3 (17.65%)	3 (17.65%)	8 (47.06%)	†p=0.7948
Have (N=27)	8 (29.63%)	5 (18.52%)	3 (11.11%)	11 (40.74%)	
TR–Type of reccurence					
LNM (N=5)	3 (60%)	0 (0%)	1 (20%)	1 (20%)	†††p=0.5485
LR (N=18)	3 (16.67%)	5 (27.78%)	1 (5.56%)	9 (50%)	†††p=0.0001*
LR+LNM (N=4)	2 (50%)	0 (0%)	1 (25%)	1 (25%)	†††p=1.000

CAFs0 = Negativni; CAFs1 = Retko; CAFs2 = Fokalno; CAFs3 = Obilno
G – stepen diferencijacije; G1 – dobro diferentovan; G2 – umeren; G3 – slab; G4 – nediferentovan (anaplastični karcinom)
R – rekurentan; TR – tip rekurencije; LNM – metastaze cervikalnih limfnih čvorova; LR – lokalni recidiv; LR + LNM – lokalni recidiv i metastaze u cervikalnim limfnim čvorovima
† Fisher–Freeman–Halton egzaktni test; † † CAFs stepen: negativan + retko/fokalno + obilan – Fisherov egzaktni test; ††† Test razlike (CAF nema/ima)
*nivo značajnosti $p < 0,05$CAFs0 = Negative; CAFs1 =Rare; CAFs2 = Focal; CAFs3 = Abundant
G-grade of differentiation; G1-well differentiated, G2-moderate; G3-poor; G4-undifferentiated (anaplastic carcinoma)
R-reccurence, TR- type of reccurence; LNM – cervical lymph node metastasis; LR – local recurrence;LR+LNM - local recurrence and cervical lymph node metastases
†Fisher Freeman Halton Exact test ;† † CAFs degree: Negative+Rare/Focal+Abundant – Fisher exact test; †††Difference test (CAFs No/Have)
*significant for $p<0,05$

Tabela 3. Distribucija OKSĆ pacijenata prema stepenu gustine CAFs a-SMA+

Table 3. Distribution of OSCC patients according to degrees of density of CAFs α-SMA+

OSCC (N=45)		
CAFs α-SMA grade / stepen	N (%)	[1]p
CAFs 0 – Negative / Negativno	11 (24.44%)	N/R – p=0.4421 N / F - p=0.1806 N/ A - p=0.0471* R / F - p=0.5617 R / A - p=0.0066* F / A - p=0.0012*
CAFs 1 – Rare / Retko	8 (17.79%)	
CAFs 2 - Focal / Fokalno	6 (13.33%)	
CAFs 3 - Abundant / Obilno	20 (44.44%)	

[1]Difference test *nivo značajnosti / [1]Difference test *significantp<0,05

Diskusija

U tumorskoj stromi OKSĆ-a, gustina CAF-a u interakciji sa kancerskim ćelijama je promenljiva. U in vitro studiji Kellermann i sar.[22] uočeno je povećanje ekspresije α-SMA u OSCC-u tokom transdiferencijacije NF u CAF posredovane stimulacijom TGF-b1[22]. Intrigantni su podaci o visoko-polimorfnom duktalnom karcinomu (dojke in situ) i neinvazivnom urotelnom karcinomu mokraćne bešike kod kojih su CAF identifikovani u stromi koja okružuje kancerske ćelije; pokazujući da faktori koji potiču iz agresivnih malignih epitelnih tumorskih ćelija mogu prelaziti bazalnu membranu koja stimuliše transformaciju MFs-a[29].

Chaudhari i sar.[30], Kapse i sar.[31] i Chauhan i sar.[32] istraživali su ulogu CAF-a u progresiji premalignih lezija u oralnom skvamoznom karcinomu i utvrdili da je povećana distribucija CAF-a u korelaciji sa progresijom potencijalno malignih lezija oralne sluzokože u invazivni fenotip, tj. kod karcinoma skvamoznih ćelija usne šupljine, zaključivši da se mogu koristiti kao stromalni markeri za maligne lezije oralne sluzokože.

U ovoj studiji klasifikovali smo gustinu CAF-a u četiri stepena, koristeći novu definiciju „fokalne" distribucije (Ocena 2)[23] i vodeći se nalazima određenih studija o raku dojke i kolorektalnom karcinomu koje su pokazale da su stepeni 2 i 3 koncentrisani na invazivnom prednjem delu tumora i sugerisale da se interakcija CAF-a sa ćelijama raka dešava upravo na invazivnom prednjem delu tumora[23,33].

Analizom T stadijuma u našoj studiji utvrđeno je da najveći procenat (75%) pacijenata sa malim tumorima (T1) nije imao CAF, kao i da je najveći procenat (66,7%) pacijenata sa velikim tumorima (T4) imao obilnu (Ocena 3) gustinu CAF-a; dakle, što je tumorska lezija veća, to je veća gustina CAF-a. Ne samo da se gustina CAF-a kvantitativno povećava u većim tumorima, u primarnim tumorima sa pozitivnim limfnim čvorovima na vratu za metastatske naslage (N+) i u uznapredovalim stadijumima bolesti, već su i veliki tumori i N+ vrata takođe značajno povezani sa „fokalnim" obrascem (Stepen 2) distribucije CAF-a. Kaplan–Mejerova analiza preživljavanja u studiji OKSĆ-a otkrila je značajno nižu stopu preživljavanja i najveći mortalitet kod pacijenata sa „fokalnom distribucijom" CAF-a (Stepen 2) u poređenju sa drugim stepenom gustine.

Discussion

In the tumor stroma of OSCC, the density of CAFs interacting with cancer cells is variable. Kellermann et al.[22] in vitro study reported an increase in α-SMA expression in OSCC during transdifferentiation of NFs into CAFs mediated by stimulation of carcinoma-derived TGF-β1[22]. Intriguing is the data on highly polymorphic ductal carcinoma in situ of the breast and non-invasive urothelial carcinoma of the bladder in which CAFs were identified in the stroma surrounding the cancer cells, demonstrating that factors derived from aggressive malignant epithelial tumor cells are able to cross the basement membrane stimulating transformation of MFs[29].

Chaudhary et al.[30], Kapse et al.[31] and Chauhan et al.[32] investigated the role of CAFs in the progression of premalignant lesions in oral squamous cell carcinoma, and determined that an increased distribution of CAFs correlated with the progression of potentially malignant lesions of the oral mucosa to an invasive phenotype ie. in oral squamous cell carcinoma, concluding that they can be used as stromal markers for malignant lesions of the oral mucosa.

In our study, we classified the density of CAFs into 4 grades, using a new definition of "focal" distribution (grade 2)[23], guided by findings of some studies of breast cancer and colorectal cancer, which demonstrated that grades 2 and 3 are concentrated at the invasive front of the tumor and suggested that the interaction of CAFs with cancer cells occurs precisely at the invasive front of the tumor[23,33].

Analysis of T-stage in our study determined that the highest percentage (75%) of patients with small tumors (T1) had no CAFs, while the highest percentage (66.7%) of patients with large tumors (T4) had abundant (Grade 3) density of CAFs, that is, the larger the tumor lesion, the higher the density of CAFs. But not only does the density of CAFs increase quantitatively in larger tumors, in primary tumors with positive neck lymph nodes for metastatic deposits (N+) and in advanced disease stages, but large tumors and N+ neck are also significantly associated with the "focal" pattern (Grade 2) of CAFs distribution. Kaplan–Meyer survival analysis in a study of OSCC revealed a significantly lower survival rate and the highest mortality in patients with a "focal distribution" of CAFs (Grade 2) compared to other density grades. They explained this by the scattered distribution of CAFs in Stage 2 which allows cancer cells to migrate between CAFs, and the interactions between these two types of cells contribute to tumor growth and disease

To je objašnjeno raštrkanom distribucijom CAF-a u fazi 2, koja omogućava kancerskim ćelijama da migriraju između CAF-a; interakcije između ovih dvaju tipova ćelija doprinose rastu tumora i progresiji bolesti[23]. Nasuprot našim rezultatima, neki istraživači nisu uspeli da pronađu povezanost gustine CAF-a sa veličinom primarnog tumora[22, 23], ali su opsežne studije ustanovile značajnu povezanost između visoke gustine CAF-a i velikih karcinoma jezika[34] i nazofarinksa[35].

Marilin Vered i sar.[36] su u studiju CAFs-a i EMT-a u metastatskom OKSĆ-u jezika uključili 19 podudarnih parova uzoraka primarnog tumora i cervikalnih limfnih čvorova sa metastazama. Korišćenjem panela imunohistohemijskih markera za identifikaciju CAF-a i EMT-a utvrđeno je da se sa EMT-om gubi epitelni fenotip karcinoma i stiču mezenhimske karakteristike neophodne za invaziju tumora i metastaze. Ulogu stromalnih miofibroblasta (MF) kao prediktivnih markera za metastaze u limfnim čvorovima potvrdili su Smitha i sar.[37]. Rezultati njihove studije pokazali su značajno veći broj CAF α-SMA+ u N+ statusu u poređenju sa N0 statusom, potvrđujući pozitivnu korelaciju između visokih gustina CAF-a i N stadijuma kod pacijenata sa OKSĆ-om, a to potvrđuje i rezultat dobijen u našoj studiji.

Određene kliničko-patološke studije pokazale su da gustina CAF-a u OKSĆ-u značajno korelira sa N statusom, VI i LI, što sugeriše da CAF pomažu u metastazama, dok obilno prisustvo CAF-a u prednjem delu invazivnog tumora korelira sa PnI i kraćim vremenom preživljavanja, tj. obilno prisustvo CAF-a u njihovoj studiji indikativno je za postojanje biološki agresivnijeg krcinoma[6].

Analiza odsustva/prisustva CAF-a u primarnim tumorima u odnosu na relaps bolesti pokazala je da nema značajne razlike u procentualnoj zastupljenosti pacijenata sa CAF-om i bez njih. Stepen 3 je preovladavao skoro podjednako kod pacijenata sa relapsom i bez recidiva. Kod pojave lokalnog recidiva, procentualna zastupljenost pacijenata koji su imali CAF bila je značajno veća u odnosu na pacijente koji nisu imali CAF, što možda predviđa da će kod pacijenata koji imaju CAF doći do eventualnog relapsa bolesti u vidu lokalnog recidiva. U studiji Kellermana i sar.[22] obilno prisustvo CAF-a u primarnom OKSĆ-u značajno je povezano sa N+ na početnoj prezentaciji i sa pojavom LNM-a na vratu nakon tretmana, odnosno visoka gustina CAF-a ukazuje na postojanje izrazito agresivnih tumora koji pokazuju tendenciju recidiva, u vidu metastaza na vratu.

progression[23]. In contrast to our results, some researchers have failed to find an association of CAFs density with the size of the primary tumor[22,23], but extensive studies have established a significant association between a high density of CAFs and large cancers of the tongue[34] and nasopharynx[35].

Marilyn Vered et al.[36] in a study of CAFs and EMT in metastatic OSCC of the tongue included 19 matched pairs of primary tumor and cervical lymph node specimens with metastatic deposits. Through the use of a panel of immunohistochemical markers for the identification of CAFs and EMT, she determined that with EMT, the epithelial phenotype of cancer is lost, and mesenchymal characteristics necessary for tumor invasion and metastasis are acquired. The role of stromal myofibroblasts (MFs) as predictive markers for lymph node metastasis was confirmed by Smitha et al.[37]. Their results demonstrated a significantly higher number of CAFs α-SMA+ in N+ status compared to N0 status, confirming a positive correlation between a high density of CAFs and N-stage in OSCC patients, which is also confirmed by the result obtained in our study.

Some clinicopathological studies have demonstrated that the density of CAFs in OSCC significantly correlates with N-status, VI, and LI, suggesting that CAFs assist in metastasis, while the abundant presence of CAFs in the invasive tumor front correlates with PnI and shorter survival time i.e. the abundant presence of CAFs in their study was indicative of the existence of a biologically more aggressive cancer[6].

The analysis of the absence/presence of CAFs in primary tumors in relation to disease relapse showed that there was no significant difference in the percentage representation of patients who did not have/ have CAFs. Grade 3 predominated almost equally in relapsed and non-relapsed patients. At the occurrence of local recurrence, the percentage representation of patients who had CAFs was significantly higher compared to patients who did not have CAFs, which perhaps anticipates that in patients who have CAFs, eventual relapse of the disease would occur in the form of local recurrence.

In the study by Kellerman et al.[22] the abundant presence of CAFs in primary OSCC was significantly associated with the N+ at the initial presentation and with the appearance of neck LNMs after treatment, i.e. the high density of CAFs indicated the existence of distinctly aggressive tumors that

Ova studija je, prema našim saznanjima, prvi zapis do sada o tome da visoka gustina CAF-a može biti korisna u predviđanju prognoze pacijenata sa oralnim karcinomom, pošto su cervikalni LNM jedan od najvažnijih prognostičkih faktora za bolest. Suprotno našim rezultatima, obilno prisustvo CAF-a u njihovoj studiji nije bilo povezano sa lokalnim recidivom bolesti.

Analiza šest lokalizacija oralnog karcinoma pokazala je da je najčešći karcinom jezika. Ovaj karcinom se razlikuje od karcinoma drugih lokalizacija i prema rezultatu koji je pokazao da je broj pacijenata sa karcinomom jezika, koji imaju CAF (70%) značajno veći od onih koji nemaju CAF. Za razliku od ovog karcinoma, svi pacijenti sa karcinomom dna usne šupljine imali su CAF, a čak 87,5% njih imalo je „obilnu" (Stepen 3) gustinu. Imajući u vidu dobijene rezultate, možda su CAF ključni akteri odgovorni za to što je karcinom ovih dveju lokalizacija najteže kontrolisati. Prema analizi baze podataka *Surveillance, Epidemiology, and End Results* (SEER), vredi napomenuti da je jezik najčešća lokalizacija i da je povezan sa većom smrtnošću oralnih karcinoma drugih lokalizacija[20].

Opšte je prihvaćeno da CAF ispoljavaju protumorski efekat stimulišući rast i progresiju tumora. Međutim, nedavne studije pokazuju efekat CAF-a na inhibiciju tumora, što sugeriše da oni pokazuju sličan stepen plastičnosti kao i druge stromalne ćelije. Recipročne interakcije sa okruženjem tumora i različitim izvorima porekla pojavljuju se kao dva važna faktora koja podržavaju heterogenost CAF-a. Ova studija naglašava nedavni napredak u razumevanju biologije CAF-a i predlaže da se proširi pojam ćelijske „polarizacije", koji je prethodno uveden kako bi se opisala različita stanja aktivacije CAF-a, čime se potvrđuje njihova fenotipska raznolikost[38].

Sa idejom da se razjasni uloga CAF-a u OSCC-u, zaključci studije Vereda i sar.[39] i Lima i sar.[40] ukazuju na to da njihova gustina odražava biološka svojstva tumora. Shodno tome, veća gustina ukazuje na agresivniji tumor, sa većom moći za recidiv i lošijom prognozom.

show a tendency to relapse, in the form of neck metastases. This study, to our knowledge, is the first record so far that a high density of CAFs can be useful in predicting the prognosis of patients with oral cancer, since cervical LNMs are one of the most important prognostic factors for the disease. Contrary to our results, the abundant presence of CAFs in their study was not associated with local disease recurrence.

The analysis of the 6 localizations of oral cancer showed that the most common was tongue cancer. Tongue carcinoma differs from carcinomas of other localizations and according to the result that indicated that the number of tongue carcinoma patients who have CAFs (70%) is significantly higher compared to those who do not have CAFs. In contrast to this carcinoma, all patients with carcinoma of the floor of the mouth had CAFs, and even 87.5% of them had "abundant" (Grade 3) density. Considering the obtained results, perhaps CAFs are the key players responsible for the fact that cancers of these two localizations are the most difficult to control. According to the analysis of the *Surveillance, Epidemiology, and End Results* (SEER) database, it is noteworthy that the tongue is the most common localization and is associated with higher mortality than oral cancers of other localizations[20].

It is generally accepted that CAFs exhibit a pro-tumor effect by stimulating tumor growth and progression. But recent studies demonstrate a tumor-inhibitory effect of CAFs suggesting that they exhibit a similar degree of plasticity as other stromal cells. Reciprocal interactions with the tumor environment and different sources of origin appear as two important factors underpinning the heterogeneity of CAFs. This study highlights recent advances in understanding of the biology of CAFs and proposes to extend the term cell "polarization" previously introduced to describe different activation states of CAFs thus confirming their phenotypic diversity[38].

With the idea of elucidating the role of CAFs in OSCC, the conclusions of the study by Vered et al.[39] and Lim et al.[40] indicated that their density reflects the biological properties of the tumor. Accordingly, a higher density indicates a more aggressive tumor, with a greater power for recurrence and a worse prognosis.

Zaključak

Nekoliko studija ukazalo je na mogućnost upotrebe CAF-a kao važnog prognostičkog faktora kod različitih tumora, iako je njihov klinički značaj u prognostičke svrhe za oralni karcinom skvamoznih ćelija retko prijavljivan. Napredak istraživanja biomarkera specifičnih za oralni karcinom skvamoznih ćelija još uvek je nezadovoljavajući; otuda postoji potreba za prospektivnim analizama za njihovu identifikaciju i upotrebu u skriningu i identifikaciji pojedinaca u riziku od razvoja primarnog karcinoma ili identifikacije agresivnih tumora sa rekurentnim karakteristikama koji imaju lošu prognozu.

Zahvalnica: Nema

Sukob interesa: Nema

Conclusion

Several studies have indicated the possibility of CAFs being used as an important prognostic factor in a variety of tumors although their clinical significance in prognostic purposes for oral squamous cell carcinoma has rarely been reported. Research progress on biomarkers specific to oral squamous cell carcinoma is still unsatisfactory. Hence, there is a need for prospective analyses for their identification and use in screening and identification of individuals at risk of developing primary cancer or identification of aggressive tumors with recurrent features that have a poor prognosis.

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MODIFIKOVANA MILOHIOIDNA ANESTEZIJA SA 4% ARTIKAINOM I ADRENALINOM I DEKSAMETAZONOM U HIRURGIJI MANDIBULARNIH MOLARA: PILOT STUDIJA

MODIFIED MYLOHYOID ANESTHESIA WITH 4% ARTICAINE AND WITH ADRENALINE AND DEXASAMETHASONE IN MANDIBULAR MOLAR SURGERY: A PILOT STUDY

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Sažetak

Uvod: *Milohioidna mandibularna anestezija nije standardna i samostalna primarna anestezija za izvođenje operacija na mandibularnim zubima.*
Cilj: *Da se ispita uspešnost postignute milohioidne anestezije za hirurgiju mandibularnih molara, ubrizgavanjem anestetika, koji može da penetrira u kost u lingvalnom predelu mandibule, tehnikom za modifikovanu milohioidnu mandibularnu anesteziju.*
Materijal i metode: *U pilot studiji, 10 pacijenata je podeljeno u 2 jednake grupe (5 pacijenata), oba pola i starosti od 18-75g., kojima je zbog hirurgije mandibularnih molara bila neophodna mandibularna anestezija. U I grupi, modifikovanim milohioidnim pristupom ubrizgan je 3,5 ml 4% artikain sa adrenalinom 1:100000 sa dodatkom 0,5ml/4mg deksametazona, u sublingvalni predeo ugla mandibule modifikovanim milohioidnim pristupom; u II grupi je pristupom za standardnu mandibularnu sprovodnu direktnu anesteziju u predeo foramena mandibule, ubrizgano 4ml 2% lidokaina sa adrenalinom 1: 100000. Primenjena je vizuelno analogna skala (VAS) za subjektivnu procenu bola u toku operacije kod pacijenata, beleženo je vreme postignute dužine trajanja postignute mandibularne anestezije, kao i ukupna efikasnost postignutih anestezija, izražena u procentima.*
Rezultati: *Kod svih pacijenata je postignuta uspešna intervencija, sa različitom ocenom VAS-a, ali u vrednostima koje označavaju uspešnu anesteziju (I grupa 17.40±11.10mm; II grupa 12.80±4.55mm). Postignuto je duže vreme trajanja anestezije u I grupi 205,2 min (3h 25'), u odnosu na drugu grupu 182min (3h 2').*
Zaključak: *Modifikovana milohioidna mandibularna anestezija sa 4% artikainom sa adrenalinom i deksametazonom mogla bi da bude, primenjena kao primarna anestezija, za uspešno postizanje standardne mandibularne anestezije.*

Ključne reči: *modifikovana, milohioidna anestezija, artikain, mandibularni molari, hirurgija*

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Abstract

Introduction: *Mylohyoid mandibular anesthesia is not a standard and independent primary anesthesia for performing surgery on mandibular teeth.*
Objective: *The objective was to examine the success of achieved mylohyoid anesthesia for mandibular molar surgery, by injecting an anesthetic that could penetrate the bone in the lingual region of the mandible, using the technique for modified mylohyoid mandibular anesthesia.*
Materials and methods: *In the pilot study, 10 patients were divided into 2 equal groups (of 5 patients each), of both sexes and aged 18–75, who required mandibular anesthesia owing to mandibular molar surgery. In group I, 3.5 ml of 4% articaine with 1:100000 adrenaline, and the addition of 0.5 ml/4 mg of dexamethasone, was injected into the sublingual region of the corner of the mandible using a modified mylohyoid approach; in group II, 4 ml of 2% lidocaine with 1:100000 adrenaline was injected into the region of the mandibular foramen using the approach for standard mandibular conduction direct anesthesia. A visual analogue scale (VAS) was used for the subjective assessment of the pain during surgery in patients, the recorded duration of the realized mandibular anesthesia, as well as the total effectiveness of the achieved anesthesia, expressed in percentages.*
Results: *A successful intervention was achieved in all patients, with different VAS scores, but within the values indicating successful anesthesia (group I: 17.40±11.10mm; group II: 12.80±4.55mm). A longer duration of anesthesia was achieved in the first group—205.2 min (3h 25 min), compared to the second group—182 min (3h 2 min).*
Conclusion: *Mylohyoid mandibular anesthesia with 4% articaine and with adrenaline and dexamethasone could be applied as primary anesthesia for the purpose of successfully achieving standard mandibular anesthesia.*

Key words: *modified, mylohyoid mandibular anesthesia, articaine, mandibular molars, surgery*

Uvod

U svakodnevnoj stomatološkoj praksi, kao i u ambulantnoj dentoalveolarnoj hirurgiji, anestezija za donji alveolarni nerv, kao i za drugu oralnu granu mandibularnog nerva (*n. lingualis*), postiže se sprovodnom direktnom mandibularnom tehnikom anestezije (Halstedova tehnika), kojom se ubrizgava lokalni anestetik u predeo foramena mandibule[1-3]. Iako je Halstedova tehnika lokalne anestezije izuzetno uspešna tehnika (zato se u kliničkoj praksi standardno naziva mandibularna anestezija), u različitim studijama zabeležen je neuspeh od 38% do 75% kod pacijenata kod kojih je primenjena Halstedova tehnika mandibularne anestezije[4,5].

Lokalni anestetik koji se masovno koristi u stomatološkoj praksi i koji može predstavljati „zlatni standard" jeste 2% lidokain sa adrenalinom (1 : 100000); on poseduje dobra farmakodinamska i farmakokinetička svojstva i spada u lokalne anestetike sa srednjom dužinom trajanja postignute lokalne anestezije (190 min). Međutim, lidokain nema svojstvo da prodire u koštana tkiva[6].

Artikain pripada grupi amidnih anestetika (zajedno sa lidokainom, mepivakainom, bupivakainom i prilokainom) i ima estarsku grupu, kao i tiofenski prsten umesto benzenskog prstena. Tiofenski prsten omogućava artikainu izuzetnu lipofilnost i brzinu prodiranja u ćelije kroz lipidnu membranu nervne ćelije, kao i u okolno tkivo[7-9]. Tiofenski prsten odgovoran je za moguću difuziju artikaina kroz kost, odnosno intramolekularna vodonična veza u artikainu može biti povezana sa superiornim koštano-tkivnim prodorom artikaina[10]. Artikain postiže viši anestetički uspeh nego lidokain za mandibularne i maksilarne molare bukalnom infiltracijom[11-13]; upravo je postojanje tiofenskog prstena objašnjenje većeg uspeha artikaina u odnosu na lidokain[14] .

Zabeleženo je i da artikain, kao dopunska infiltraciona anestezija za mandibularne zube, daje bolji anestetički efekat pulpalne anestezije kod neuspešnih mandibularnih anestezija sa lidokainom[15].

Podaci iz literature pružili su dokaze o uspešnoj primeni deksametazona u kombinaciji sa lokalnim anesteticima dugog dejstva u obezbeđivanju perioperativne anestezije / analgezije[16-18].

Jedan od mogućih razloga za neuspeh standardne mandibularne anestezije jeste i dopunska senzitivna inervacija mandibularnih zuba od 10% do 20%, od strane milohioidnog nerva, koji primarno obezbeđuje motornu inervaciju za digastrični mišić i milohioidni mišić[19].

Introduction

In daily dental practice, as well as in ambulatory dentoalveolar surgery, anesthesia for the lower alveolar nerve, as well as for the second oral branch of the mandibular nerve (*n. lingualis*), is achieved with the direct mandibular anesthesia technique (the Halsted technique), where a local anesthetic is injected into the foramen area of the mandible[1-3]. Although the Halsted technique of local anesthesia is an extremely successful technique, which is why it is called mandibular anesthesia as a standard in clinical practice, various studies have recorded a failure rate of 38–75% in patients to whom the Halsted technique of mandibular anesthesia was administred[4,5].

Lidocaine 2% with adrenaline (1:100000) is a local anesthetic widely used in dental practice, which can represent the "gold standard"; it possesses good pharmacodynamic and pharmacokinetic properties, and belongs to a group of local anesthetics with a medium duration of realized local anesthesia (190 min). However, lidocaine does not possess the ability to penetrate bone tissues[6].

Articaine belongs to the group of amide anesthetics (along with lidocaine, mepivacaine, bupivacaine and prilocaine), and has an ester group, as well as a thiophene ring instead of a benzene ring. The thiophene ring enables articaine's exceptional lipophilicity and speed of penetration into cells through the lipid membrane of the nerve cell, as well as into the surrounding tissue[7–9]. The thiophene ring is responsible for the possible diffusion of articaine through the bone, i.e., the intramolecular hydrogen bond in articaine can be connected to the superior bone tissue via articaine penetration[10]. Through buccal infiltration, articaine achieves a higher anesthetic success for mandibular and maxillary molars than lidocaine does[11–13] and the existence of the thiophene ring is the explanation for the greater success of articaine compared to lidocaine[14].

It has also been noted that articaine gives a better anesthetic effect of pulpal anesthesia as a supplementary infiltration anesthesia for mandibular teeth, in case of unsuccessful mandibular anesthesia with lidocaine[15].

Literature data have provided evidence of the successful application of dexamethasone in combination with long-acting local anesthetics for the provision of perioperative anesthesia/analgesia[16–18].

One of the possible reasons for the failure of standard mandibular anesthesia is

U nama dostupnoj literaturi na engleskom jeziku, oskudni su podaci koji ukazuju na to da je uspešno korišćena milohioidna anestezija kao primarna anestezija za hirurgiju mandibularnih molara. Neki autori su zabeležili da je postignut uspeh anestezije u predelu prvog molara sa milohioidnom anestezijom,[20] kod 21% pacijenata. Ayberk i saradnici[21] su sa milohioidnom anestezijom, kod 54,2% pacijenata postigli uspešnu endostealnu implantaciju u mandibuli, koristeći 1 ml 4% artikaina sa adrenalinom 1 : 200000.

Clark i Tebo[22] utvrdili su da u 90% slučajeva postoje dopunski otvori na lingvalnoj strani mandibule iza trećeg molara i u predelu milohioidnog mišića, koji sadrže nervne i vaskularne anatomske elemente[23-25].

Na osnovu ovih podataka, smatrali smo da bi bilo interesantno postaviti kao cilj rada, ispitivanje uspešnosti ubrizgavanja lokalnog anestetika artikaina u sublingvalni predeo mandibule suprakortikalno, modifikovanom tehnikom za milohioidnu anesteziju, kako bi artikain, kao infiltraciona anestezija, mogao da prodire kroz lingvalni korteks mandibule i prodre u predeo molara i da izvrši dovoljno duboku primarnu anesteziju za uspešnu hirurgiju mandibularnih zuba.

Materijal i metode

Kliničko ispitivanje efikasnosti milohioidne anestezije u hirurgiji mandibularnih zuba urađeno je u skladu sa principima Helsinške deklaracije o zaštiti pacijenata kod kojih se primenjuju anestetička sredstva[26], odnosno onda kada je primenjena lokalna anestezija u hirurgiji donjih molara[17]. U ovoj pilot studiji deset pacijenata (ASA I – zdravi pacijenti)[27] podeljeno je u dve jednake grupe (po pet pacijenata). Odabrani su pacijenti oba pola, starosti od 18 do 75 godina, kojima je zbog hirurgije mandibularnih molara bila neophodna mandibularna anestezija. Svi ispitanici su bili zdravi i bez anamnestičkih podataka o hroničnim ili akutnim oboljenjima i alergijama na lokalne anestetike, kao i o drugim bolestima koje mogu biti kontraindikacija za predviđenu operaciju. Takođe, svi ispitanici dali su pismenu saglasnost na prethodno obrazloženu predloženu proceduru i predložene tehnike anestezije sa ispitivanim anesteticima.

Postavljanje definitivne dijagnoze i indikacija za operativni zahvat na mandibularnim molarima rađeno je na osnovu kliničkog pregleda i odgovarajuće rendgen dijagnostike.

the supplemental sensory innervation of the mandibular teeth in 10–20%, by the mylohyoid nerve, which primarily provides motor innervation for the digastric muscle and the mylohyoid muscle[19].

In the literature available to us in the English language, there is not enough information to indicate that mylohyoid anesthesia has been successfully used as primary anesthesia for mandibular molar surgery. Some authors have noted that anesthesia success was achieved in 21% of the patients in the region of the first molar with mylohyoid anesthesia[20]. Ayberk et al.[21] achieved successful endosteal implantation in the mandible with mylohyoid anesthesia in 54.2% of patients, using 1 ml of 4% articaine with 1:200000 adrenaline.

Clark and Tebo[22] found that, in 90% of the cases, there are additional openings on the lingual side of the mandible behind the third molar and in the area of the mylohyoid muscle, which contain nervous and vascular anatomical elements[23–25].

Based on these data, we believed that it would be interesting to set the goal of this work, which would examine the success of injecting the local anesthetic articaine into the sublingual region of the mandible supracortically, using the modified technique for mylohyoid anesthesia, so that articaine would be able to penetrate through the lingual cortex of the mandible in the form of infiltration anesthesia, penetrate the molar area and perform a sufficiently deep primary anesthesia for successful mandibular tooth surgery.

Material and methods

A clinical trial of the effectiveness of mylohyoid anesthesia in mandibular dental surgery was performed in accordance with the principles of the Helsinki Declaration on Patient Safety when anesthetic agents are administered to the mentioned[26], i.e., when local anesthesia is applied in lower molar surgery[17]. In this pilot study, 10 patients (ASA I—healthy patients)[27], were divided into 2 equal groups (5 patients), of both sexes and aged 18—75, who required mandibular anesthesia owing to mandibular molar surgery. All the subjects were healthy, and without anamnestic data on chronic or acute diseases and allergies to local anesthetics, as well as other diseases that could be a contraindication for the intended operation. In addition, all the subjects gave their written consent to the previously explained proposed procedure and proposed anesthesia techniques with the anesthetics tested.

Pacijenti su selektovani u grupe za ispitivanje slučajnim odabirom, tehnikom zatvorene koverte, kako bi primili jedan od ispitivanih anestetika sa određenom tehnikom lokalne anestezije[28] zbog operacija na mandibularnim molarima.

U prvoj grupi, modifikovanom tehnikom milohioidne anestezije, u brizgalicu od 5 ml uvučen je rastvor 3,5 ml 4% artikaina sa adrenalinom 1 : 100000 (Artinibsa, 40 mg/ml + 0,01 mg/ml adrenalina; Inibsa Dental S.L.U., 08185 Lliçà de Vall, Barcelona, Spain), koji je zatim direktno pomešan u brizgalici sa dodatih 0,5 ml / 4 mg deksametazona (4 mg/ml; Galenika a.d., Beograd, Republika Srbija), čime je dobijena ukupna količina anestetičkog rastvora (AaD) od 4 ml za ubrizgavanje u tkivo. Od ove količine anestetičkog rastvora ubrizgano je 3,5 ml u bolusu u sublingvalni predeo mandibule (videti dole opis tehnike), gde je ova količina služila i za anesteziju *n. lingualisa*, dok je preostalih 0,5 ml služilo za anesteziju *n. buccalisa* u bukalni sulkus mandibule. Originalna tehnika milohioidne anestezije opisuje da vrh igle brizgalice sa anestezijom dostiže predeo iza distalnog korena prvog mandibularnog molara ispod milohioidnog mišića[20].

U ovoj studiji urađena je modifikacija opisane originalne tehnike, jer su ubadanje i prodor vrha zakrivljene, angulirane igle (107°) kroz meko tkivo pomereni distalnije od prvog mandibularnog molara, iza distalnog korena trećeg molara u sublingvalnom/suprakortikalnom predelu mandibule, ispod predela pripojne linije milohioidnog mišića na mandibuli, i sa ubadanjem vrha igle nadole i lateralno, u dubini do 15 mm, odnosno do kontakta sa unutrašnjom stranom kortikalne kosti mandibule[22]. U drugoj grupi je takođe upotrebljena brizgalica od 5 ml u koju je uvučena količina od 4 ml anestetičkog rastvora (Lidokain 2% – adrenalin 40 mg / 2 ml + 0,025 mg / 2 ml; Galenika a.d., Beograd) – La. Pristupom za standardnu mandibularnu sprovodnu direktnu anesteziju u predeo foramena mandibule (Halsted tehnika) ubrizgano je 3,0 ml 2% lidokaina sa adrenalinom za anesteziju *n. alveolaris inferiora*, 0,5 ml za anesteziju *n. lingualisa* i 0,5 ml za anesteziju *n. buccalisa*. Primenjena je vizuelno-analogna skala (VAS) za subjektivnu procenu bola kod pacijenata u toku operacije[29], koja predstavlja horizontalnu liniju od 0 mm do 100 mm (10 cm), gde 0 mm označava da nema bolova, dok je 100 mm oznaka za najgori mogući bol; na samoj liniji pacijenti su olovkom povukli vertikalnu liniju da bi označili svoj doživljeni bol u toku operacije.

Establishing a definitive diagnosis and indications for surgery on the mandibular molars was based on a clinical examination and the appropriate X-ray diagnostics.

Patients were selected into study groups, by random selection, using the closed envelope technique, to receive one of the investigated anesthetics with a specific local anesthesia technique[28], for the purpose of undergoing surgery on mandibular molars.

In the first group, employing the technique of modified mylohyoid anesthesia, a solution of 3.5 ml of 4% articaine with 1:100000 adrenaline (Artinibsa, 40 mg/ml + 0.01mg/ml adrenaline, Inibsa Dental S.L.U., 08185 Lliçà de Vall, Barcelona, Spain), was injected into a 5 ml syringe, which was then directly mixed in the syringe with added 0.5 ml/4 mg of dexamethasone (4 mg/ml, Galenika a.d., Belgrade, Republic of Serbia), resulting in a total amount of anesthetic solution (AaD) of 4 ml for injection into tissue. From this amount of the anesthetic solution, 3.5 ml was injected, in the form of a bolus, into the sublingual area of the mandible (see below for the description of the technique), where this amount was also used for the anesthesia of *n.lingualis*, while the remaining 0.5 ml was used for anesthesia of the *buccal nerve* in the buccal sulcus of the mandible. The original technique of mylohyoid anesthesia requires that the tip of the needle with the anesthetic syringe reach the area behind the distal root of the first mandibular molar below the mylohyoid muscle[20].

In this study, a modification of the described original technique was performed, so the insertion and penetration of the tip of the curved-angled needle (107°) through the soft tissue was moved distally, behind the distal root of the third molar in the sublingual/supracortical area of the mandible, below and in the area of the attachment line of the mylohyoid muscle on the mandible, and with the tip of the needle inserted downwards and laterally at a depth of 15 mm, i.e., until contact was made with the inner side of the cortical mandible bone[22]. In the second group, a 5 ml syringe was also used, into which a quantity of 4 ml of the anesthetic solution was drawn (2% lidocaine–adrenaline 40 mg/2 ml +0.025 mg/2 ml, Galenika a.d., Belgrade) (La); by using the approach of standard mandibular conduction direct anesthesia in the region of the foramen of the mandible (the Halsted technique), 3.0 ml of 2% lidocaine with adrenaline was injected for the anesthesia of the inferior alveolar nerve, 0.5 ml for the anesthesia of the lingual nerve and 0.5 ml for the anesthesia of the buccal nerve.

Anestezija je smatrana uspešnom ako je zub hirurški izvađen i ako pacijent nije osetio bol (VAS do 4 mm) ili je doživeo umereni bol (VAS do 44 mm)[30]. Dužina trajanja anestezije (u minutima) praćena je od momenta pune utrnulosti donje usne na operativnoj strani i neosetljivosti mukoze u zoni rada, koja se proveravala punktiranjem mukoze sa tupom sondom, do trenutka kada pacijent više nije osećao utrnulost usne na strani operacije.

Pacijentima je naloženo da zabeleže vreme prestanka utrnulosti donje usne na strani prethodno urađene operacije. Takođe, pacijentima je ordinirana i analgetska i antibiotska profilaksa, uz dati specijalistički nalog za svakog operisanog pacijenta, ponaosob. Svi dobijeni podaci beleženi su u istraživački karton.

Statistička obrada podataka

Podaci su prikazani u vidu aritmetičke sredine i standardne devijacije, odnosno u vidu apsolutnih i relativnih brojeva. Poređenje numeričkih varijabli vršeno je T-testom ili Mann–Whitney testom u zavisnosti od distribucije podataka. Nulta hipoteza je testirana sa pragom značajnosti $p<0,05$. Statistička obrada podataka vršena je u programskom paketu SPSS 16,0.

Rezultati

U pilot istraživanje uključeno je 10 pacijenata (5 muškog i 5 ženskog pola). Prosečna starost ispitivane populacije bila je 29,50 godina ± 7,26 godina (minimum 20 godina, maksimum 43 godina). U Tabeli 1 data je distribucija zuba. Prosečna vrednost VAS-a bila je 15,10 ± 8,36 (minimum 0, maksimum 29). Prosečno trajanje anestezije je 193,60 min ± 98,89 min (minimum 70 min, maksimum 410 min). Kod pet pacijenata primenjena je AaD (3,5 D + 0,5 D), a kod pet pacijenata Lid+a anestezija (tabela 1).

Pacijenti su podeljeni u dve grupe (Grupa I i Grupa II). Grupu I činili su muški pacijenti kod kojih je primenjivana AaD (3,5 Aa + 0,5 D), a Grupa II pacijenti ženskog pola kod kojih je primenjivana Lid+a.

Utvrđeno je da ne postoji statistički značajna razlika u odnosu na starost pacijenata po grupama ($p = 0,069$). Prosečna vrednost VAS-a ne razlikuje se statistički značajno u grupama ($p = 0,207$).

Trajanje anestezije ne razlikuje se statistički značajno u ispitivanim grupama ($p=0,754$)(Tabela 2).

A visual analog scale (VAS) was applied for the subjective assessment of pain in patients during surgery[29]. The scale represents a horizontal line from 0 to 100 mm (10 cm), where mark 0 signifies no pain and mark 100 mm signifies the worst possible pain; on the line itself, patients drew a vertical line with a pencil to mark the pain they experienced during the operation. Anesthesia was successful if the tooth was surgically extracted and if the patient did not feel pain (VAS up to 4 mm) or experienced moderate pain (VAS up to 44 mm)[30]. The duration of anesthesia (in minutes) was monitored from the moment of the full numbness of the lower lip at the side which was undergoing surgery and insensitivity of the mucosa in the operation zone, which was checked by puncturing the mucosa with a blunt metal probe, until the moment when the patient no longer felt the numbness of the lip or the oral mucosa around the tooth on the side where the surgery was conducted.

The patients were instructed to record the time when the numbness of the lower lip on the side of the previously performed surgery stopped. What is more, the patients were prescribed analgesic and antibiotic prophylaxis with a referral given for each individual patient who was operated on. All the obtained data were recorded in the research file.

Statistical data processing

The data are presented in the form of arithmetic mean and standard deviation, that is, in the form of absolute and relative numbers. Comparison of numerical variables was performed by t-test or Mann-Whitney test depending on the data distribution. The null hypothesis was tested with a significance threshold of $p< 0.05$. Statistical data processing was performed in the SPSS 16.0 software package.

Results

Ten patients (5 male and 5 female) were included in the pilot study. The average age of the studied population was 29.50±7.26 years (min: 20 years, max: 43 years). Table 1 shows the distribution of teeth. The average value of VAS was 15.10±8.36 (min: 0, max: 29). The average duration of anesthesia was 193.60±98.89 min (min: 70 min, max: 410 min). AaD (3.5Aa+0.5D) was used in five patients, and Lid+a(4) anesthesia in five patients (Table 1). Patients were divided into two groups (Group I and Group II). Group I

VAS skala je pokazala ujednačene rezultate sa prosečnim vrednostima, što je pokazalo da pacijenti ukazuju na bolne senzacije u rasponu od „bez bola do umerenog bola“; prosečan VAS u grupi I bio je 17.40±11.10 mm, dok je u grupi II bio 12.80±4.55 mm. Trajanje anestezije je bilo duže u prvoj grupi, u proseku 205,2 minuta (3h 25 minuta), dok je trajanje anestezije bilo 182 minuta (3h 02 minuta) u drugoj grupi (tabela 1). Primenjene anestezije u obe grupe ispitanika su bile uspešne kod svih ispitanika (100%).

Comprised male patients who received AaD , and Group II comprised female patients who received Lid+a.

It was found that there was no statistically significant difference in relation to the age of the patients by group (p=0.069). The average value of VAS did not differ statistically significantly in relation to the groups (p=0.207).

The duration of anesthesia did not differ statistically significantly in relation to the studied groups (p=0.754) (Table 2).

The VAS scale showed uniform results with average values, which showed that patients indicated a painful sensation ranging from “no pain to moderate pain”; the average VAS in the Group I was 17.40±11.10 mm, while the one in the Group II was 12.80±4.55 mm. The duration of anesthesia was longer in the Group I, with an average of 205.2 min (3h 25 min), while the duration of anesthesia was 182 min (3h 02 min) in the Group II (Table 1). In both groups, the applied anesthesia was successful in all patients (100%).

Tabela 1. Demografske i kliničke karakteristike ispitivane populacije

Table 1. Demographic and clinical characteristics of the studied population

Parametar Parameter	Broj Number	%
Starost† Age	29.50±7.26	20-43
Pol Gender		
Muški Male	5	50.0
Ženski Female	5	50.0
Zub Tooth		
38	3	30.0
46	1	10.0
48	6	60.0
Vas	15.10±8.36min	0-29
Trajanje anestezije (min) † Duration of Anesthesia	193.60±98.89min	70-410
Vrsta i količina anestetika† Type and Amount(ml) of anesthetic		
AaD (**3,5+0.5)**	5	50.0
Lid+a(4ml)	5	50.0

† podaci su prikazani vidu aritmetičke sredine±standardne devijacije, minimalne i maksimalne vrednosti
† data are presented as arithmetic mean ± standard deviation, minimum and maximum values

Tabela 2. Demografske i kliničke karakteristike u odnosu na ispitivane grupe

Table 2. Demographic and clinical characteristics in relation to the studied groups

Parametar Parameter	Grupa I Group I		Grupa II Group II		p
Starost Age	33.60±7.23		25.40±4.93		0.069[1]
Pol Gender					
Muški Male	5	100,0			
Ženski Female			5	100,0	
Zub Tooth					
38	2	40.0	1	20.0	
46	1	2.0	0	0.0	
48	2	40.0	4	80.0	
VAS†	17.40±11.10		12.80±4.55		0.207[2]
Trajanje anestezije (min) † Duration of anesthesia	205.20±139.58		182.00±46.72		0.754[2]
Vrsta i količina anestetika Type and amount(ml) of anesthetic					
AaD (3,5+0.5)	5	50.0			
Lid+a(4)			5	50.0	

[1] t -test, [2] Mann-Whitney test, † podaci su prikazani vidu aritmetičke sredine±standardne devijacije, minimalne i maksimalne vrednosti

t –test[1]’ Mann-Whitney test[2], † data are presented as arithmetic mean±standard deviation, minimum and maximum values

Diskusija

U ovoj studiji postignuta je uspešna anestezija u obe grupe ispitanika i urađene su predviđene operacije (ekstrakcije) na mandibularnim molarima. Od kliničke važnosti je uspešna modifikovana milohioidna anestezija kao primarna anestezija, koja je omogućila privremenu farmakološku desenzibilizaciju molarne mandibularne regije za izvršenje operacija. Smatramo da su ovo prvi originalni pozitivni rezultati koji idu u prilog primeni AaD anestetika za modifikovanu milohioidnu tehniku mandibularne anestezije, s obzirom na to da su u celoj prvoj grupi ispitanici iskazali uniformne pozitivne rezultate.

Nasuprot postignutom uspehu i efikasnoj milohioidnoj mandibularnoj anesteziji sa primenom AaD u ovoj studiji, Clark i saradnici[5] u svojoj studiji nisu dobili rezultate koji pokazuju da milohioidna anestezija može uspešno biti primenjena kao primarna anestezija, odnosno dopunska anestezija kod obezbeđivanja pulpalne anestezije kao test anestezije. Smatramo da se razlog gorih rezultata iz studije Clarka i saradnika[5] može potražiti u činjenici, da su pomenuti autori primenili anestetik lidokain 1,8 ml 2% sa adrenalinom 1 : 100000. Već smo prethodno istakli da lidokain, uprkos tome što ima dobra farmakološka svojstva i daje dobre rezultate u postizanju anestezije kod standardne Halstedove tehnike mandibularne anestezije, ne obezbeđuje potentnost za prodor kroz koštano tkivo, kako bi izvršio desenzibilizaciju molarne mandibularne regije[7,9]. U našoj studiji, uspešni rezultati anestetičkih varijabli postignuti su zahvaljujući izuzetnim farmakološkim svojstvima AaD-a, koji je jedini sposoban da prodre u koštano tkivo i koji je u bolusu ubrizgan sublingvalno u predeo milohiodnog mišića i supraperiostealno/suprakortikalno, u dubinu od 15 mm od površine sluzokože sublingvalne regije. AaD je verovatno na dva načina uspeo da obezbedi uspešnu milohioidnu anesteziju: direktnom difuzijom kroz nutritivne otvore na lingvalnoj strani mandibule prodirao je do nerva i natapao i sledstveno desenzibilisao *n. alveolaris inferior*, kao i direktnim prodorom kroz lingvalni korteks u predeo mandibularnog kanala, odnosno *n. alveolaris inferiora*; u isto vreme je zbog količine anestetika obuhvatio sublingvalno i *n. lingualis*. S druge strane, dodatak deksametazona Aa, nov je način da se poboljšaju farmakodinamska svojstva ovog anestetika. Deksametazon je u prethodnim studijama pokazao izuzetna pozitivna svojstva u podizanju potetnosti lokalnih anestetika.

Discussion

In this study, successful anesthesia was achieved in both groups of subjects, and the planned surgeries of the mandibular molars were performed. The successful modified mylohyoid anesthesia, utilized as a primary anesthesia, which enabled temporary pharmacological desensitization of the molar mandibular region for performing surgery, is of clinical importance. We believe that these are the first original positive results which support the use of AaD anesthetics for the modified mylohyoid technique of mandibular anesthesia, considering the fact that, in the entire first group, the subjects showed uniform positive results.

Contrary to the achieved success and effective mylohyoid mandibular anesthesia with the use of AaD in this study, the study performed by Clark et al.[5] did not yield results that would allow mylohyoid anesthesia to be successfully applied as primary anesthesia, i.e. supplementary anesthesia when providing pulpal anesthesia as a test anesthesia. We consider that the reason for such unfavorable results in the study by Clark et al.[5] can be found in the fact that these authors used 1,8 ml of anesthetic lidocaine 2% with 1:100000 adrenaline. It has previously been indicated that, although lidocaine has good pharmacological properties and provides good results in achieving anesthesia in the standard Halsted technique of mandibular anesthesia, it does not provide the potency for penetration through the bone tissue for the purpose of achieving the desensitization of the molar mandibular region[7,9]. In our study, the successful results of the anesthetic variables are the result of the exceptional pharmacological properties of AaD, which alone has the ability to penetrate bone tissue, and which was injected in the form of a bolus sublingually into the region of the mylohyoid muscle and supraperiosteally/supracortically, at a depth of 15 mm from the surface of the mucosa of the sublingual region. AaD probably managed to provide successful mylohyoid anesthesia in two ways: by direct diffusion through the nutritional openings on the lingual side of the mandible, it penetrated to the nerve and soaked the inferior alveolar nerve, thus desensitizing it, as well as by direct penetration through the lingual cortex into the region of the mandibular canal, i.e. *n.alveolaris inferior*, and at the same time, owing to the amount of the anesthetic, it sublingually included *n.lingualis*. On the other hand, the addition of dexamethasone AaD is a new way to improve the pharmacodynamic properties of this anesthetic. In previous studies, dexamethasone has shown exceptional positive properties in increasing the potency of local

U studiji u kojoj je deksametazon pomešan sa 0,75% ropivakainom postignuta perioperativna anestezija bila je skoro dva puta duža i trajala je 625,5 min (10,4 h); u drugoj grupi, u kojoj je bio primenjen samo 0,75% ropivakain, mandibularna anestezija trajala je 290 min (4,8 h)[17].

U ovoj studiji je klinički značajno produženo vreme trajanja milohioidne anestezije AaD (prosečno 205,2 min, tj. 3 h 25 min) u prvoj grupi, u odnosu na drugu grupu, u kojoj je prosečno vreme trajanja mandibularne anestezije bilo 182 min/3h 2 min), dakle, milohioidna anestezija trajala je 1,12 puta duže od standardne mandibularne anestezije Halstedovom tehnikom sa Lid + a; ovakav rezultat je iznenađenje, jer artikain ima prosečno vreme delovanja maksimalno do 1 h.[6] Ovakvi rezultati upućuju na to da je verovatno došlo do direktnih stimulativnih lokalnih efekata deksametazona, koji je, direktno pomešan sa AaD, na nervno vlakno (*n. alveolaris inferiora*), omogućio efikasnije sprečavanje prenosa bolnog impulsa. Opisani pozitivni efekat deksametazona na intezitet i produženje lokalne anestezije može se objasniti činjenicom da deksametazon direktno utiče na produženje nervne blokade, budući da sprečava prenos nociceptivnih bolnih impulsa duž mijelizovanog C nervnog vlakna kada je perineuralno primenjen, što su i drugi autori zabeležili[18,31-33]. Do dinamičnog i pozitivnog farmakološkog sleda događaja u ovoj studiji, verovatno je došlo kada je deksametazon, koji je sa artikainom direktno pomešan u brizgalici i ubrizgan u ciljno mesto opisanom modifikovanom tehnikom milohioidne anestezije, ispoljio prethodno opisana pozitivna farmakološka svojstva.

Zaključak

S obzirom na jednostavnost opisane tehnike modifikovane milohioidne anestezije sa artikainom i deksametazonom i postignute uspešne anestetičke efekte u hirurgiji mandibularnih molara, ova metoda bi, kao samostalna anestezija ili dopunska anestezija, mogla biti alternativa standardnoj mandibularnoj anesteziji po Halstedu, mada su potrebna dalja dopunska istraživanja anestetičkih varijabli.

Zahvalnica: Nema

Sukob interesa: Nema

anesthetics. In the study where dexamethasone was mixed with 0.75% ropivacaine, the achieved perioperative anesthesia was almost twice as long and lasted 625.5 min (10.4 h), while mandibular anesthesia lasted 290 min (4.8h) in the Group II, where only 0.75% ropivacaine was administered[17].

In this study, the duration of mylohyoid anesthesia was clinically significantly prolonged (average of 205.2 min/3h 25 min) in Group I than in Group II, where the average duration of mandibular anesthesia was 182 min/3h 02 min), that is, modified mylohyoid anesthesia lasted 1.12 times longer compared to standard mandibular anesthesia using the Halsted technique with Lid+a; this result is a surprise, because articaine has an average duration of action of up to 1 hour[6]. This indicates that there were probably direct stimulatory local effects of dexamethasone, which enabled a more efficient prevention of pain impulse transmission by being directly mixed with AaD on the nerve fiber (*n.alveolaris inferior*). Such a positive effect of dexamethasone on the intensity and prolongation of local anesthesia can be explained by the fact that dexamethasone directly affects the prolongation of the nerve blockade, because it prevents the transmission of nociceptive pain impulses along the myelized C nerve fiber, when dexamethasone is applied perineurally, which was also noted by other authors[18,31-33]. Such a dynamic and positive pharmacological sequence of events probably occurred in this study when dexamethasone, which was directly mixed with articaine in a syringe and injected into the target site using the described modified technique of mylohyoid anesthesia, exhibited the previously described positive pharmacological properties.

Conclusion

Considering the simplicity of the described technique of modified mylohyoid anesthesia with articaine and dexamethasone, and the successful anesthetic effects achieved in mandibular molar surgery, as independent anesthesia or supplementary anesthesia, this method could be an alternative to standard mandibular anesthesia acc., to Halsted, with further supplementary research of anesthetic variables.

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Conflict of Interest: Nil

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FAKTORI KOJI UTIČU NA TRAJANJE ORTODONSKE TERAPIJE NA STOMATOLOŠKIM FAKULTETSKIM KLINIKAMA

FACTORS INFLUENCING THE ORTHODONTIC TREATMENT DURATION AT DENTAL TEACHING HOSPITALS

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Sažetak

Uvod: *Jedan od primarnih ciljeva u zbrinjavanju ortodontskih pacijenata, pored konačnih rezultata, jeste i briga o ukupnom periodu lečenja. Razumevanje dužine ortodontskog tretmana, kao i faktora koji na to utiču, dragoceno je za produktivno vođenje pacijenata i poboljšanje kliničke performanse.*
Cilj *istraživanja bio je analiza faktora koji utiču na dužinu lečenja pacijenata su fiksnim ortodontskim aparatima u Stomatološkoj nastavnoj bolnici na Stomatološkom fakultetu Univerziteta u Bagdadu.*
Materijal i metode: *Istorije osamdeset definitivno zbrinutih ortodontskih slučajeva (četrdeset zbrinutih angažovanjem jednog operatera i četrdeset zbrinutih angažovanjem više operatera) odabrane su iz arhive ortodontskog odeljenja kako bi se analiziralo sledećih šest parametara: trajanje lečenja, broj supervizora, broj poseta, vrsta malokluzije, metod lečenja, prisustvo ili odsustvo ukrštenog zagrižaja. Hi-kvadrat test korišćen je za ispitivanje razlika između grupa i za proučavanje povezanosti između trajanja lečenja i tipova malokluzije sa indikacijom za vađenje zuba u obema grupama.*
Rezultati*: Rezultati su pokazali značajnu razliku između ispitivanih grupa u pogledu svih analiziranih parametara, osim prisustva ili odsustva ukrštenog zagrižaja. S druge strane, nije pronađena značajna povezanost između vrste malokluzije i trajanja lečenja sa indikacijom za vađenje zuba u obema grupama.*
Zaključak: *Broj supervizora različitih mišljenja u vezi sa lečenjem i vođenjem ortodontskih slučajeva i vrsta malokluzije mogu biti glavni faktori koji utiču na trajanje lečenja ortodontskih pacijenata.*

Ključne reči: *trajanje lečenja, fiksni ortodontski aparat, malokluzije*

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Abstract

Introduction: *One of the primary worries of orthodontic patients, aside from the final results, is the total period of treatment. A superior comprehension of orthodontic treatment period just as variable influencing the treatment length is valuable for productive patient guiding and improved clinical performance.*
The aim *of the study was analysis of factors influencing the length of treatment of finished casestreated with fixed orthodontic appliance at the dental teaching hospital in the College of Dentistry/ University of Baghdad.*
Materials and Methods: *Eighty case sheets belonging to 80 finished orthodontic cases (forty finished with a single operator and fortyfinished with multi-operators) were selected from the archive of the orthodontic department to collect six parameters, namely duration of treatment, number of supervisors, number of visits, type of malocclusion, treatment method, presence or absence of crossbite. Chi-square test was used to test group differences and to study the association between the duration of treatment and the types of malocclusion with the indication for dental extraction in both groups.*
Results: *The results showed highly significant group difference regarding all parameters except the presence or absence of crossbite. On the other hand, no significant association was found between the type of malocclusion andduration of treatment with the indication of extraction in both groups.*
Conclusions:*The number of supervisors with their different opinions in treating and managing orthodontic casesand the type of malocclusion may be the main contributing factor affecting the treatment duration of the finished orthodontic cases.*

Key words: *treatment duration, fixed orthodontic appliance*

Uvod

Uspešan tretman pacijenata fiksnim ortodontskim aparatima, koji uključuje tri glavne faze (početno razmatranje, zbrinjavanje prostora i završna obrada i preciziranje okluzije), može trajati više meseci[1,2]. U najnovijem sistematskom pregledu Tsichlaki i saradnici[3] utvrdili su da je prosečno vreme lečenja fiksnim ortodontskim aparatima zahtevalo manje od dve godine, uz širok spektar trajanja lečenja, koji je varirao između 14 meseci i 33 meseca u pregledanim studijama. To može negativno uticati na pacijente ili ih čak sprečiti da se podvrgnu ovom tipu lečenja.

U pogledu kvaliteta i trajanja lečenja, postoji određena svest o pacijentima koje leče studenti postdiplomskih studija na stomatološkim fakultetima, naročito ukoliko je u tretman ovakvih pacijenata bilo uključeno više operatera. Studenti na postdiplomskim studijama redovno su se menjali svake dve godine nakon završetka kursa, ostavljajući neke od svojih slučajeva nezavršenim, tako da su se morali napraviti aranžmani, kako bi lečenje pacijenata mogao da nastavi drugi student. Promena operatera tokom lečenja može dovesti do dužeg trajanja lečenja, ali do sada nema nikakvih podataka ili dokaza koji to potkrepljuju; izuzetak je studija McGuinnessa i McDonalda[4], koji su zaključili da će promena operatera značajno produžiti trajanje lečenja, u proseku, za 8,43 meseca.

Dugo trajanje lečenja može dovesti do jatrogenih posledica terapije fiksnim aparatom, uključujući resorpciju korena, demineralizaciju gleđi, gingivitis, karijes i lošu usaglašenost pacijenata u pogledu održavanja oralnog zdravlja i redovnih poseta[5,6]. S druge strane, budući da može postojati novčana motivacija u prenošenju progresivnog stručnog tretmana, kraće lečenje nudi povoljne okolnosti za pacijente i operatera i nesumnjivo je povezano sa manjim brojem poseta[7].

U mnogim studijama istraživane su varijable koje bi mogle uticati na trajanje lečenja kod adolescenata i odraslih. Među ovim faktorima su starost[8-12], pol pacijenata[9,11,13,14], molarni odnos na početku lečenja[8,14-19], debljina kortikalne kosti mandibule[8], vrsta bravica, veličina prostora i protokol koji se koristi u tretmanu[11,14,20-22], početna težina malokluzije, tj. teskoba ili rastresitost [9,11,13,14,16,23,24], tretman zasnovan na vađenju zuba, tj. vađenje zuba, bez vađenja zuba i odloženo vađenje uz broj izvađenih zuba[8,9,11,12,14,15,25-33], način postavljanja bravica[14], multidisciplinarni tretman, koji uključuje hipodonciju ili ortognatsku hirurgiju

Introduction

Fixed orthodontic treatment, including three main stages—initial alignment, space management and finishing and detailing of the occlusion—may last for many months to complete perfectly[1,2]. In the latest systematic review, Tsichlaki et al.[3] found that the average treatment time for comprehensive orthodontic treatment with fixed appliances necessitated less than two years with a wide range of treatment durations between 14 to 33 months were reported in the reviewed studies. This may compromise or even halt patients from undergoing the treatment course.

There is some awareness about the patients treated by postgraduate students in the dental schools regarding the quality and duration of treatment especially if those patients were treated with more than one operator. The postgraduate students changed regularly every two years after completing their courses leaving some of their cases uncompleted, so arrangements must be made for patients' treatment to be continued by another student. Changing operator during the course of treatment may result in longer treatment duration, but till now no data or evidence supports that except the study of McGuinness and McDonald[4] who concluded that changing operator would lengthen the treatment duration significantly by an average of 8.43 months.

Long treatment duration may lead to iatrogenic consequences of fixed appliance therapy including root resorption, enamel demineralization[5], gingivitis, caries and poor patient's compliance regarding the maintenance of oral health and in attendance their regular visits[6]. On the other hand, short treatment terms offers favorable circumstances to the patients and operator as there might be monetary motivations in conveying progressively proficient treatment, no doubt connected with less visits and shorter seat side occasions[7].

Many studies have explored the variables that could affect the treatment duration in adolescents and adults. Among these factors are age[8-12], gender of the patients[9,11,13,14], molar relationship at the starting of treatment[8,14-19], mandibular cortical bone thickness[8], type of brackets, slot size and prescription used in treatment [11,14,20-22], initial severity of the malocclusioni.e. crowding or spacing[9,11,13,14,16,23,24], extraction-based treatment i.e. extraction, non-extraction and delayed extraction in addition to the number of teeth extracted[8,9,11,12,14,15,25-33], method of bracket placement[14], multi-disciplinary treatment involving hypodontia

i oslobađanje impaktiranih zuba[12], uz usaglašenost pacijenata uključujući broj propuštenih termina kontrolnih pregleda[9-12], problem sa ortodontskim aparatom (lomovi)[9-12,14], oralna higijena pacijenata[11,13,14,33] i neusaglašenost pacijenata u korišćenju intraoralnih gumica[11,14].

Nedavno su, zahvaljujući razvijenoj tehnologiji, ortodontski aparati napredovali, stvarajući niz terapijskih opcija sa specifičnim indikacijama. Ovi aparati moraju biti pažljivo odabrani; u suprotnom, pogoršanje početne malokluzije biće neizbežno[34]. Na terapijske opcije, koje daju supervizori u stomatološkim ordinacijama, mogu uticati mnogi faktori – njihova starost, vrsta i kvalitet stečenog obrazovanja, lične i psihološke karakteristike.

Stariji operateri imaju iskustvo u donošenju odluka. Uočene su velike varijacije između mlađih i starijih supervizora u vezi sa terapijskim opcijama koje su korišćene godinama (preferirani od strane starijih supervizora) ili pristupima koji se razvijaju (privilegovani od strane mlađih supervizora)[35]. Pored toga, uspostavljena je direktna veza između prednosti ortodontskog lečenja i vremena koje je supervizorima bilo potrebno da završe fakultet. Generalno, stariji supervizori više cene ove prednosti od mlađih supervizora[36].

Što se tiče kvaliteta obrazovanja, danas se terapijske odluke moraju donositi na osnovu naučnih dokaza, koji pružaju najbolji tretman za datog pacijenta[2]. Lečenje fiksnim ortodontskim aparatom može se razlikovati u zavisnosti od tehnika koje su stariji ortodonti primili. Nedostatak osnovnog znanja može dovesti do pogrešne primene ovih tehnika, tako da starije osobe sa dobrom obukom imaju veće šanse da donesu ispravne terapijske odluke[37].

Lične osobine, uverenja i vrednosti značajno utiču na planiranje lečenja, budući da početne odluke o lečenju mogu odražavati sposobnost ortodonata da reprodukuju i razmenjuju ideje sa drugim profesionalcima[38], kao i njihov stav prema alternativnim metodama lečenja i odabiru metode[39].

Konačno, psihološke karakteristike mogu uticati na odluku o lečenju; npr. opsesivna ličnost pokušava da odluku učini komplikovanijom procedurom, dok impulsivni supervizori teže ka donošenju jednostavnih i jasnih odluka[40].

Cilj ovog istraživanja bila je procena određenih faktora koji utiču na trajanje lečenja ortodontskih slučajeva fiksnim aparatom. Za lečenje pomenutih slučajeva bili su zaduženi studenti postdiplomskih studija u Stomatološkoj nastavnoj bolnici na Stomatološkom fakultetu Univerziteta u Bagdadu.

or orthognathic surgery and alignment of impacted teeth[12], in addition to the patient compliance including the number of missed appointments[9-12], problems with the orthodontic appliance (breakages)[9-12,14], patients' oral hygiene[11,13,14,33], and the patients' non-compliance in the use of intraoral elastics[11,14].

Recently, orthodontic appliances have been evolved with advancing technology creating a variety of therapeutic options with specific indications. These appliances must be selected carefully otherwise worsening the initial malocclusion is inevitable[34]. The therapeutic options given by supervisors in the dental teaching hospitals may be influenced by many factors including their age, the type and quality of education received, personal and psychological characteristics.

The senior's age has been related to decision-making. Wide variations between younger and older supervisors were observed regarding their therapeutic options used for many years (preferred by older supervisors) or approaches being evolved (privileged by younger supervisors)[35]. Additionally, a direct relation had been established between the advantages of orthodontic treatment and the time the supervisors took to complete their degree. Generally, older supervisors esteem these advantages more contrasted with more youthful supervisors[36].

Regarding the quality of education, nowadays therapeutic decisions must be made on scientific evidence that provides the finest treatment for a given patient[2]. Treatment with fixed orthodontic appliance may differ according to the techniques the seniors received. Lack of essential knowledge may lead to wrong application of these techniques, so seniors with good training have a high chance in making right therapeutic decisions[37].

Personal characteristics, beliefs and values significantly affect the treatment planning as the initial treatment decisions may reflect their ability to reproduce and exchange ideas with other professionals[38] also reflect their attitude to alternative treatment methods and select the method of choice[39].

Lastly, the psychological characteristics may influence the treatment decision, e.g. obsessive personality try to make decision a more complicated procedure, contrary, impulsive supervisors tend to make decisions simple and clear[40].

The aim of this study was to assess some factors influencing the duration of treating orthodontic cases with fixed appliance by the postgraduate students at the dental teaching hospital in the College of Dentistry/ University of Baghdad.

Materijal i metode

Ova retrospektivna opservaciona studija sprovedena je u aprilu 2019. godine, nakon dobijanja odobrenja od strane naučnog komiteta na Odeljenju za ortodonciju Stomatološkog fakulteta Univerziteta u Bagdadu za 80 istorija završenih ortodontskih slučajeva lečenih fiksnim ortodontskim aparatom od strane master studentata Postdiplomske ortodontske klinike. Četrdeset slučajeva zbrinjavao je po jedan operater, dok je u terapiji preostalih četrdeset slučajeva učestvovalo više operatera.

Starosni raspon pacijenata na početku lečenja bio je od 12 do 27 godina (17,83 godine ± 3,79 godina) za slučajeve u čijem je zbrinjavanju bio angažovan jednan operater, odnosno od 12 godina do 33 godine (20,56 godina ± 4,63 godine) za slučajeve u čije je zbrinjavanje bio uključen veći broj operatera.

Iz istorija slučajeva prikupljene su sledeće varijable:

1) trajanje lečenja;
2) broj supervizora;
3) broj poseta;
4) vrsta malokluzije;
5) metoda lečenja (da li je tretman podrazumevao vađenje zuba ili nije);
6) prisustvo ili odsustvo ukrštenog zagrižaja.

Statističke analize obavljene su korišćenjem softvera SPSS (Statistički paketi društvenih nauka), verzija 24. Korišćene su sledeće statistike:

1) **Deskriptivna statistika**, koja je obuhvatila srednje vrednosti, standardne devijacije, minimalne i maksimalne vrednosti, učestalost (br.) i procente;

2) **Inferencijalna statistika**, koja je obuhvatila Hi-kvadrat test za testiranje bilo koje statistički značajne razlike između grupa i za proučavanje efekta vađenja zuba na trajanje ortodontskog tretmana i (ne)postojanje povezanosti između tipova malokluzije i indikacija za vađenje zuba u obema grupama.

U statističkoj proceni nivo značajnosti bio je postavljen na 0,05.

Materials and methods

This retrospective observational study was conducted on 80 case sheets of finished orthodontic cases treated with fixed orthodontic appliance by the M.Sc. students in the postgraduate orthodontic clinic in April 2019 after gaining approval from the scientific committee in the Department of Orthodontics, College of Dentistry, University of Baghdad. Forty of them finished the treatment with a single operator and the other forty cases with multi-operators.

The age range of the patients at the start of the treatment was 12−27 years (17.83 ±3.79 years) for the finished cases with single operator and 12−33 years (20.56±4.63 years) for the finished cases with multi-operators.

The following variables were elicited from the case sheets:

1. Duration of treatment.
2. Number of supervisors.
3. Number of visits.
4. Type of malocclusion.
5. Treatment method (whether the treatment entailed dental extraction or not).
6. Presence or absence of crossbite.

Statistical analyses were performed using SPSS (statistical packages of social sciences) software version[24]. The following statistics were used:

1. **Descriptive statistics:** including means, standard deviations, minimum and maximum values, frequency (No.) and percentages.
2. **Inferential statistics:** including Chi-square test to test any statistically significant differences between the groups and to study the effect of dental extraction on the duration of orthodontic treatment and whether there is association between the types of malocclusion and the indication for dental extraction in both groups.

In the statistical evaluation, the level of significance was set at 0.05.

Rezultati

Tabela 1 pokazuje distribuciju frekvencija i procente izmerenih parametara za slučajeve zbrinute angažovanjem jednog operatera ili više njih. Rezultati su otkrili da je više od polovine slučajeva (22 slučaja) završeno u roku od godinu dana ili manje angažovanjem jednog operatera; nasuprot tome, svi slučajevi u koje je bilo uključeno više operatera završeni su za više od godinu dana.

Broj supervizora značajno je uticao na završetak terapije i to kada je jedan operater završio 37 slučajeva sa od 2 do 4 supervizora, u odnosu na 3 kod slučajeva sa više operatera.

U 32 slučaja jedan operater završio je postupak za 12 poseta, što se smatra značajnim u odnosu na slučajeve sa više operatera, kojima je za zbrinjavanje bilo potrebno više od 12 poseta.

Najčešći tip malokluzije koji je lečio jedan operater bila je malokluzija klase I; veći broj operatera lečio je 23 slučaja malokluzije klase II.

Results

Table 1 showed the frequency distributions and percentages of the parameters measured for both single and multi-operators finished cases. The results revealed that more than half of the cases (22 cases) were finished significantly within one year or less by the single operator, in contrast, all of the multi-operators' cases finished in more than one year.

The number of supervisors had highly significant effect on the completion of the cases when single operator finished 37 cases with 2−4 supervisors versus 3 only in multi-operator cases.

Single operator finished significantly 32 cases within 12 visits while all of the multi-operator cases finished with more than 12 visits.

The most prevalent type of malocclusion treated by single operator was class I malocclusion in contrast to multi-operators' cases who treated 23 cases of class II.

Extraction was not indicated in thirty four cases treated by single operator, while half of the finished cases were treated with extraction in multi-operators' cases.

Tabela 1: Raspodela frekvencija, procenti i poređenje varijabli između završenih slučajeva zbrinutih sa jednim ili više operatera

***Table 1*:** Frequency distributions, percentages and comparison the measured variables between single and multi-operator finished cases

Parameters Parametri	**Descriptions Opisi**	**No. of operators Br.operatera**				**Comparison Poređenje**	
		Single Jedan		**Multi Više**			
		No.	**%**	**No.**	**%**	**X^2**	**p-value vrednost**
Duration of treatment Trajanje tretmana	**≤ 1 year 1 godine**	22	55	0	0	23.23	0.001
	> 1 year 1 godine	18	45	40	100		
No. of supervisors Br. supervizora	**2-4**	37	92.5	3	7.5	57.8	0.001
	5-8	3	7.5	37	92.5		
No. of visits Broj poseta	**≤ 12**	32	80	0	0	53.33	0.001
	> 12	8	20	40	100		
Types of malocclusion Tip malokluzije	**I**	27	67.5	10	25	15.76	0.001
	II	12	30	23	57.5		
	III	1	2.5	7	17.5		
Method of treatment Metod terapije	**Extraction Vađenje zuba**	6	15	20	50	11.17	0.001
	Non extraction Bez vađenja zuba	34	85	20	50		
Presence of crossbite Prisustvo ukrštenog zagrižaja	**Crossbite Bez ukrštenog zagiržaja**	6	15	7	17.5	0.09	0.762
	No crossbite	34	85	33	82.5		

Tabela 2: Povezanost tipa malokluzije i ekstrakcije kod slučajeva zbrinutih jednim operaterom
Table 2*:* Association between type of malocclusion and extraction in single operator

Type of malocclusion Tip malokluzije		Cases Slučajevi		
		No extraction Bez vađenja zuba	Extraction Vađenje zuba	Total Ukupno
I	N	24	3	27
	%	70.59	50	67.50
II	N	9	3	12
	%	26.47	50	30
III	N	1	0	1
	%	2.94	0	2.50
Total Ukupno	N	34	6	40
	%	100	100	100

X^2= 1,484, df= 2, p-vrednost= 0,476

Tabela 3: Povezanost tipa malokluzije i ekstrakcije kod slučajeva zbrinutih od strane više operatera
Table 3: Association between type of malocclusion and extraction in multi-operator

Type of malocclusion Tip malokluzije		Cases Slučajevi		
		No extraction Bez vađenja zuba	Extraction Vađenje zuba	Total Ukupno
I	N	7	3	10
	%	35	15	25
II	N	12	11	23
	%	60	55	57.5
III	N	1	6	7
	%	5	30	17.5
Total Ukupno	N	20	20	40
	%	100	100	100

X^2= 5.652, d.f.= 2, p-value= 0.059

***Tabela 4*:** Povezanost između trajanja tretmana i terapije vađenjem zuba kod slučajeva zbrinutih jednim operaterom
Table 4: Association between duration of treatment and extraction in single operator

Duration Trajanje	No extraction Bez vađenja zuba		Extraction Vađenje zuba		Total Ukupno	
	N	%	N	%	N	%
≤ 1 year godine	19	86.364	3	13.636	22	100
> 1 year godine	15	83.333	3	16.667	18	100
Total Ukupno	34	85	6	15	40	100

X^2= 0.032, d.f.= 1, p-value= 0.858

Tabela 5: Povezanost između trajanja tretmana i terapije vađenjem zuba kod slučajeva od strane više operatera
Table 5: Association between duration of treatment and extraction in multi-operator

Duration Trajanje	No extraction Bez vađenja zuba		ExtractionVađenje zuba		Total Ukupno	
	N	%	N	%	N	%
≤ 1 year godine	0	0	0	0	0	0
> 1 year godine	20	50	20	50	40	100
Total Ukupno	20	50	20	50	40	100

Vađenje zuba nije bilo indikovano u 34 slučaja tretirana od strane jednog operatera, dok je polovina slučajeva zbrinutih od strane više operatera tretirana vađenjem zuba.

Prisustvo ukrštenog zagrižaja nije imalo značajnog uticaja u rezultatima završetka slučajeva, kako onih tretiranih od strane jednog operatera, tako i onih koje je tretiralo više operatera.

Pregledom Tabele 2 i Tabele 3 nije otkrivena značajna povezanost između tipova malokluzije i indikacija za vađenje zuba u obema grupama. Isto je važilo i za trajanje lečenja – nije bilo značajne povezanosti između trajanja lečenja i indikacije za vađenje zuba u obema ispitivanim grupama (Tabela 3 i Tabela 4).

Diskusija

Master program iz ortodoncije traje dve godine. Ove dve godine bile su isprekidane periodima letnjh, prolećnih i ispitnih raspusta, tako da mnogi studenti možda nisu završili sa zbrinjavanjem nekih od primljenih pacijenata; u takvim slučajevima, pacijenti su u narednoj godini bili prebačeni drugom postdiplomcu.

Osnovni cilj ove studije bio je da ukaže na najvažnije faktore koji utiču na trajanje lečenja pacijenata lečenih fiksnim ortodontskim aparatom u Poslediplomskoj ortodontskoj klinici, zbrinutih od strane jednog operatera ili većeg broja njih.

Glavna ograničenja trenutne studije jesu mala veličina uzorka i nedostatak modela studija pre tretmana, tako da istraživači ne mogu proceniti ozbiljnost i poboljšanje zbrinutih slučajeva koristeći PAR i IOTN indekse; stoga, preporučuju se dalje studije za ispitivanje mnogih faktora koji utiču na vreme tretmana, kao što su npr. PAR indeks, tehnika zatvaranja prostora (dva koraka naspram jednog), vrste protokola (Roth naspram MBT), vrste bravica (nerđajući čelik, keramika ili safir), stepen skeletnih malrelacija u tri prostorne ravni, tipovi lica, efekat odvezivanja

The presence of crossbite had no significant impact on the results of finishing of the cases treated by single and multi-operators.

Reviewing Tables 2 and 3 revealed no significant association between the types of malocclusion and the indication of extraction in both groups. The same was true for the duration where there was no significant association between the duration of treatment and the indication of extraction in both groups (Tables 3 and 4).

Discussion

The duration of M.Sc. program in orthodontics is two years. These two years are interspersed with periods of interruption regarding Summer, Spring and examination holidays, so many students may not finish some of received patients who will be transferred to the follower postgraduate student in the next year.

The major goal of the present study is to highlight the most important factors affecting the treatment duration of single and multi-operators treated cases with fixed orthodontic appliance in the postgraduate orthodontic clinic.

The major limitations of the current study are practically the small sample size and lack of the pre-treatment study models, so researchers can not estimate the severity and improvement of the finished cases using PAR and IOTN indices, hence further studies are recommended to address many factors affecting the treatment time like PAR index, technique of space closure (two versus one step), types of prescription (Roth versus MBT), types of brackets (stainless steel, ceramic or sapphire), the degree of skeletal malrelations in three planes of space, facial types, effect of de-bonding/ de-banding between appointments, holidays, the number of missed appointments, duration between

/razvezivanja između termina, praznici, broj propuštenih termina, trajanje između prenosa slučajeva između učenika, pol, starost i stanje zuba pacijenata na početku lečenja, oralna higijena pacijenata i saradnja u nošenju gumica. Štaviše, treba obratiti pažnju na vreme provedeno u završnoj obradi i kvalitet te završne obrade, zadovoljstvo pacijenata i adekvatnost dijagnoze i plana lečenja. Predmet diskusije biće sledeći parametri dobijeni na osnovu istorija predmeta.

Trajanje lečenja

Analizom Tabele 1 otkriveno je da su 22 slučaja od njih 40 završena u roku od jedne godine od strane jednog operatera; nasuprot tome, svih 40 slučajeva u čijem je zbrinjavanju učestvovalo više operatera završeno je za više od godinu dana, a trajanje tretmana izgledalo je značajno drugačije. Generalno, jedan operater završavao je svoje slučajeve u roku od 12,1 meseca ± 2,92 meseca, dok je u slučaju angažovanja većeg broja operatera bilo potrebno 24,28 meseci ± 4,85 meseci za završetak tretmana.

Uticaj promene operatera na trajanje tretmana u nastavnom okruženju obrađen je u jednoj retrospektivnoj komparativnoj studiji koju su sproveli McGuinness i McDonald 1998 godine[4]. Identifikovane su dve grupe pacijenata, tretirane istim sistemom aparata i za oba zubna luka. Prvu grupu činili su slučajevi koje je tretirao isti operater od početka do kraja, a drugu grupu slučajevi čiji je tretman započeo jedan, a završio drugi operater. Rezultati su otkrili značajnu razliku u vremenu lečenja između dveju grupa (17,67 meseci ± 4,15 meseci za jednog operatera, a 26,1 mesec ± 6,78 meseci za dva operatera). Rezultati McGuinnessove i McDonaldove studije podržali su nalaze ove studije, budući da je 100% prenetih slučajeva značajno završeno za više od godinu dana.

Broj supervizora

Planiranje lečenja može se razlikovati među ortodontima, u zavisnosti od njihovih mišljenja i strategija u lečenju ortodontskih slučajeva. Neki preferiraju terapiju vađenjem zuba, a neki ekspanzionu terapiju. Može se razlikovati i vreme vađenja zuba – do toga može doći na početku lečenja ili nakon nivelisanja i poravnanja.

transferring the cases between the students, the genders, age and state of dentition of the patients at the start of treatment, patient's oral hygiene and cooperation in wearing elastics. Moreover, attention should be paid to the time spent in finishing and the quality of that finish, satisfaction of patient, and the suitability of the original diagnosisand treatment plan.

Regarding the information obtained from the case sheets, the following parameters will be discussed:

Duration of treatment

Reviewing Table 1 revealed that 22 out of 40 cases were finished within one year by single operator, in contrast, all of the cases (40 cases) were finished in more than one year by multi-operators and the duration of treatment appeared significantly different. Generally, single operator finished their cases within 12.1±2.92 months, while multi-operators took about 24.28±4.85 months to finish their cases.

The effect of changing operators on the treatment duration in the teaching environment was addressed in one retrospective comparative study performed by McGuinness and McDonald[4] in 1998. Two groups of patients were identified, treated with same appliance system (edgewise) and for both dental arches. The first group treated by the same operator from the starting to the finishing point and the other group started the treatment with one operator and finished the treatment by other. The results revealed significant difference in the treatment time between the two groups (17.67±4.15 months for single operator and 26.1±6.78 months for two operators). The results of McGuinness and McDonalds'study supported the findings of the present study as 100% of the transferred cases were finished significantly by more than one year.

The number of supervisors

Treatment planning may differ among orthodontists according to their opinions and strategies in treating orthodontic cases. Some prefer to extract teeth while some prefer to expand, and even the timing of dental extraction at the beginning of treatment or after leveling and alignment. The mechanics of space closure also differed between en masse retraction and two steps retraction,

Mehanika zatvaranja prostora takođe se razlikovala (masovno povlačenje ili povlačenje u dva koraka), kao i metoda pripreme sidrenja (pomoću TAD-a ili TPA).

U ovoj studiji, većinu slučajeva zbrinutih od strane jednog operatera nadgledalo je od 2 do 4 supervizora; u slučajevima sa više operatera, 37 slučajeva od njih 40 nadgledalo je od 5 do 8 supervizora. Ovaj nalaz je vrlo važan u produžavanju trajanja lečenja, jer su tipovi malokluzije i planiranja lečenja u vezi sa vađenjem zuba pokazali neznačajnu povezanost (Tabele 2 – 5).

Broj poseta

Rezultati prikazani u Tabeli 1 pokazuju da je jedan operater završio 32 slučaja od njih 40 u okviru 12 poseta, kao i da su svi slučajevi sa više operatera (40 slučajeva) završeni u više od 12 poseta. Ovo se može objasniti strategijom tretmana koju su usvojili supervizori i kvalitetom slučajeva prema vrsti malokluzije, gde je 67,5% slučajeva I klase lečio jedan operater, naspram 57,5% slučajeva II klase lečenih od strane više operatera; kod slučaja III klase koji su bili jedan u odnosu na sedam slučajeva. Štaviše, odluka o vađenju zuba doneta je u pedeset slučajeva tretiranih od strane više operatera, naspram 15% slučajeva tretiranih od strane jednog operatera (Tabela 1).

Tip malokluzije

Jedan od faktora koji utiču na vreme lečenja jeste vrsta malokluzije. Skidmore i sar.[14], Colela i sar.[17] i Venger i sar.[18] otkrili su da je malokluzija klase I zahtevala manje vremena za lečenje nego malokluzija klase II i III.

Landin-Ramos i sar.[8] i Vig i sar.[19] otkrili su da se malokluzije klase II ili klase III duže leče, s tim što je propušten ili prekinut termin imao dvostruko veći efekat u slučajevima malokluzije klase II. Saradnja pacijenata imala je važnu ulogu u smanjenju trajanja lečenja za pacijente sa klasom II malokluzije, ali ne i za pacijente sa I klasom.

U ovoj studiji, tip malokluzije utiče na sve slučajeve, bez obzira na broj operatera zaduženih za njihovo zbrinjavanje. Bilo je 27 slučajeva malokluzije klase I koje je zbrinjavao jedan operater, a deset slučajeva koje je zbrinjavalo više operatera, 12 slučajeva naspram 23 slučaja za klasu II i jedan slučaj prema sedam slučajeva za klasu III, tako da je utvrđena značajna razlika između ispitivanih grupa, koja potvrđuje nalaze prethodnih studija[14,17-19].

moreover the method of anchorage preparation using TADs or TPA.

In the present study, the majority of the finished cases by single operator were supervised by 2−4 seniors and the opposite was true in multi-operator cases where 37 cases out of 40 were supervised by 5−8 supervisors. This finding is so important in lengthening the treatment duration of the cases as the types of malocclusion and treatment planning regarding teeth extraction showed non-significant association (Tables 2−5).

The number of visits

The results obtained from Table 1 showed that single operator finished 32 out of 40 cases within 12 visits; while all multi-operator cases (40 cases) were finished in more than 12 visits. This can be explained by the strategy of treatment adopted by the supervisors also the quality of the cases according to the type of malocclusion where 67.5% of the cases were class I treated by single operator against 57.5% class II cases treated by multi-operators; in addition to the class III cases which were one against 7 cases. Moreover, the decision of extraction was in fifty of the cases treated by multi-operator against 15% in single operator (Table 1).

Type of malocclusion

One of the factors affecting the treatment time is the type of malocclusion. Skidmore et al.[14], Colela et al.[17] and Wenger et al.[18] found that class I malocclusion took less treatment time than class II and III.

Landin-Ramos et al.[8] and Vig et al.[19] found that class II or class III malocclusions needed longer to treat but the missed or broken appointment had twice as great as the effect in class II cases and the patient cooperation played an important role in reducing treatment duration for Class II but not Class I patients.

In the current study, the type of malocclusion has an influence on the cases finished by single and multi-operators. Single operator received 27 cases of class I versus 10 for the multi-operators, 12 cases versus 23 for class II and 1 versus 7 cases for class III, so a significant difference was reported between the studied groups confirming the previous findings[14,17-19].

Metoda lečenja

Drugi faktor koji može uticati na trajanje ortodontskog tretmana jeste izabrana metoda lečenja, odnosno terpaija sa vađenjem zuba ili bez vađenja zuba.

Mnoga istraživanja pripisivala su duže vreme tretmana ortodontskih slučajeva vađenju zuba, koje se smatra jednim od glavnih rešenja za otklanjanje velike teskobe, posebno kada se radi o premolarima[2,8,9,30,32]. U nekim studijama ističe se da vađenje zuba nije imalo uticaja na trajanje lečenja[11,33], te je efekat vađenja zuba ostao sporan.

Shia[31] je istakao da je promena planiranja tretmana u toku terapijske procedure značajan razlog za preticanje vremena, posebno kada je započet tretman bez vađenja zuba; tada je vađenje zuba vršeno ubrzo nakon celog tretmana (zakasnelo vađenje zuba).

U sprovedenoj studiji, metode lečenja nisu uticale na trajanje lečenja, čime su potvrđeni rezultati Bekvita i Akermana[11] i Kelija i Springatea[33].

Prisustvo ili odsustvo ukrštenog zagrižaja

Više od 80% tretiranih slučajeva bilo je bez ukrštenog zagrižaja, tako da ukršten zagrižaj nije imao značajnog uticaja na trajanje lečenja između dveju ispitivanih grupa. Valja istaći i da se ukršteni zagrižaj može rano korigovati lečenjem pomoću quadhelix ili hyrax aparata.

Zaključak

U okviru ograničenja ove studije, glavni faktor koji je uticao na trajanje lečenja ortodontskih slučajeva bio je broj supervizora sa različitim mišljenjima u vezi sa lečenjem i vođenjem ortodontskih slučajeva. Osim toga, tip malokluzije može imati uticaja na trajanje lečenja orotodontskih slučajeva.

Zahvalnica: Nema

Sukob interesa: Nema

The treatment method

The other factor that may influence the duration of orthodontic treatment is the treatment method chosen i.e. extraction or non-extraction.

Many researches[2,8,9,30,32] attributed the longer treatment times of orthodontic cases to the dental extraction which is considered as one of major solutions for resolving severe crowding especially premolars extraction. Some studies reported that dental extraction had no effect on the treatment duration[11,33], so the effect of dental extraction remain edcontentious.

Shia[31] notified that changing the treatment planning at the mid-treatment was a significant reason of time overtook; particularly when non-extraction treatment was commenced then dental extractions were performed soon after throughout the treatment (overdue extractions).

In the current study, the treatment methods did not affect the treatment duration confirming the results of Beckwith and Ackerman[11] and Kelly and Springate[33].

Presence or absence of crossbite

More than 80% of the treated cases were crossbite-free, so crossbite had a non-significant effect on the treatment duration between the two groups, on the other hand, crossbite can be corrected early in treatment by quadhelix or hyrax.

Conclusions

Within the limitations of the present study, the main contributing factor affecting the treatment duration of the finished orthodontic cases was the number of supervisors with their different opinions in treating and managing orthodontic cases, moreover, the type of malocclusion may have an effect.

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ISPITIVANJE POUZDANOSTI POZICIONIRANJA TAČAKA PRI ANALIZI ASIMETRIJE LICA NA FOTOGRAFIJAMA: PILOT STUDIJA

TESTING THE RELIABILITY OF POINT POSITIONING IN THE ANALYSIS OF FACIAL ASYMMETRY IN PHOTOGRAPHY: A PILOT STUDY

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Sažetak

Uvod: *U kliničkoj praksi mobilni telefoni i DSLR aparati (Digital Single Lens Reflex) koriste se za snimanje intraoralnih i ekstraoralnih fotografija. Postojanje velikog broja istraživanja omogućilo bi uspostavljanje standarda za analizu fotografija i kao i njihovu širu upotrebu u svakodnevnoj praksi radi uspostavljanja brze dijagnoze, predvidljivosti rezultata i razvoja teledentologije tokom pandemije COVID-19.*
Cilj *pilot studije je da se utvrdi ponovljivost pozicioniranja tačaka u analizi simetrije lica na digitalnim 2D fotografijama.*
Materijali i metode: *Jedno lice je fotografisano korišćenjem dve različite tehnike fotografisanja. Tačke su pozicionirane na jednoj fotografiji i korišćene za svako sledeće merenje. Dva ocenjivača su pozicionirala 20 poena u tri vremenski razdvojena perioda.*
Rezultati: *Rezultati sugerišu relativno visok stepen saglasnosti pozicioniranja tačaka koje su dala dva evaluatora. Apsolutno poklapanje procena registrovano je na 22 parametra (ICCs = 1.00), dok je na još 17 ova vrednost bila visoka (ICCs> .96.)*
Zaključak: *Ovo istraživanje pokazuje da su vrednosti međuklase koeficijenata korelacije izračunate metodom dvosmernih slučajnih efekata za svaki od šest indeksa veće od vrednosti donje granice prihvatljivosti (ICC> 0,70). Neophodno je uraditi dodatna istraživanja koja će obuhvatiti veći uzorak i različite modele telefona za utvrđivanje dijagnoze asimetrije lica i razvoja teledentologije.*

Ključne reči*: fotografija, teledentizam, asimetrija lica, covid19*

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Abstract

Introduction: *In dental clinical practice, devices such as mobile phones and DSLR cameras (Digital Single Lens Reflex) are used to take intraoral and extraoral photographs. The existence of a large number of studies would allow the establishment of standards for the analysis of photographs and their wider use in daily practice in order to establish a rapid diagnosis, predictability of results and the development of teledentology during the COVID-19 pandemic.*
The aim *of the pilot study was to determine the repeatability of point positioning in the analysis of facial symmetry in digital 2D photography.*
Materials and methods: *One face was photographed using two different photography techniques. Points were positioned in one photo and used for each subsequent measurement. Two evaluators positioned 20 points in three time-separated periods.*
Results: *The results suggest a relatively high degree of agreement of the point positioning provided by the two evaluators. Absolute matching of estimates was registered on 22 parameters (ICCs = 1.00), while on another 17 this value was high (ICCs >.96)*
Conclusion: *This study shows that the values of the interclass of correlation coefficients calculated by the method of two-way random effects for each of the six indices are higher than the values of the lower limit of acceptability (ICC> 0.70). It is necessary to do additional research that will include a larger sample and different phone models to establish the diagnosis of facial asymmetry and the development of teledentistry.*

Key words: *photography, teledentistry, facial asymmetry, Covid-19*

Uvod

U kliničkoj praksi mobilni telefoni i DSLR aparati (Digital Single Lens Reflex) koriste se za snimanje intraoralnih i ekstraoralnih fotografija. Primena fotografije nastale pametnim telefonom u stomatologiji je jednostavna, brza i vrlo korisna za dokumentaciju kliničkih postupaka, kao i za pomoć u edukaciji pacijenata i za klinička ispitivanja[1,2,3]. Bez značajnih statističkih rezultata, možemo smatrati da će u narednim godinama fotografski aparat i opremu zameniti lagani pametni telefon[3]. Imajući na umu brzi napredak informacijskih tehnologija i mobilnih i računarskih sistema, očekuje se, u bliskoj budućnosti, da će se određivanje parametara lica pacijenata i analiza dobijenih podataka vršiti pomoću pametnih telefona[4,5]. Softver može pozicionirati tačke, izračunati parametre i analizirati ih za vreme koje je potrebno ortodontu da odabere sliku za analizu – otprilike jednu sekundu[5]. Trodimenzionalna analiza lica (3D analiza lica) nije dostupna u svakodnevnoj kliničkoj praksi, i to zbog velikog troška snimanja i potrebnih aparata[5]. Ključni zahtev u dvodimenzionalnoj fotografiji je adekvatna standardizacija fotografske postavke, posebno kod pozicioniranja pacijenta. Ovakvim pristupom mogu se postići odgovarajući nivoi reproduktivnosti, s ciljem da se tematska merenja mogu dobro povezati s kliničkim mišljenjem[6]. U ortodonciji se upotrebljavaju tri standardna prikaza fotografije lica. To su *en face*, snimak profila i *en face* sa osmehom. Udaljenost između spoljnjeg ugla oka i gornjeg ruba uha treba biti upoređena sa interpupilarnom linijom[7].

Danas se upotrebljavaju različite tehnike merenja vrednosti asimetrije lica. Za analizu lica putem 2D fotografije (dvodimenzionalna fotografija) neophodno je koristiti referentne tačke, koje imaju tačan broj, tačnu distribuciju i ponovljivost za dobijanje rezultata. Fotografije se pregledaju, analiziraju i utvrđuje se prisustvo asimetrije putem matematičkih formula, kao što su opisali Berlin i sar.[8] Standardizovane fotografije, sa kojih su dobijena današnja merenja, pružaju jedinstvenu priliku za proučavanje rasta lica. Uprkos ograničenjima merenja dobijenih pomoću dvodimenzionalnih fotografija, smatra se da prikupljeni podaci predstavljaju prilično precizan opis promena na licu. Ovaj se nalaz može primeniti za procenu promena, koje se događaju tokom ortodontskog lečenja i da pomogne u pronalasku nestale dece[9].

Introduction

In dental clinical practice, devices such as mobile phones and DSLR cameras (Digital Single Lens Reflex) are used to take intraoral and extraoral photographs. Using a photography taken by a mobile phone in dentistry is simple, fast, and very useful for documenting clinical procedures, help in patients' education and clinical trials[1,2,3]. We can assume that in the coming years, the lightweight mobile phone will replace the DSLR camera and its equipment[3]. Given the rapid advances in information technology and mobile computer systems, determining the parameters of patients' faces and analysing the data obtained via mobile phones are expected soon[4,5]. A software can position the points, calculate the parameters, and analyze them in the same time it takes the orthodontist to select an image for analysis—approximately one second. 3D facial analysis (three-dimensional facial analysis) is not available in everyday clinical practice due to the high cost of photography and the necessary devices[5]. The key requirement in two-dimensional photography is adequate standardization of the photographic setting, especially when positioning the patient. With this approach, appropriate levels of reproducibility can be achieved with the aim that thematic measurements can be well linked to clinical thinking[6]. In orthodontics, when photographing a patient, three standard facial positions are used. These are *en face*, profile shot, and *en face* with a smile. The distance between the outer corner of the eye and the upper edge of the ear should be compared to a horizontal plane[7].

Various techniques for measuring facial asymmetry values are used today. For facial analysis, 2D photography (two-dimensional photography), it is necessary to use landmarks with the correct number, correct distribution, and repeatability to obtain results. Photographs are examined, analysed, and the presence of asymmetry is determined by mathematical formulas, as described by Berlin et al.[8]. The standardized photographs from which today's measurements were obtained provide a unique opportunity to study facial growth. Despite the limitations of the measurements obtained on the two-dimensional photographs, the collected data represent a reasonably accurate description of the changes on the face. This finding can be used to assess changes that occur during orthodontic treatments and help locate missing children[9].

Ne postoje apsolutni standardi za ono što daje idealnu estetiku lica, mada su neki parametri korisni za kliničara u procesu planiranja lečenja. Možda su najvažniji elementi u analizi estetike lica simetrija, koncept prosečnosti ili norme, proporcija i rodni dismorfizam[10]. Nedostatak standardizacije u (digitalnim) metodama prikupljanja i bodovanja podataka ugrožava uporedivost nalaza i ograničava procenu asimetrije[11]. Uspostavljanje dijagnoze paralize *n. facialis*, procenjivanje odnosa malokluzije i držanja tela, kao i upotreba aplikacije *WhatsApp TM* za slanje fotografija, prikazuju upotrebu informacijskih tehnologija u cilju uspostavljanja dijagnoze, razmene kliničkih informacija putem digitalne fotografije[12,13,14].

Teledentistika je oblast telemedicine koja omogućava razmenu fotografija i kliničkih informacija putem interneta. Teledentistika je nov način pružanja stomatološke usluge i predstavlja ogroman potencijal za razvoj u sistemu javnog zdravstva. Naime, stomatološki pregledi na daljinu postaju mogući, a posebno mesto zauzimaju u primarnom nivou zdravstvene zaštite[15]. Konsultacije sa pacijentom obuhvataju snimanje fotografija od interesa, merenja i klasifikaciju merenja, psiho--socijalnu podršku i motivaciju[10]. Za razvoj teledentistike zasnovane na dokazima nisu potrebni samo tehnološki resursi već i prihvatanje teledentistike od strane opšte populacije, pacijenta, ali i zdravstvenih radnika. Teledentistika može biti primenjiva za lečenje pacijenata sa stanjima poput oralne bolesti sluznice, parodontitisa, malokluzija, temporomandibularnih poremećaja i oralnih bolova[15]. Fotografija kao digitalni materijal koristi se za procenu u napretku dentalnih bolesti i daje široke mogućnosti istraživanja[16].

Za vreme pandemije virusa COVID-19 nije bila dopuštena poseta ortodontu; upravo to je omogućilo prikazivanje prednosti korišćenja digitalnih tehnika u ortodonciji za sprovođenje terapije kod kuće, Skeniranje, planiranje, praćenje i odgovor na hitne situacije prednosti su teleortodoncije[17]. Teleortodoncija može pružiti značajno ortodontsko usmerenje stomatolozima u situacijama kada odlazak specijalisti ortodontu nije izvodljiv. ortodontsko lečenje nadzirano na daljinu putem teleortodoncije pokazalo se kao obećavajući pristup smanjenju ozbiljnosti malokluzija, onda kada odlazak ortodontu nije bio moguć[18]. Ključ budućnosti teleortodoncije bilo bi obezbeđivanje odlične usluge, individualnog pristupa i balansiranje poseta pacijenta ortodontu[19].

There are no absolute standards for an ideal facial aesthetics, but some parameters are useful for the clinician in the treatment planning process. Perhaps the most important element in the analysis of facial aesthetics is symmetry, the concept of mediocrity or norm, proportion, and gender dysmorphism[10]. The results of research linking facial asymmetry and clinical disorders, comparing asymmetry before and after surgery in facial plastic surgery, are heterogeneous. The lack of standardization in (digital) data collection and scoring methods jeopardizes the comparability of findings and limits the assessment of asymmetry[11]. Establishing a diagnosis of facial nerve paralysis, assessing the relationship of malocclusion and posture, as well as the use of the *WhatsApp TM* application to send photographs, show the use of information technology to establish a diagnosis, and exchange clinical information through digital photography[12,13,14].

Teledentistry is a new way of providing dental services and has a vast potential to develop in the public health system. Remote dental examinations are possible and occupy a special place in health care[15]. Consultations with the patient include taking photographs of interest, measurement and measurement classification, psychosocial support, and motivation[10]. The development of evidence-based teledentistry requires technological resources and the acceptance of teledentistry by the general population, patients, and health professionals. Teledentistry may be applied to treat patients with conditions such as oral mucosal disease, periodontitis, malocclusion, temporomandibular disorders, and oral pain[15]. Photography as a digital material is used to assess the progress of dental diseases and for the wide range of research opportunities[16].

During the COVID-19 pandemic, visits to the orthodontist were not allowed. However, the benefits of using digital techniques in orthodontics to conduct therapy at home were demonstrated with an estimate of the costs and benefits of a remote orthodontic approach in everyday practice in the near future. Scanning, planning, monitoring, and responding to emergencies are the benefits of tele-orthodontics. Teleorthodontics is fundamental not only for the possibility of continuing orthodontic therapy but also from a psychological point of view in order to convince patients of the positive development of their smiles[17]. Teleorthodontics can provide significant orthodontic guidance to dentists in situations where referral to an orthodontist is not feasible. Between the groups, interceptive orthodontic treatment monitored remotely via teleorthodontics proved to be a promising approach to reducing the severity of

Stopa prihvatljivosti teledentistike (95,3%) među pacijentima i njihovim porodicama bila je izvrsna[20]. Teledentistika bi mogla biti važan faktor u smanjenju neprikladne stope upućivanja pacijenata ortodontu. To bi značajno smanjilo vreme čekanja na ortodontske tretmane preporuke[21]. U ovako visokoj potražnji za ortodontskim lečenjem, neophodno je utvrditi potrebu za ortodontskim lečenjem kao osnovnu, tako da se osobama sa najvećim potrebama može dodeliti prioritet[22].

Stoga, uprkos naprednim antropometrijskim metodama poput trodimenzionalne stereofotogrametrije, fotogrametrija ostaje optimalan izbor za velike epidemiološke studije, koje za cilj imaju uspostavljanja populacijskih normi, posebno u zemljama u razvoju, u kojima sofisticirana oprema nije dostupna. Rezultati različitih antropometrijskih metoda nisu direktno uporedivi. Wen YF i sar. navode potrebu za kvalitetnijim fotogrametrijskim studijama, koje koriste standardizovane fotografske tehnike, i koje bi, po mogućnosti, bile izvedene iz velikog randomizovanog uzorka, koji uključuje različite etničke/rasne skupine[23].

Iz navedenog proizilazi da je potrebno sprovesti što više istraživanja kako bi se došlo do standarda za analizu fotografija, kao i proširila njihova upotreba u svakodnevnoj praksi, sa ciljem uspostavljanja brze dijagnoze, predvidivosti rezultata i razvoja teledentistike za vreme trajanja pandemije virusa COVID-19.

Cilj pilot studije je da se utvrdi ponovljivost pozicioniranja tačaka i merenja pri analizi simetrije lica na digitalnim 2D fotografijama. Glavna studija biće izvodiva ako vrednosti interklasnih koeficijenata korelacije, izračunatih putem metode dvosmernih nasumičnih efekata (engl. two-way random effects), za svaki od šest indeksa bude iznad vrednosti donje granice prihvatljivosti (ICCs > .70).

Metodologija rada

U pilot istraživanju jedno lice starosti 12 godina fotografisano je pomoću dve različite tehnike snimanja. Na jednoj fotografiji su se pozicionirale tačke; ista fotofrafija koristila se za svako naredno merenje. Kada je reč o prvoj tehnici fotografisanja, fotografija je slikana digitalnim foto-aparatom DSLR *Nikon* D 850, objektiva 105 mm, f/8, ISO 100, a od ispitanika je traženo da napravi neutralnu facijalnu ekspresiju, bez pogleda u ogledalo.

malocclusions when referral to an orthodontist was not feasible[18]. The key to the future of teleorthodontics would be to provide excellent service, an individual approach, and to balance patient visits to the orthodontist[19].

The acceptance rate of teledentistry (95.3%) among patients and their families was excellent[20]. Teledentistry is a valid system for the positive identification of appropriate new orthodontic referrals of the patient. Teledentistry could potentially be an important factor in reducing unnecessary referral rates. This would significantly reduce the waiting time for orthodontic recommendations[21]. In such a high demand for orthodontic treatment, it is necessary to identify the basis of the need for orthodontic treatment so that priority can be given to people with high treatment needs[22]. Therefore, despite advanced anthropometric methods such as three-dimensional stereophotogrammetry, photogrammetry remains the optimal choice for extensive epidemiological studies aimed at establishing population norms, especially in developing countries where sophisticated equipment is not available. The results of different anthropometric methods are not directly comparable. Wen YF et al. specify the need for better photogrammetric studies that use standardized photographic techniques, preferably from a large randomized sample of different ethnic/racial groups[23].

From the above, it is necessary to do as much research as possible to reach standards for photo analysis and expand their use in everyday practice to establish a fast diagnosis, predictability of results, and development of teledentistry during the COVID-19 pandemic.

The aim of the pilot study was to determine the repeatability of point positioning and measurements in the analysis of facial symmetry in digital 2D photographs. The main study will be feasible if the values of the interclass correlation coefficients, calculated using the two-way random effects method, are above the lower acceptability limit value for each of the six indices (ICCs >.70).

Material and methods

A 12-year-old person participated in the pilot study. The face was photographed using two different photography techniques. Points were positioned in one photo and used for each subsequent measurement. The first photography technique was performed using a digital camera with settings: Nikon D 850 DSLR camera, 105 mm lens, f/8, ISO 100 with neutral facial expression without looking in the mirror.

U istraživanju koristila se fotografija rezolucije 4128 x 2752 i veličinom od 32,5 M. Druga tehnika fotografisanja je urađena mobilnim telefonom (*Samsung Galaxy Note 9*), uz pomoć aplikacije *Dentalshooting*, App sa okvirom za lice. Drugom tehnikom fotografisanja u istraživanju koristila se fotografija rezolucije 2548x3377 i veličinom od 24,6 M. Nakon fotografisanja, izvršena je analiza fotografija pomoću programa *Photoshop CC 2019, Adobe Systems USA. Dva procenjivača pozicionirala su 20 tačaka u tri vremenski odvojena perioda.*

Pisani informisani pristanak za korišćenje fotografija za objavljivanje pribavljen je od roditelja pacijenta jer je pacijent maloletnik, te je za objavljivanje njegove fotografije u naučnim knjigama i/ili časopisima potrebna pisana dozvola roditelja.

Centralni indeks asimetrije (AI)

Za analizu asimetrije na fotografijama frontalnog pogleda korišćene su apsolutne vrednosti indeksa asimetrije (AI), izračunate pomoću formule AI = | (R-L) / (R+L) x 100%, Orjentiri za merenje uključuju zenicu (Pu), bočni ugao oka (La), sella-nasion (Sn) i ugao usta (Am). Za merenje referentnih linija koristili smo liniju koja povezuje desnu i levu zenicu (Pu) kao vodoravnu referentnu liniju (a) i liniju okomitu na vodoravnu referentnu liniju za medijalnu liniju lica (b)[24].

Facijalna asimetrija (FA) i centralna facijalna asimetrija (CFA)

Ukupna asimetrija lica (FA) temeljila se na zbiru svih mogućih razlika između srednjih tačaka šest vodoravnih linija, i to između sledećih parova tačaka: P1–P2, P3–P4, P5–P6, P7–P8, P9–P10 i P11–P12. Pozicija tačaka prikazana je na Figuri 1. Ovih šest linija označeno je kao Dl, D2, D3, D4, D5, odnosno D6. Sredina svake linije izračunata je formulom ((leva tačka - desna tačka) + 2) + desna tačka. Na savršeno simetričnom licu sve središnje tačke leže na istoj vertikalnoj liniji, a zbir svih mogućih srednjih razlika je nula. Pozicija tačaka, linija i sredina svake linije prikazana je na Figuri 1.

Centralna facijalna asimetrija (CFA) fokusira se na razlike između srednjih tačaka susednih linija, posebno u središtu lica. CFA odgovara zbiru razlika srednjih tačaka linija Dl i D2, D2 i D3, D3 i D4, D4 i D5 i D5 i D6[25].

Horizontalna angularna asimetrija lica

Ugao između vodoravne linije i linije kroz obostrane uglove usta meren je na fotografiji lica. U pilot studiji analizirane su tačke desni cheilion(chr)i levi cheilion(chl).

The analysis of the photos was performed with a resolution of 4128 x 2752 and a size of 32.5 M.

Another photographic technique was performed using a mobile phone (Samsung Galaxy Note 9) with the help of the Dental Shooting app (with a face frame). The analysis of the photos was performed with a resolution of 2548x3377 and a size of 24.6 M. After photographing, the analysis of the photos was performed using Adobe Photoshop CC 2019, Adobe Systems USA. Two evaluators positioned 20 points in three time-separated periods.

Written informed consent to use photographs for publication was obtained from the patient's parents as the patient was a minor for publishing in scientific books and/or periodicals.

Asymmetry index (AI)

Absolute values of the asymmetry index (AI), calculated using the formula AI = | (R-L) / (R + L) x 100%, were used to analyse the asymmetry in the frontal view photographs. Measurement landmarks included pupil (Pu), lateral angle of the eye (La), *sella-nasion* (Sn), and the angle of the mouth (Am). To measure the reference lines, we used a line connecting the right and left pupils (Pu) as the horizontal reference line (a) and a line perpendicular to the horizontal reference line for the medial line of the face (b)[24].

Facial asymmetry (FA) and central facial asymmetry (CFA)

The total facial asymmetry (FA) was based on the sum of all possible unnecessary differences between the midpoints of the six horizontal lines, between the following pairs of points: P1-P2, P3-P4, P5-P6, P7-P8, P9-P10, and P11-P12. The position of the points is shown in Figure 1. These six lines were marked as D1, D2, D3, D4, D5, and D6. The middle of each line was calculated using the formula ((Left point - Right point) + 2) + Right point. On a perfectly symmetrical face, all midpoints lie on the same vertical line, and the sum of all possible nonredundant differences is zero. The position of the points, the line, and the middle of each line are shown in Figure 1.

Central facial asymmetry (CFA) focuses on the differences between the midpoints of adjacent lines, especially in the centre of the face. CFA corresponds to the sum of the differences of the midpoints of the lines D1 and D2, D2 and D3, D3 and D4, D4 and D5, and D5 and D6[25].

Na osnovu veličine ugla, lica se razvrstavaju u sledeća tri tipa: paralelni tip obuhvata uglove veće od jednog stepena i manje od jednog stepena, levo dominantni tip sastoji se od uglova manjih od jednog stepena ili jednakih jednom stepenu, a desno dominantni uglovi veći su od jednog stepena ili jednaki jednom stepenu[26].

Rezultati

U Tabeli 1. predstavljene su vrednosti indeksa asimetrije izračunatih na osnovu informacija o pozicijama 20 tačaka postavljenih od strane dva procenjivača u tri vremenski odvojene tačke, i to na dve fotografije snimljene mobilnim telefonom i foto-aparatom. Centralni indeks asimetrije (AI) izračunat je nivoima oka (AI gornji), nosa (AI srednji) i usana (AI donji), a srednja vrednost za ova tri pojedinačna indeksa korišćena je kao mera opšteg indeksa centralne asimetrije (AI prosečni). Pored toga, izračunati su i indeksi facijalne asimetrije (FA) i centralne facijalne asimetrije lica (CFA), te horizontalne angularne asimetrije lica. (Tabela 1.)

U Tabeli 2. prikazani su podaci o prosečnim vrednostima i pratećim standardnim devijacijama, izračunati na osnovu tri vremenski odvojene procene za svakog od dvaju procenjivača, koje su date zasebno za dve tehnike fotografisanja. Rezultati Man–Vitni testa prikazani u poslednjim dvema kolonama ukazuju na to da nisu postojale statistički značajne razlike u vrednostima izračunatih indeksa asimetrije (ps > .05) među procenjivačima i tako posredno svedoče o zadovoljavajuće visokom stepenu slaganja pozicioniranja tačaka na fotografijama.

Dodatnu potvrdu visokog stepena opšteg slaganja pozicioniranja tačaka postavljenih od strane dvaju procenjivača pružaju podaci prikazani u okviru Tabele 3. i na Grafikonu 1. Naime, vrednosti interklasnih koeficijenata korelacije, izračunatih putem metode dvosmernih nasumičnih efekata (engl. two-way random effects), za svaki od šest indeksa bile su iznad donje granice prihvatljivosti (ICCs > 0.70), pri čemu je vrednost ICC za FA indeks bila najniža (ICC = .74), za AI gornji .83, dok je za ostale indekse vrednost ICC bila iznad granice 0.90. Dodatno, stepen slaganja indeksa asimetrije, koji su analizirala dva procenjivača, prikazan je i putem Bland–Altmanovih dijagrama saglasnosti, na kojima se može primetiti da nijedna procena indeksa asimetrije ne odstupa značajno od okvira postavljenih putem devedesetpetoprocentnog intervala slaganja.

Horizontal angular asymmetry of the face

The angle between the horizontal line and the line through the bilateral corners of the mouth was measured in a photograph of the face.

In the pilot study, the points chr (right cheilion) and chl (left cheilion) were analyzed. Based on the size of the angle, faces were classified into the following three types: the parallel type included angles greater than ⩾1 degree and less than 1 degree, the left dominant type consisted of angles less than or equal to ⩾1 degree, and the right dominant angles were greater than one degree or equal to one degree[26].

The results

Table 1 presents the values of the asymmetry index calculated on the basis of information on the positions of 20 points set by two evaluators in three time-separated points on two photographs taken with a mobile phone and a camera. The central asymmetry index (AI) was calculated by the levels of the eye (AI upper), nose (AI middle), and lips (AI lower), and the mean value for these three individual indices were used as a measure of the general index of central asymmetry (AI average). In addition, the indices of facial asymmetry (FA) and central facial asymmetry (CFA), and horizontal angular facial asymmetry were calculated. (Table 1)

Table 2 shows data on average values and accompanying deviation standards calculated on the basis of three time-separated estimates for each of the two evaluators given separately for the two photography techniques. The results of the Mann-Whitney test presented in the last two columns indicate that there were no statistically significant differences between the evaluators in the values of the calculated asymmetry indices (ps >.05) and thus indirectly testify to a satisfactorily high degree of agreement of their point positioning in photographs.

Additional confirmation of the high degree of general agreement of the point positioning of the two evaluators is provided by the data shown in Table 3 and Graph 1. Namely, the values of interclass correlation coefficients, calculated using the two-way random effects method, for each of the six indices were above the lower limit of acceptability (ICCs >.70), with the ICC value for FA index being the lowest (ICC = .74), for AI upper .83, while for other indices the ICC

U nastavku su sprovedene dodatne analize, ali ovoga puta na nivou vrednosti pozicija tačaka, a ne indeksa asimetrije. Naime, analizirana je saglasnost pozicioniranja 20 pojedinačnih tačaka na dvema osama (x – horizontalnoj, y – vertikalnoj), kao i izračunatih vrednosti ugla.

U Tabeli 4. prikazane su prosečne vrednosti pozicioniranja ovih tačaka postavljenih od strane dvaju procenjivača u slučaju fotografije dobijene putem foto-aparata, kao i vrednosti razmaka, odnosno razlike u prosečnim procenama, te rezultati statističkog testiranja značajnosti ovih razlika. Od ukupno 41 analiziranog parametra, samo je na jednom parametru (Snb_L_x) detektovana statistički značajna razlika ($U = 0.00$, $p = .04$); kod preostalih 40 parametara ova razlika nije bila statistički značajna ($p \geq .05$).

U slučaju kada su procenjivane fotografije dobijene putem mobilnog telefona, nijedna razlika nije bila statistički značajna. (Tabela 5)

value was above the limit of .90. In addition, the degree of agreement of the asymmetry index of the two evaluators is shown by Bland-Altman agreement diagrams on which it can be observed that no estimate of the asymmetry index deviates significantly from the limits set by the 95% agreement interval.

Additional analyses were performed below, but this time at point position values rather than asymmetry indices. Namely, the agreement of the positioning of 20 individual points on two axes (x - horizontal and y - vertical) and the calculated values of the angle was analyzed.

Table 4 shows the average values of the positioning of these points for two evaluators in the case of a photograph obtained with a camera, as well as the spacing values, i.e., differences in average estimates, and the results of statistical testing of the significance of these differences. Out of a total of 41 analyzed parameters, only one (Snb_L_x) had a statistically significant difference detected ($U = 0.00$, $p = .04$), while on the remaining 40 this difference was not statistically significant ($p \geq .05$).

When it comes to evaluating the photographs obtained via mobile phone, no difference was statistically significant. (Table 5)

Tabela 1. Veličine indeksa asimetrije na osnovu tačaka koje su postavila dva procenjivača u tri navrata na fotografijama načinjenim fotoaparatom i mobilnim telefonom
Table 1. Asymmetry index values based on points set by two evaluators on three occasions in photographs taken with a camera and mobile phone

Procenjivač Evaluator	Tehnika Technique	Mjerenje Measurement	AI gornji AI upper	AI srednji AI middle	AI donji AI lower	AI prosečni AI average	FA	CFA
A	Aparat Camera	1	6.59	4.88	4.94	5.47	39.31	20.14
A	Aparat Camera	2	4.57	5.13	4.75	4.82	40.16	20.62
A	Aparat Camera	3	4.82	5.28	4.64	4.91	39.68	20.43
A	Telefon Phone	1	1.86	2.64	3.38	2.63	36.36	18.61
A	Telefon Phone	2	1.40	2.47	3.19	2.35	36.71	18.88
A	Telefon Phone	3	2.48	2.73	3.18	2.80	35.83	18.41
B	Aparat Camera	1	5.04	4.94	4.70	4.89	39.18	20.13
B	Aparat Camera	2	5.11	5.57	5.40	5.36	47.50	22.14
B	Aparat Camera	3	6.75	5.14	5.05	5.65	39.36	20.32
B	Telefon Phone	1	1.66	2.80	3.99	2.82	36.48	18.76
B	Telefon Phone	2	4.04	2.62	3.40	3.35	36.39	18.71
B	Telefon Phone	3	2.37	2.46	3.50	2.78	36.41	18.72

Legenda: A - procenjivač, B- procenjivač, AI -index asimetrije, FA- facijalna asimetrija, CFA- centralna facijalna asimetrija
Legend: A - estimator, B - estimator, AI - asymmetry index, FA - facial asymmetry, CFA - central facial asymmetry

Tabela 2. Razlike u procenama asimetrije između dva procenjivača
Table 2. The differences in asymmetry estimates between the two evaluators

Tehnika Technique	Indeks Index	Procenjivač A Evaluator A		Procenjivač B Evaluator B		Značajnost razlika DifferenceSignificance	
		M	SD	M	SD	U	p
Aparat Camera	AI gornji AI upper	5.33	1.10	5.63	0.97	2.00	.28
	AI srednji AI middle	5.10	0.20	5.22	0.32	3.00	.51
	AI donji AI lower	4.78	0.15	5.05	0.35	2.00	.28
	AI prosečni AI average	5.07	0.35	5.30	0.38	3.00	.51
	FA	39.72	0.43	42.02	4.75	4.00	.83
	CFA	20.40	0.24	20.87	1.11	4.00	.83
Telefon Phone	AI gornji AI upper	1.91	0.54	2.69	1.22	3.00	.51
	AI srednji AI middle	2.61	0.13	2.63	0.17	4.00	.83
	AI donji AI lower	3.25	0.11	3.63	0.32	0.00	.05
	AI prosječni AI awerage	2.59	0.22	2.98	0.32	1.00	.13
	FA	36.30	0.44	36.43	0.05	3.00	.51
	CFA	18.64	0.24	18.73	0.03	3.00	.51

Legenda: AI -indeks asimetrije, FA- facijalna asimetrija, CFA- centralna facijalna asimetrija
Legend: AI−asymmetry index, FA - facial asymmetry, CFA−central facial asymmetry

Tabela 3. Interklasni koeficijenti korelacije (ICC) za indekse asimetrije
Table 3. Interclass correlation coefficients (ICC) for asymmetry indices

Tačka Point	ICC	95% CI	Prosečna razlika (SD) Average difference (SD)	95% granice slaganja 95% agreement limit
AI gornji AI upper	.826	-.105 – .975	-0.54 (1.53)	-3.54 – 2.46
AI srednji AI middle	.993	.954 – .999	-0.07 (0.25)	-0.56 – 0.42
AI donji AI lower	.931	.311 – .991	-0.33 (0.32)	-0.96 – 0.31
AI prosječniAI average	.947	.679 – .992	-0.31 (0.57)	-1.43 – 0.80
FA	.740	-.588 – .963	-1.21 (3.02)	-7.13 – 4.71
CFA	.922	.536 – .989	-0.28 (0.63)	-1.53 – 0.96

Legenda: AI -indeks asimetrije, FA- facijalna asimetrija, CFA- centralna facijalna asimetrija
Legend: AI−index asymmetry, FA−facial asymmetry, CFA−central facial asymmetry

Tabela 4. Razlike u pozicioniranju tačaka između dva procenjivača (tehnika 1)
Table 4. Differences in point positioning between two evaluators (technique 1)

Tačka Point	**Procenjivač A Evaluator A**		**Procenjivač B Evaluator B**		**Značajnost razlike Difference significance**		
	M	**SD**	**M**	**SD**		U	p
Lab_D_x	21.82	0.04	21.82	0.11	-0.01	4.00	.83
Lab_D_y	18.01	0.03	18.04	0.04	-0.03	2.00	.27
Lab_L_x	30.64	0.04	30.56	0.07	0.08	0.50	.08
Lab_L_y	17.96	0.04	17.65	0.48	0.31	1.50	.18
Snb_D_x	20.10	0.01	20.12	0.03	-0.01	3.50	.65
Snb_D_y	22.04	0.01	22.04	0.03	0.00	4.00	.82
Snb_L_x	32.20	0.01	32.12	0.04	0.08	0.00	.04
Snb_L_y	22.04	0.02	22.05	0.03	-0.01	3.50	.66
Amb_D_x	20.72	0.01	20.73	0.03	-0.01	3.50	.66
Amb_D_y	24.08	0.03	24.06	0.02	0.02	2.00	.28
Amb_L_x	31.67	0.02	31.61	0.01	0.06	0.00	.05
Amb_L_y	24.08	0.03	24.06	0.02	0.02	2.00	.28
P1_x	21.97	0.14	21.82	0.12	0.15	2.00	.28
P1_y	18.10	0.13	18.23	0.41	-0.13	3.50	.66
P2_x	30.69	0.19	30.60	0.09	0.10	3.00	.51
P2_y	18.64	1.13	17.93	0.04	0.71	2.50	.38
P3_x	24.94	0.16	24.79	0.04	0.15	0.00	.05
P3_y	18.31	0.12	18.22	0.03	0.09	2.00	.26
P4_x	27.93	0.19	27.81	0.03	0.11	3.00	.51
P4_y	18.26	0.12	18.17	0.03	0.09	1.00	.13
P5_x	19.57	0.13	19.53	0.01	0.03	4.00	.82
P5_y	19.23	0.25	19.35	0.05	-0.12	3.00	.51
P6_x	32.82	0.23	32.65	0.02	0.17	0.00	.05
P6_y	19.22	0.21	19.11	0.19	0.11	2.00	.28
P7_x	24.84	0.16	24.69	0.03	0.15	0.50	.08
P7_y	21.41	0.10	21.39	0.03	0.02	4.00	.83
P8_x	28.34	0.21	28.21	0.02	0.14	0.50	.08
P8_y	21.40	0.07	21.39	0.03	0.01	3.50	.66
P9_x	20.59	0.15	20.49	0.02	0.11	3.00	.51
P9_y	23.63	0.20	23.46	0.12	0.17	1.00	.13
P10_x	31.95	0.31	31.78	0.06	0.18	2.00	.28
P10_y	23.63	0.16	23.50	0.15	0.13	2.00	.28
P11_x	24.46	0.15	24.36	0.04	0.10	2.00	.27
P11_y	24.19	0.19	24.11	0.02	0.08	3.00	.51
P12_x	28.62	0.23	27.14	2.31	1.48	2.00	.28
P12_y	24.15	0.19	24.08	0.04	0.07	4.00	.82
Chr_x	24.50	0.18	24.28	0.04	0.22	2.50	.38
Chr_y	24.20	0.18	24.08	0.02	0.12	1.50	.18
Chl_x	28.65	0.22	28.47	0.03	0.18	0.00	.05
Chl_y	24.17	0.18	24.05	0.02	0.12	1.50	.18
Degree	0.47	0.10	0.41	0.34	0.06	3.00	.51

Tabela 5. Razlike u pozicioniranju tačaka između dva procenjivača (tehnika 2)
Table 5. Differences in point positioning between two evaluators (technique 2)

Tačka Point	Procenjivač A EvaluatorA		Procenjivač B Evaluator B		Značajnost razlike Difference significance		
	M	SD	M	SD	Razmak	U	p
Lab_D_x	9.94	0.03	9.90	0.15	0.05	3.50	.66
Lab_D_y	19.69	0.01	19.73	0.02	-0.04	0.00	.05
Lab_L_x	19.15	0.03	19.12	0.06	0.03	2.00	.27
Lab_L_y	19.83	0.04	19.87	0.03	-0.03	2.00	.27
Snb_D_x	8.81	0.02	8.76	0.04	0.05	0.50	.08
Snb_D_y	24.03	0.01	23.99	0.04	0.05	1.00	.10
Snb_L_x	20.16	0.01	20.16	0.00	0.00	3.00	.32
Snb_L_y	24.04	0.01	23.96	0.05	0.08	0.00	.05
Amb_D_x	9.45	0.01	9.43	0.03	0.01	3.50	.64
Amb_D_y	26.12	0.01	26.11	0.05	0.01	3.00	.50
Amb_L_x	19.47	0.01	19.46	0.02	0.02	2.00	.20
Amb_L_y	26.12	0.00	26.11	0.03	0.01	4.50	1.00
P1_x	9.92	0.06	9.83	0.03	0.09	0.50	.08
P1_y	19.66	0.08	19.68	0.02	-0.02	4.00	.83
P2_x	19.10	0.06	19.14	0.07	-0.04	2.00	.28
P2_y	19.80	0.03	19.80	0.04	0.00	4.50	1.00
P3_x	12.97	0.02	12.98	0.02	0.00	4.00	.82
P3_y	19.97	0.04	19.97	0.01	0.00	4.50	1.00
P4_x	16.10	0.02	16.09	0.03	0.01	3.00	.50
P4_y	19.98	0.01	19.98	0.05	0.00	3.50	.65
P5_x	8.17	0.04	8.16	0.01	0.02	3.00	.51
P5_y	20.98	0.27	21.06	0.05	-0.09	3.00	.51
P6_x	20.81	0.04	20.80	0.02	0.01	3.00	.51
P6_y	20.97	0.39	21.04	0.02	-0.07	3.00	.51
P7_x	12.65	0.02	12.66	0.01	-0.01	2.50	.37
P7_y	23.18	0.11	23.31	0.02	-0.13	1.50	.18
P8_x	16.48	0.15	16.45	0.02	0.03	4.50	1.00
P8_y	23.10	0.17	23.27	0.06	-0.17	2.00	.28
P9_x	9.14	0.04	9.13	0.04	0.01	3.00	.51
P9_y	25.39	0.09	25.38	0.04	0.01	4.00	.83
P10_x	19.76	0.03	19.71	0.03	0.04	1.00	.13
P10_y	25.40	0.10	25.44	0.03	-0.05	3.00	.51
P11_x	12.23	0.01	12.21	0.03	0.03	1.00	.10
P11_y	26.12	0.02	26.11	0.02	0.01	2.00	.27
P12_x	16.75	0.02	16.72	0.01	0.03	0.00	.05
P12_y	26.13	0.03	26.09	0.04	0.05	1.50	.18
Chr_x	12.32	0.03	12.29	0.05	0.03	0.00	.05
Chr_y	26.10	0.02	26.10	0.01	0	3.00	.49
Chl_x	16.76	0.01	16.73	0.04	0.03	2.00	.27
Chl_y	21.13	0.01	26.12	0.02	-4.99	0.00	.05
Ugao Degree	0.11	0.02	0.13	0.05	-0.02	2.50	.35

Tabela 6. ICC za tačke
Table 6. ICC for point

Tačka Point	ICC	95% CI
Lab_D_x	1.00	1.00 – 1.00
Lab_D_y	.999	.992 – 1.00
Lab_L_x	1.00	.999 – 1.00
Lab_L_y	.977	.863 – .997
Snb_D_x	1.00	1.00 – 1.00
Snb_D_y	1.00	.997 – 1.00
Snb_L_x	1.00	1.00 – 1.00
Snb_L_y	.999	.994 – 1.00
Amb_D_x	1.00	1.00 – 1.00
Amb_D_y	1.00	.998 – 1.00
Amb_L_x	1.00	1.00 – 1.00
Amb_L_y	1.00	.999 – 1.00
P1_x	1.00	.998 – 1.00
P1_y	.967	.784 – .995
P2_x	1.00	.999 – 1.00
P2_y	.795	-.199 – .971
P3_x	1.00	.999 – 1.00
P3_y	.997	.980 – 1.00
P4_x	1.00	.999 – 1.00
P4_y	.997	.982 – 1.00
P5_x	1.00	1.00 – 1.00
P5_y	.981	.886 – .997
P6_x	1.00	.999 – 1.00
P6_y	.975	.815 – .996
P7_x	1.00	.999 – 1.00
P7_y	.996	.974 – .999
P8_x	1.00	.999 – 1.00
P8_y	.992	.954 – .999
P9_x	1.00	.999 – 1.00
P9_y	.993	.954 – .999
P10_x	1.00	.998 – 1.00
P10_y	.993	.954 – .999
P11_x	1.00	1.00 – 1.00
P11_y	.997	.984 – 1.00
P12_x	.979	.871 – .997
P12_y	.997	.983 – 1.00
Chr_x	1.00	.998 – 1.00
Chr_y	.996	.978 – .999
Chl_x	1.00	.998 – 1.00
Chl_y	.996	.975 – .999
Ugao Degree	.456	-.550 – .930

Diskusija

Metodološki pristup pilot studije oslanja se na sprovedena istraživanja[27]. Velika zastupljenost heterogenosti rezultata posledica je nedostatka standarda, kao i metoda koje se koriste za facijalnu analizu. Različiti formati fotografija, tačnost mernog sistema, kao i odabir digitalnog markera za markiranje tačaka prilikom merenja, mogu uticati na rezultate[11,28].

U pilot studiji rezultati svedoče o relativno visokom stepenu slaganja pozicioniranja tačaka, koji su pružila dva procenjivača. Kod čak 22 parametra registrovano je apsolutno podudaranje procena (*ICC*s = 1.00), dok je kod još 17 parametara ova vrednost bila izuzetno visoka (*ICC*s > .96). Jedino je u slučaju P2_y registrovana nešto niža, ali i dalje veoma zadovoljavajuća stopa saglasnosti (ICC = .80); jedina realno niska vrednost pak dobijena je za parametar ugla (ICC = .46).

Od ukupno 41 analiziranog parametra, samo je na jednom (Snb_L_x) detektovana statistički značajna razlika (U = 0.00, p = .04), dok na preostalih 40 parametara ova razlika nije bila statistički značajna (p ≥ .05). U slučaju u kome su procenjivane fotografije dobijene putem mobilnog telefona, nijedna razlika nije bila statistički značajna. Pametni telefon omogućava brzo određivanje parametara lica pacijenta i analizu dobijenih podataka, uz poboljšanja u interakciji i saradnji sa pacijentom[5].

U antropometrijskom istraživanju koje su sproveli, autori su dokazali da stereofotogrametrija i njen protokol za lokaciju orijentira daju vrlo dobru pouzdanost za seriju 2D i 3D linearnih i ugaonih merenja. Rezultati pokazuju da je ICCs 0,88, 0,99 i 0,97 i 0,98 i 0,92[29]. Za dalja istraživanja treba koristiti poboljšanu šemu klasifikacije za antropometriju i poboljšanu nomenklaturu za kraniofacijalne orijentire, koji omogućavaju jasno razlikovanje kako za meka, tako i za tvrda tkiva. Posebnu važnost imaju za fotogrametriju lica, gde su orijentiri mekih tkiva loše definisani i često se pogrešno predstavljaju kao kraniometrijski analozi. Korišćenjem nove notacije obezbeđuje se standardizovani niz kraniometrijskih (lobanja) i kapulometrijskih (lice mekog tkiva) orijentacija, koje omogućavaju izbegavanje trenutnih zabuna[30].

Discussion

The methodological approach of the pilot study relies on the conducted research[27]. The high prevalence of heterogeneity of results is due to the lack of standards and the methods used for facial analysis. Different photograph formats, the accuracy of the measuring system, the choice of a digital marker to mark the points when measuring can affect the results[11,28].

In the pilot study, the results suggest a relatively high degree of agreement of the point positioning provided by the two evaluators. Absolute matching of estimates was registered on 22 parameters (ICCs = 1.00), while on another 17 this value was high (ICCs >.96). Only in the case of P2_y, a slightly lower agreement rate was registered (ICC = .80), but still satisfactory, while the only exceedingly low value was obtained for the angle parameter (ICC = .46).

Out of a total of 41 analyzed parameters, only one (Snb_L_x) had a statistically significant difference detected (U = 0.00, p = .04), while on the remaining 40 this difference was not statistically significant (p ≥.05). In the case of the evaluated photographs obtained via mobile phone, no difference was statistically significant. The mobile phone will enable fast determination of the patient's face parameters and analysis of the obtained data, with improvements in interaction and cooperation with the patient[5]. In an anthropometric study they conducted, the authors proved that stereo-photogrammetry and their landmark location protocol provide very good reliability for a series of 2D and 3D linear and angular measurements. The results show ICCs 0.88, 0.99 and 0.97, and 0.98 and 0.92[29]. For further research, an improved classification scheme for anthropometry and an improved nomenclature for craniofacial landmark should be used to allow a clear distinction to be made for both soft and hard tissues. They are of special importance for facial photogrammetry, where soft tissue landmarks are poorly defined and are often misrepresented as craniometric analogs.

Using the new notation, a standardized set of craniometric (skull) and cephalometric (soft tissue face) orientations is provided, which makes it possible to avoid current confusion[30]. In routine cases of orthognathic surgery, cephalometry and 2-D photogrammetry are common and less expensive tools that can have the potential to analyze and predict the resulting profile.

U rutinskim slučajevima ortognatske hirurgije, cefalometrija i 2D fotogrametrija uobičajeni su i jeftiniji alati, koji mogu imati potencijal za analizu i predviđanje rezultirajućeg profila. 2D fotogrametrija je jednostavna i isplativa tehnika i može se koristiti za procenu promena mekog tkiva nakon ortognatske operacije[31].

Istraživanje iz 2018. godine prikazalo je komparaciju analize lica na 2D slikama lica sa analizom na 3D rekonstruisanim modelima ljudskih lica korišćenjem tehnologije skeniranja lica. 3D rekonstruisani modeli lica bolje ilustruju klinička standardna mjerenja u odnosu analiza na 2D fotografijama. Kvalitativno, Wilcoxon test je pokazao da su posmatrači za subjektivnu procenu analize lica izazili uvjerenost u 3D rekontsrukciju modela lica kao i u 2D fotografiie[32].

Merenja zabeležena 3D sistemom dovoljno su tačna i dovoljno pouzdana za kliničku upotrebu. Najveće razlike između direktnog i indirektnog (tj. 2D) merenja uzrokovane su fotografskim izobličenjem. Bilo bi očekivano da se 2D merenja neće usko poreditі sa ručnim ili 3D merenjima, prilikom kojih tačke lokacije nisu u istoj ravni kao kalibraciiski kvadrat. Jedna od potencijalnih upotreba 3D slike volumetriiska upoređivania pomoću superponiranja slike –snažno zavisi od preciznosti identifikacije orijentira, kako je prikazano u istraživanju H. Ghoddousi et al.[28]. Nalazi autora Guyot et al. pokazali su da su fotogrametrijska merenja pouzdana. Nije pronađena statistička razlika u 10 od 14 merenja (P > 0,05). Ovo istraživanje pokazuje da je digitalna fotogrametrija korisno sredstvo, ali i da još uvek ne postoji pouzdana standardna tehnika fotografskog merenja[33]. Analiza koju su izvršili Bland i Altman pokazala je da su obe tehnike, direktna antropometrija i 2D fotogrametrija, slično valjane i da mogu zameniti jedna drugu. Mora se imati na umu da su udaljenosti dobiiene direktnom antro-pometriiom obično kraće od udaljenosti dobiiene direktnom antropometriiom, verovatno zbog pritiska na meko tkivo kada antropometar dodirne kožu[34]. Razvoi digitalnih aplikacija za ortodonciju tek treba u potpunosti istražiti i iskoristiti. Upotrebu 2D fotografije u analizi lica prikazali su autori Rao et al. Inovativan sistem pruža automatizovan i učinkovit pristup merenju orijentira na licu pomoću fotometrijskih tačaka na osnovu 2D slika. Sistem se može kombinovati sa tehnologijom proširene stvarnosti (AR) kako bi se postigla bolja vizualizacija i 3D rekreacija struktura[35].

2-D photogrammetry is simple, cost-effective, and can be used to assess soft tissue changes after orthognathic surgery[31].

A comparison of 3D scans and 2D photography to identify soft tissue landmarks on the face included a study of thirty Caucasians. Five soft tissue facial observers were identified twice from three observers in 2D and 3D images. The correlation coefficient within the observer (ICC) revealed a better agreement between the observer in 3D for issues related to face shape, lip pitch, and chin posture[32].

The measurements recorded by the 3D system are sufficiently accurate and reliable enough for clinical use. The largest differences between direct and indirect (i.e., 2D) measurements are caused by photographic distortion. It would be expected that 2D measurements would not be closely compared to manual or 3D measurements, where the location points are not in the same plane as the calibration square. One of the potential uses of 3D imaging, namely, volumetric comparisons using image superposition, strongly depends on the accuracy of landmark identification, as shown in the study by H. Ghoddousi et al.[28] Findings of Guyot et al. have shown that photogrammetric measurements are reliable. No statistical difference was found between 10 of 14 measurements (P >0.05). This research shows that digital photogrammetry is a useful tool but there is no reliable standard photographic measurement technique yet[33]. Bland-Altman's analysis showed that both techniques, direct anthropometry and 2-D photogrammetry, are similarly valid and can replace each other. It must be borne in mind that the cephalometric distances obtained by direct anthropometry are usually shorter than the distances obtained by direct anthropometry, possibly due to the pressure on the soft tissue when the anthropometer touches the skin[34]. The development of digital applications for orthodontics has yet to be fully explored and exploited. The use of 2D photography in facial analysis was demonstrated by the authors Rao et al. The innovative system provides an automated and efficient approach to measuring face landmarks using photometric points based on 2D images. The system can be combined with augmented reality (AR) technology to achieve better visualization and 3D recreation of structures[35].

Zaključak

Prikazani rezultati svedoče o tome da različiti procenjivači u različitim vremenskim tačkama daju zadovoljavajući pouzdane, odnosno dosledne i međusobno saglasne procene pozicija tačaka važnih za razumevanje asimetrije lica. Iako su rezultati analize fotografija načinjenih mobilnim telefonom pouzdani, rezultati dobijeni analizom fotografija načinjenih foto aparatom su precizniji. Kako bi se ustanovila dijagnoza asimetrije lica i razvoja teledentistike, potrebno je sprovesti dodatna istraživanja, koja će obuhvatiti veći uzorak i različite modele telefona.

Zahvalnica: Autori se zahvaljuju Aleksić dr Bojani (procenjivaču B), bez čijeg napora u tačnom i preciznom prikupljanju podataka ova studija ne bi bila moguća.

Sukob interesa: Nema

Conclusion

The presented results indicate that different evaluators at different time points give satisfactorily reliable, mutually consistent estimates of the positions of points important for understanding facial asymmetry.The results obtained by the mobile phone are reliable but the camera is more accurate.From the above, it is necessary to do additional research that will include a larger sample and different phone models to establish the diagnosis of facial asymmetry and the development of teledentistry.

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Conflict of interest: Nil

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ULTRAZVUČNA TERAPIJA U ZBRINJAVANJU POREMEĆAJA TEMPOROMANDIBULARNOG ZGLOBA

ULTRASOUND THERAPY IN THE MANAGEMENT OF TEMPOROMANDIBULAR JOINT DISORDERS

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.

Sažetak

Uvod: *Poremećaji temporomandibularnog zgloba (TMP) su zajednički naziv za poremećaje koji pogađaju temporomandibularni zglob (TMZ), mastikatorne mišiće i njihove okolne strukture. Etiologija TMP-a je složena, a njihovo lečenje uključuje različite invazivne i neinvazivne metode. Sve veći trend neinvazivnih, nefarmakoloških intervencija za lečenje bola u TMZ-u doveo je do razvoja modaliteta u okviru fizikalne terapije. Ultrazvuk je elektrofizički modalitet lečenja, koji se koristi u lečenju TMP-a.*
Cilj *ovog rada je pružanje uvida u modalitete lečenja zasnovane na ultrazvuku, koji se koriste za efikasno lečenje TMP-a.*
Materjali i metode: *Pretraga elektronske baze podataka izvršena je u Google Scholar-u i PubMed-u, i to korišćenjem sledećih termina: „terapija ultrazvukom"; „terapeutski ultrazvuk"; „poremećaji temporomandibularnog zgloba".*
Rezultat*i dobijeni pretraživanjem baze podataka pregledani su i uključeni u ovaj pregledni rad. Ovde su razmatrane najčešće korišćene terapijske ultrazvučne metode u lečenju poremećaja temporomandibularnog zgloba, zajedno sa protokolima lečenja, prednostima, ograničenjima i drugim faktorima, koje treba uzeti u obzir kako bi ishod lečenia bio efikasan.*
Zakliučak*: U bliskoi budućnosti mogu se razviti različiti novi terapijski modaliteti TMZ zasnovani na ultrazvuku.*

Ključne reči: *fizikalna terapija, fonoforeza, ultrazvučna terapija, poremećaji temporomandibularnog zgloba*

Abstract

Introduction: *Temporomandibular joint disorder (TMD) is a collective term given to the disorders affecting the Temporomandibular joint(TMJ), masticatory muscles and their related structures. The aetiology of TMD is complex and their management includes various invasive and non-invasive methods. The increasing trend in non-invasive, non-pharmacological interventions for the management of TMJ pain has led to the development of modalities of physical therapy. Ultrasound is an electrophysical treatment modality used in the management of TMD.*
The aim *of this study is to provide an insight into ultrasound based treatment modalities used for the effective management of TMD.*
Materials and methods:*Electronic database search was carried out in Google Scholar and PubMedusing the search terms "ultrasound therapy", "therapeutic ultrasound" and "temporomandibular joint disorders".*
The results *obtained from the database search were screened and included for the review. Commonly used therapeutic ultrasound methods in the management of temporomandibular joint disorders with the treatment protocols, advantages, limitations and other factors to be considered for an effective treatment outcome is discussed in the present review.*
Conclusion: *Various new ultrasound-based TMJ therapeutic modalities may be developed in the near future.*

Key words: *physical therapy, phonophoresis, ultrasonic therapy, temporomandibularjoint disorders*

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Uvod

Temporomandibularni zglob (TMZ) je jedan od složenih sinovijalnih zglobova u ljudskom telu. Poremećaji koji uključuju TMZ, mastikatorne mišiće i njihove okolne strukture zajedno se nazivaju poremećajima temporomandibularnog zgloba (TMP)[1]. Ova grupa poremećaja predstavlja jedan od najčešćih uzroka orofacijalnog bola. Etiologija TMP-a je složena, a njihovo lečenje uključuje različite invazivne i neinvazivne metode. Sve veći trend traganja za neinvazivnim, nefarmakološkim intervencijama za lečenje bola u TMZ-u doveo je do razvoja modaliteta fizikalne terapije. Različiti elektrofizički terapijski modaliteti koji se trenutno koriste za ublažavanje bolova povezanih sa TMP-om uključuju ultrazvuk (UZ), mikrotalase, transkutanu električnu stimulaciju nerva i lasersku terapiju niskog nivoa[2]. Ultrazvuk je dobro uspostavljen modalitet lečenja u opštoj fizioterapiji mišićno-skeletnog bola[3]. Postoje različiti oblici terapeutskog ultrazvuka, koji se koriste u lečenju TMP-a. Cilj ovog preglednog rada je da pruži kratak opis različitih modaliteta lečenja zasnovanih na ultrazvučnoj terapiji TMP-a. Pretražili smo elektronske baze podataka Google Scholar i PubMed koristeći termine „ultrazvučna terapija", „terapeutski ultrazvuk" i „poremećaji temporo-mandibularnog zgloba". Rezultati dobijeni pretraživanjem baze podataka pregledani su i obuhvaćeni ovim preglednim radom.

Terapeutski ultrazvuk

Ultrazvuk se odnosi na zvučne talase koji osciliraju sa frekvencijom većom od 20.000 ciklusa u sekundi – herc (Hz). Nazivaju se i visokofrekventnim talasima. Ultrazvuk (UZ) je dobro poznati imidžing i terapeutski modalitet, koji je učvrstio svoju primenu u oblasti medicine. Terapeutski ultrazvuk može se definisati kao upotreba ultrazvučnih talasa za lečenje obolelih ili povređenih organa ili telesnih struktura. Terapeutski UZ radi na frekvencijskom opsegu od 0,7 MHz do 3,3 MHz[3,4]. Primena terapeutskog ultrazvuka (Th UZ) u medicini datira od ranih tridesetih godina dvadesetog veka. Početne primene bile su zasnovane na mehanizmu zagrevanja tkiva. Ogroman napredak u nauci i tehnologiji doveo je do raznih drugih primena terapijskog ultrazvuka, uključujući lečenje Menierove bolesti za uništavanje vestibularnog nerva i korišćenje fokusiranog ultrazvuka u lečenju Parkinsonove bolesti lokalizovanim uništavanjem tkiva u mozgu.

Introduction

Temporomandibular joint (TMJ) is one of the complex synovial joints in the human body. Disorders involving the TMJ, masticatory muscles and their related structures are grouped together as Temporomandibular joint disorder (TMD)[1]. These group of disorders remain one of the most common causes of orofacial pain. The aetiology of TMD is complex and its management includes various invasive and non-invasive methods. The increasing trend in the need of non-invasive, non-pharmacological interventions for the management of TMJ pain hasled to the development of modalities of physical therapy. Various electrophysical therapeutic modalities that are currently used in relieving pain associated with TMD include ultrasound (US), microwaves, transcutaneous electrical nerve stimulation and low-level laser therapy[2]. Ultrasound is a well-established treatment modality in general physiotherapy for musculoskeletal pain[3]. There are various forms of therapeutic ultrasound that are being used in the management of TMD. The aim of this review is to provide a brief description of various ultrasound based treatment modalities for the management of TMD. We conducted an electronic database search in Google Scholar and PubMed using the search terms "ultrasound therapy", "therapeutic ultrasound" and "temporo-mandibular joint disorder". The results obtained from the database search were screened and included for the review.

Therapeutic Ultrasound

Ultrasound refers to sound waves that oscillatewith a frequency greater than 20,000 cycles per second/Hertz (Hz). They are also called high frequency waves. Ultrasound (US) is a well-known imaging and therapeutic modality that has established its applications in the field of medicine. Therapeutic ultrasound can be defined as the use of ultrasonic waves for the treatment of diseased or injured organs or bodily structures. Therapeutic US works on a frequency range of 0.7 MHz to 3.3 MHz[3,4]. Applications of therapeutic ultrasound (Th Us) in medicine dates back to the early 1930s. The initial applications were based on the mechanism of tissue heating.

Tremendous advancements in science and technology led to various other application of therapeutic ultrasound including the

Kasnije, 1970. godine, terapeutski ultrazvuk stekao je popularnost u oblasti fizioterapije. Terapijski ultrazvuk se u poslednje vreme koristi i u neurohirurgiji i onkologiji. Osim lečenja mišićno-skeletnog bola, druge opšte terapeutske primene ultrazvuka u medicini uključuju upotrebu u cilju zarastanja preloma, oseointegracije, zarastanja povreda kože i mekih tkiva, terapija karcinoma i urooloških primena[5,6].

Mehanizam i biofizički efekti terapijskog ultrazvuka

Kada je ultrazvuk fokusiran na određeno mesto u telu, UZ talasi prodiru u tkiva i proizvode biofizičke efekte. Biofizički efekti ultrazvuka mogu se globalno klasifikovati na termičke i netermičke efekte[6]. Prodor UZ u tkiva izaziva lokalno stvaranje toplote. Apsorpcija i penetracija ultrazvuka uslovljene su u velikoj meri, sadržajem proteina u tkivu (Figura 1). Tkiva sa nižim sadržajem vode i većim sadržajem proteina pokazaće veću apsorpciju ultrazvuka. Poznato je da tkiva sa visokim sadržajem kolagena, kao što su ligamenti, fascije i kapsularni deo zglobova, pokazuju maksimalnu apsorpciju UZ talasa[7,8]. Ultrazvučni talasi izazivaju vibracije makromolekula u tkivu, što dovodi do zagrevanja tkiva. Ova toplotna energija će dovesti do lokalne vazodilatacije, što nadalje dovodi do povećanog ćelijskog metabolizma. Da bi se postigao značajan termički efekat, temperatura tkiva mora se podići na 40 °C do 45 °C u trajanju od minimalno pet minuta. Ovo termičko svojstvo može dovesti do ublažavanja bolova i smanjenja ukočenosti zglobova[9].

Netermički efekti ultrazvuka zasnovani su na principima kavitacije i akustičnog strujanja. Ultrazvučni talasi vrše određenu silu na gasove mikrookoline prisutne u tkivnim tečnostima. Ova sila dovodi do razređivanja i kompresije gasa, što rezultira stvaranjem mikroskopskih gasnih mehurića u tkivnoj tečnosti. Ovo svojstvo naziva se kavitacija. Mehurići gasa mogu biti podvrgnuti brzim promenama pritiska zbog nestabilne kavitacije i mogu izazvati oštećenje ćelija; stoga je potreban oprez kada je ultrazvučna terapija fokusirana na regione u blizini šupljina ispunjenih vazduhom[10].

Sposobnost fizičkih sila koje vrše ultrazvučni talasi kako bi izazvali pomeranje jona i malih molekula naziva se akustičnim strujanjem.

treatment of Meniere's disease for the destruction of the vestibular nerve, the use of focused ultrasound in the management of Parkinson's disease by localized tissue destruction in the brain. Later in 1970, therapeutic ultrasound gained popularity in the field of physiotherapy. Recently, therapeutic ultrasoundis being used in neurosurgery and oncology as well. Apart from the management of musculoskeletal pain, other general therapeutic applications of ultrasound in medicine include fracture healing, osseointegration, healing of skin and soft tissue injuries, cancer therapy and urological applications[5,6].

Mechanism and Biophysical effects of Therapeutic Ultrasound

When ultrasound is focused on a particular site of the body, the US waves penetrate the tissues and produce biophysical effects. The biophysical effects of ultrasound can be broadly classified into thermal and nonthermal effects[6]. The penetration of US into the tissues causes local heat generation. The absorption and penetration of ultrasound differs widely based on the protein content of the tissue (Figure 1). Tissues with a lower water content and a higher protein content will show higher absorption of ultrasound.Tissues with high collagen content such as ligaments, fascia and capsular part of the joints are known to exhibit maximum absorption[7,8].The ultrasound waves cause vibration of macromolecules in the tissue resulting in the heating of the tissues. This thermal energy induces local vasodilation, resulting in increased cellular metabolism. To achieve a significant thermal effect the temperature of the tissue has to be raised upto 40−45°C for a minimum duration of 5 minutes. This thermal property can provide pain relief and decrease in joint stiffness[9].

The non-thermal effects of ultrasound are based on the principles of cavitation and acoustic streaming. The ultrasound waves exert certain force on the microenvironmental gases present within the tissue fluids. This force results in rare faction and compression of gas resulting in formation of microscopic gas bubbles in the tissue fluid. This property is termed as cavitation. The gas bubbles can undergo rapid pressure changes due to unstable cavitation and may cause cell injury. Therefore, caution needs to be exercised when ultrasound therapy is focused in regions near air-filled cavities[10].

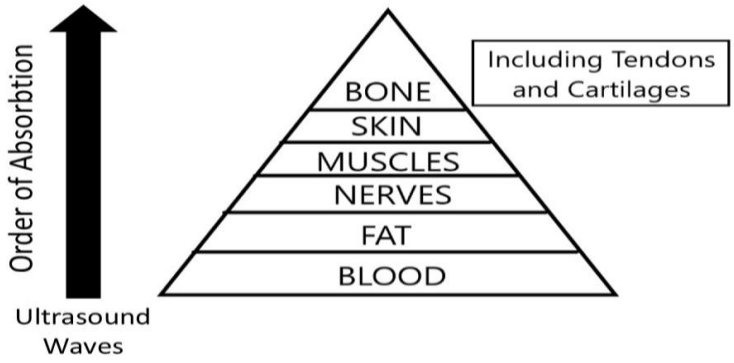

Figura 1. Redosled ultrazvučne apsorpcije
***Figure 1*:** Order of ultrasonic absorption

Mehanički pritisak koji vrši akustična struja dovodi do jednosmernog kretanja tečnosti oko ćelijskih membrana i može promeniti permeabilnost ćelije. Ovo svojstvo akustičnog strujanja ultrazvuka ima različite biomedicinske primene[10,11].

Toplotni efekti ultrazvuka mogu dovesti do modifikacije svojstava kolagena povećavajući rastegljivost, odnosno dovode do mobilizacije zglobova i istezanja[12]. Neto rezultat ultrazvuka na ćelijskom nivou uključuje povećanje sinteze proteina, degranulaciju mastocita, proizvodnju faktora rasta, unos kalcijuma, promene u jonskim kanalima i pokretljivost fibro-blasta. Poznato je da ove ćelijske promene imaju analgetički efekat, kao i da podstiču popravku tkiva uzrokovanu upalom[6].

Tehnički parametri

Terapeutski ultrazvuk je modalitet čiji odgovor zavisi od doze[13]. Tehnički parametri ultrazvučne opreme mogu se definisati kao tehnička podešavanja za određeni cilj lečenja i uključuju intenzitet, učestalost, radni ciklus i vreme tretmana. Svi ovi parametri imaju direktan uticaj na ishod lečenja[14]. Terapeutski ultrazvuk se na osnovu frekvencije može klasifikovati na ultrazvuk velike i ultrazvuk male snage. Primene ultrazvuka velike snage uključuju fokusirani ultrazvuk visokog intenziteta (VIFU) za hirurške ablacije i litotripsiju, dok ultrazvuk male snage uključuje terapiju bola i zarastanje, sonoforezu i sonoporaciju[4,15].

Sredstvo za spajanje potrebno je da prenese UZ talase iz sonde u tkivo, pošto vazduh prisutan između njih reflektuje UZ talase.

The ability of the physical forces exerted by the ultrasound waves to cause displacement of ions and small molecules is termed acoustic streaming. The mechanical pressure exerted by the acoustic streaming results in unidirectional movement of fluid around cell membranes and may alter cell permeability. This property of acoustic streaming of ultrasound has various biomedical applications[10,11].

The thermal effects of ultrasound can lead to modifications of the collagen properties that increase extensibility, thus promoting joint mobilization and stretching[12].The net result of ultrasound at the cellularlevel includes increase in protein synthesis, mast cell degranulation, growth factor production, uptake of calcium, alterations in the ion channels and fibro-blast mobility. These cellular changes are known to have analgesic effect and also to promote the tissue repair caused due to inflammation[6].

Technical Parameters

Therapeutic ultrasound is a modality that produces dose based response[13]. The technical parameters of the ultrasound equipment can be defined as the technical settings for a specific treatment goal and include, intensity, frequency, duty cycle, treatment time. All these parameters have a direct effect on the treatment outcome[14]. Therapeutic ultrasound can be broadly classified as high power and low power ultrasound based on the frequency. Applications of high power US include high intensity focused US (HIFU) for surgical ablations and lithotripsy, while low power US includes pain therapy and healing, sonophoresis and sonoporation[4,15].

A coupling agent is required to transmit the US waves from the transducer into the tissue, as air present between them reflects the US waves.

Ova sredstva za spajanje treba da imaju nizak koeficijent apsorpcije, a njihova akustična impedansa treba da bude slična tretiranom tkivu ili viša od njega. Najviše korišćena sredstva za spajanje u tehnici direktnog kontakta jesu gelovi, mineralna ulja i beli vazelin, dok se u tehnici potapanja koristi voda[16]. Frekvencija je jedan od najvažnijih tehničkih parametara i bira se na osnovu dubine tkiva koje se tretira. Penetracija ultrazvuka u različite dubine može se opisati u smislu dubine poluvrednosti. Dubina poluvrednosti može se definisati kao dubina ili udaljenost u tkivu na kojoj se 50% ultrazvučne energije raspršuje. Prema podacima iz literature, približna dubina poluvrednosti od 1 MHz je oko 2,3 cm, dok je kod kontinuiranog ultrazvuka od 3 MHz oko 0,8 cm. Dakle, 3MHz koriste se za površinska tkiva do dubine od 2 cm, a 1 MHz koristi se za dublja tkiva do dubine od 5 cm[17-19]. Postoje dva režima rada terapeutskog ultrazvuka – kontinuirani i pulsni režim. Kontinualni režim emituje tok ultrazvučnih talasa kao kontinuirani, dok pulsni režim emituje UZ talase u redovnim intervalima u zavisnosti od radnog ciklusa. U tipičnom odnosu impulsa 1 : 1, mašina nudi izlaz za 2 ms, nakon čega slede 2 ms odmora. Impulsna UZ terapija preporučuje se za akutni bol, a kontinuirana UZ za hronični bol. Slično, niski intenziteti koriste se za akutni bol, a veći intenzitet za terapiju hroničnog bola[9]. Prema Ilteru i sar.[20], kontinuirana UZ terapija je efikasnija u smanjenju bola od pulsne UZ terapije kod pacijenata sa miofascijalnim bolom. Slično, niski intenziteti koriste se za akutni bol, a veći intenzitet za terapiju hroničnog bola[9]. Prema Ilteru i sar.[20], kontinuirana UZ terapija je efikasnija u smanjenju bola od pulsne UZ terapije kod pacijenata sa miofascijalnim bolom.

Obični terapijski ultrazvuk

Terapijski ultrazvuk koristi se kod poremećaja temporomandibularnog zgloba za ublažavanje muskuloskeletnog bola, za smanjenje upale i za obnavljanje funkcije zgloba. Terapijski UZ primenjuje se pomoću sonde pogodne veličine, koja se plasira na ciljnu regiju u sporim kružnim pokretima. Grej i sar.[21] sproveli su studiju kako bi uporedili efekte kratkotalasne dijatermije, ultrazvuka niskog intenziteta i laserske terapije niskog nivoa (LLNT) kod pacijenata sa disfunkcijom TMZ-a.

These coupling agents should have as a low-absorption coefficient and their acoustic impedance should be similar or higher than the treated tissue. The most-used coupling agents in the direct-contact technique are gels, mineral oils, and white petrolatum jelly, while water is used in the immersion technique[16]. Frequency is one of the most important technical parameters and it is selected based on the depth of the tissue to be treated. The penetration of ultrasound to varied depth can be described in terms of the half-value depth.

The half-value depth can be defined as the depth or distance in the tissue at which 50% of the ultrasound energy gets dissipated. According to the literature evidences, the approximate half-value depth of 1MHz is about 2.3 cm and 3-MHz continuous ultrasound is about 0.8 cm. Hence, 3MHz is used for superficial tissues up to 2 cm deep and 1MHz is used for deeper tissues up to 5 cm deep[17-19]. There are two operating modes of therapeutic ultrasound such as continuous and pulsed mode. The continuous mode emits as continuous stream of ultrasound waves while the pulsed mode emits US waves at regular intervals depending on the duty cycle. In a typical 1:1 pulse ratio, the machine offers an output for 2 ms followed by 2 ms rest. Pulsed US therapy is recommended for acute pain and continuous US is recommended for chronic pain. Similarly, low intensities are used for acute pain and higher intensities are used for chronic pain[9]. According to Ilter et al[20] continuous US therapy is more effective in reducing pain than pulsed US therapy, in patients with myofascial pain.

Plain Therapeutic Ultrasound

Therapeutic ultrasound is used in temporomandibular join disorders to relieve musculoskeletal pain, to reduce inflammation, and to restore the joint function. Therapeutic US is applied by a transducer of convenient size based on the target area in slow circular motions. Gray et al[21] conducted a study to compare the effects of short-wave diathermy, low intensity ultrasound and low level laser therapy (LLLT) in patients with TMJ dysfunction.

They found no significant difference in comparative efficacy among the four modalities, but all the four modalities were equally effective in improving the clinical signs and symptoms.

Nisu našli značajnu razliku u komparativnoj efikasnosti između četiri modaliteta, ali su sva četiri modaliteta bila podjednako efikasna u poboljšanju kliničkih znakova i simptoma.

Rai S i sar.[22] sproveli su komparativnu studiju kako bi utvrdili efikasnost terapijskog ultrazvuka i TENS-a u lečenju miofascijalnog bola kod pacijenata koji imaju TMP i otkrili su da je terapijski ultrazvuk efikasniji u smanjenju skora vizuelne analogne skale (VAS) mišićnog bola, smetnjama u svakodnevnom životu i utiska masaže. Slično tome, Kirupa i sar.[23] otkrili su da je ultrazvučna terapija kod TMP-a efikasnija u smanjenju bola od TENS-a. Elgohari i sar.[24] upoređivali su efekte ultrazvuka niskog intenziteta, tradicionalne terapije vežbanjem, kombinacije LLLT i TET na bol i trizmus TMZ-a kod pacijenata koji se oporavljaju od karcinoma glave i vrata (KGV); otkrili su da su ultrazvuk i tradicionalna terapija vežbanjem efikasniji u smanjenju bolova u TMZ-u i trizmusu nakon HKGV-a. Studija Handa R i sar.[25] pokazala je da UZ masažna terapija služi kao moćan i nezavisan terapeutski modalitet kod TMP-a. Parametri koji se tiču tretmana, broja tretmana i intervala između svake sesije uveliko se razlikuju od studije do studije. Parametri tretmana za lečenje TMP-a korišćeni u studijama koje su uključene u ovaj pregledni rad prikazuju se u Tabeli 1.

Fonoforeza

Fonoforeza predstavlja upotrebu terapijskog ultrazvuka za uvođenje farmakoloških agenasa kroz netaknutu kožu u potkožno tkivo. Obično se koriste antiinflamatorni ili analgetski lekovi[26]. Fonoforeza može povećati apsorpciju kože i prodiranje lokalnih lekova u dublja tkiva. Terapeutski efekti lokalno primenjenih lekova zavise od različitih faktora, kao što su brzina, količina, penetracija leka i dubina kože[27]. Vijaialakshmi i sar.[28] sproveli su kliničko ispitivanje kako bi procenili efikasnost fonoforeze aceklofenak gela u lečenju TMP-a. Njihovi rezultati pokazali su značajno povećanje srednjeg maksimalnog otvaranja usta, lateralne ekskurzije i smanjenje skorova VAS-a, Helkimo anamnestičkog indeksa i indeksa kliničke disfunkcije u grupi fonoforeze aceklofenaka u poređenju sa lokalnom primenom ovog leka. Prema Fernandez-Cuadrosu i sar.[28], fonoforeza diklofenaka može delovati kao efikasna fizikalna terapija za lečenje TMP-a.

Rai S. et al.[22] conducted a comparative study to determine the efficacy of therapeutic Ultrasound and TENS in the management of myofascial pain in TMD patients. They found therapeutic ultrasound to be more effective in reducing the Visual analogue scale (VAS) score of muscle pain, impediment to daily life, and massage impression. Similarly, Kirupa et al[23] also found ultrasound therapy to be more efficient in reducing pain in TMD than TENS. Elgohary et al[24] compared the effects of low intensity ultrasound, traditional exercise therapy, combination of LLLT and TET on TMJ pain and trismus in patients recovering from head and neck cancer (HNC). They found ultrasound and traditional exercise therapy to be more effective reducing TMJ pain and trismus following HNC. Handa R. et al.[25] study stated that US massage therapy serves as a potent and independent therapeutic modality in TMDs. The treatment parameters, number of treatment sessions and the interval between each session differs widely among various studies. Treatment parameters used in the studies included in the present review for the management of TMD sare summarized in Table 1.

Phonophoresis

Use of therapeutic ultrasound to introduce pharmacologic agents through intact skin into the subcutaneous tissues is phonophoresis. Usually anti-inflammatory or analgesic drugs are used[26]. Phonophoresis can increase the skin absorption and penetration of the topical medications to the deeper tissues. Therapeutic effects of topically applied drugs depend on various factors such as rate, amount, drug penetration, depth of the skin[27]. Vijayalakshmi et al[28] conducted a clinical trial to assess the effectiveness of aceclofenac gel phonophoresis in the management of TMD. Their results showed significant increase in mean maximum mouth opening, lateral excursion and a reduction in scores of VAS, Helkimo anamnestic, and clinical dysfunction index in aceclofenac phonophoresis group as compared to the topical application of acelcofenac. According to Fernandez-Cuadros. et al.[28] diclofenac phonophoresis can acts as an effective physical therapy for the management of TMD. Ramakrishnan. et al.[30] conducted a study to compare the efficacy of aceclofenac phonophoresis and plain ultrasound therapy in patients with TMD.

Ramakrishnan i sar.[30] sproveli su studiju u cilju poređenja efikasnosti fonoforeze aceklofenaka i obične ultrazvučne terapije kod pacijenata sa TMP-om. Otkrili su da je fonoforeza aceklofenaka unekoliko bolja od terapije običnim ultrazvukom.

Poznato je da je fonoforeza sa kortikosteroidima, kao što je lokalno aplikovani hidrokortizon, efikasna u lečenju bola u TMZ-u[31]. Koncentracija i vrsta leka koji se koristi (Tabela 2), kao i trajanje fonoforeze, variraju u zavisnosti od kliničkih zahteva.

They found aceclofenac phonophores is to be slightly superior than Plain ultrasound therapy. Phonophoresis with corticosteroids such as topical hydrocortisone is also known to be effective in management of TMJ pain[31]. The concentration and type of the drug to be used (Table 2) and duration of phonophoresis vary depending on the clinical requirement.

Tabela 1. Terapijski parametri za običnu ultrazvučnu terapiju
Table 1. Treatment parameters for plain ultrasound therapy

Parametri Parameters		**Rai S i sar.[22] (2016) Rai S. et al.[22](**	**Kirupa i sar.[23] (2018) Kirupa et al.[23]**	**Elgohary i sar.[24] (2018) Elgohary et al.[24]**	**Handa i sar.[25] (2018) Handa et al.[25]**
Veličina uzorka (Muškarci i žene) Sample size (males andfemales)		90 (25 muškaraca i 65 žena) (25 males,65 female)	30	60 (33 muškarca i 27 žena) (25 males,65 female)	10 (tri muškarca i sedam žena) (3 males,7 females)
Starost populacije iz studije Age group of study population		20 – 60 godina / years	20 – 40 godina / years	/	18–50 godina years
Režim Mode		/	Kontinuirano/continuous	pulsno pulsed	pulsno (1 : 1) pulsed
Frekvencija Frequency		/	1 i 3 MHz	1 MHz	1 MHz
Doza Dose		/	/	1,0 W/cm^2	/
Trajanje terapije Treatment duration		/	pet minuta 5 minutes	pet minuta 5 minutes	osam minuta 8 minutes
Terapijske sesije Treatment sessions		tri puta svake dve nedelje tokom 12 nedelja / 3 times every 2 weeks for 12 weeks	/	pet puta nedeljno tokom četiri nedelje 5 times/week for 4 weeks	jednom nedeljno tokom četiri nedelje once in a week for 4 weeks
Parametri korišćeni za pristup Parameter used to access		maksimalno otvaranje usta bez bola; subjektivna procena bolova u mišićima pomoću VAS-a; subjektivna procena smetnji u svakodnevnom životu na osnovu VAS-a i otiska masaže maximum mouth opening without pain, subjective evaluation of muscle pain using VAS, subjective evaluation regarding impediment to daily life based on VAS and massage impression	procena bola pomoću VAS-apain assessment by VAS	merenje maksimalnog otvaranja usta, merenje intenziteta bola pomoću VAS-ameasurement of maximum mouth opening, measurement of pain intensity by VAS	procena otvaranja usta i procena bola na osnovu VAS-a assessment of mouth opening and pain assessment based on VAS
VAS rezultati običnom ultrazvučnom terapijom Results of VAS by Plain Ultrasound therapy	**Pre tretmana Pre-treatment**	247,87 ± 26,53	7,32 ± 1,16	7,75 ± 1,41	7,30 ± 1,70
	Posle tretmana Post-treatment	20,87 ± 6,35	3,73 ± 3,96	2,65 ± 1,50*	4,00 ± 2,53

*Kombinacija ultrazvučne terapije niskog intenziteta sa tradicionalnom terapijom vežbanjem.
* Combination of low intensity ultrasound therapy along with traditional exercise therapy

Tabela 2. Terapijski parametri za fonoforezu
Table 2. Treatment parameters for phonophoresis

Parametar Parameter		**Vijayalakshmi i sar.** [28] **(2015) Vijayalakshmi et al.**[28]	**Ramakrishnan i sar.** [30] **(2019) Ramakrishnan et al.**[30]	**Fernandez-Cuadros i sar.** [29] **(2020) Fernandez-Cuadros et al.**[29]**]**	**Sequeira i sar.** [31] **(2020) Sequeira et al.**[31]
Veličina uzorka (Muškarci & Žene) Sample size (males andfemales		60 (23 muškarca i 37 žena) males, females	50	50 (devet muškaraca i 41 žena) (males, females)	20 (jedan muškarac i 19 žena) (males, females)
Starosna grupa Age group		70–80 godina years	/	/	20–50 godina years
Režim Mode		kontinuirano continuous	kontinuirano continuous	kontinuirano continuous	Pulsno pulsed
Frekvencija Frequency		1 MHz	1 MHz	1 MHz	3 MHz
Doza Dose		0.8 W/cm^2 – 1.5 W/cm^2	1.5 W/cm^2	1 W/cm^2	1,5 W/cm^2 – 2,0 W/cm^2
Trajanje terapije Treatment duration		deset minuta minutes	osam minuta minutes	pet minuta minutes	od sedam do deset minuta minutes
Terapijske sesije Treatment sessions		tri puta nedeljno tokom dve nedelje3 times/week for 2 week	tri puta nedeljno tokom dve nedelje3 times/week for 2 weeks	jedna sesija na dan 20 uzastopnih dana1 session/day for 20 consecutive days	sedam dana uzastopno7 consecutive days
Parametri korišćeni za pristup Parameter used to access		procena bola pomoću VAS-a, procena pokreta mandibule, maksimalno aktivno otvaranje usta (AMO), maksimalno pasivno otvaranje usta (PMO), bočni ekskurzivni i protruzivni pokreti vilice (RLE i LLE), procena Helkimo indeksa, procena brzine sedimentacije eritrocita (ESR) pain assessment by VAS, assessment of mandibular movements, maximum active mouth opening(AMO), maximum passive mouth opening(PMO), lateral excursive and protrusive jaw movement(RLE and LLE), Helkimo index assessment, assessment of erythrocyte sedimentation rate(ESR)	nivo VAS-a i C-reaktivnog proteina VAS and C-reactive protein level	otvaranje usta, rastojanje od usana do usana i međuincizivno rastojanjemouth opening, lip to lip distance andinter incisal distance	maksimalno otvaranje usta i intenzitet bola maximum mouth opening andpain intensity
VAS Rezultati fonoforezom Results of VAS by Phonophoresis	**Pre terapije Pre-treatment**	7.57 ± 1.04	6.40	6.67 ± 0.82	9 ± 1.05
	Posle terapije Post-treatment	3.10 ± 2.77	2.12	3.48 ± 0.75	0

Pulsni ultrazvuk niskog intenziteta (PUNI)

PUNI je novi napredak u oblasti terapije zasnovane na ultrazvuku. Ima potencijal da se koristi u lečenju različitih nervnih, skeletnih i mišićnih bolesti. PUNI se odnosi na pulsni UZ sa intenzitetom manjim od 100 mV/cm² za ciljanje obolelog područja[32]. PUNI olakšava prenos relativno male količine energije do ciljnog tkiva, čime se sprečava termičko oštećenje izazvano prekomernim stvaranjem toplote tretiranog područja[33]. Poslednjih godina, PUNI je istraživan kao modalitet lečenja osteoartritisa (OA) TMZ-a zbog svog potencijala za regeneraciju tkiva[34]. Mehaničko preopterećenje kondilarne hrskavice donje vilice izaziva ekspresiju IL-1b, inflamatornog citokina, koji je blisko povezan sa progresijom TMJ-OA[35]. *In vitro* studije Uddina i sar.[36] pokazale su da PUNI može sprečiti destrukciju hrskavice inhibiranjem kataboličkog dejstva IL-1b, a takođe je poznato da stimuliše migraciju, proliferaciju i diferencijaciju hondrocita. Liang i sar.[37] demonstrirali su upotrebu PUNI na pacovima i dokazali da može efikasno inhibirati povredu kondilarne hrskavice izazvane hroničnom deprivacijom sna. Dakle, PUNI može poslužiti kao efikasan neinvazivni modalitet lečenja u lečenju TMZ OA.

Prednosti i mane UZ

Praksa primene ultrazvučne terapije kod poremećaja temporomandibularnog zgloba ima različite prednosti, koje se ogledaju u ekonomičnosti, lakoći tehnike, neinvazivnoj prirodi procedure i sposobnosti da se obezbedi značajno ublažavanje bola[3,4,11]. Ultrazvučna fonoforeza ima dodatnu prednost u smanjenju rizika od oštećenja jetre i bubrega usled eliminacije leka, jer eliminiše potrebu za sistemskim lekovima; takođe, pacijenti je dobro podnose[30]. Rašid i dr. sproveli su nacionalnu anketu među konsultantima za oralnu i maksilofacijalnu hirurgiju Ujedinjenog Kraljevstva (UK); u njoj je 52% konsultanata izjavilo da je ultrazvuk efikasan elektrofizički modalitet u lečenju TMD-a[38]. Jedan od glavnih nedostataka ultrazvučne terapije proističe iz činjenice da zahteva više poseta.

Low-intensity pulsed ultrasound (LIPUS)

LIPUS is an emerging advancement in the field of ultrasound based therapeutics. It has the potential to be used in management of various nerve, skeletal and muscular diseases. LIPUS refers to pulsed US with an intensity less than 100 mW/cm^2 to target the affected area[32]. LIPUS facilitates transmission of a comparatively lesser amount of energy to the target tissue, thereby preventing thermal damage caused by excessive heat generation at the treatment site[33]. In the recent years including LIPUS including has been explored as a treatment modality for osteoarthritis (OA)of TMJ because of its potential for tissue regeneration[34]. Mechanical overloading of the mandibular condylar cartilage induces the expression of IL-1b, an inflammatory cytokine related closely to the progression of TMJ-OA[35]. In vitro studies by Uddin et al[36] demonstrated that LIPUS can prevent cartilage destruction by inhibiting the catabolic action of IL-1b and they are also known to stimulate migration, proliferation, and differentiation of chondrocytes. Liang et al[37] demonstrated LIPUS in rats and proved that LIPUS can effectively inhibit Chronic sleep deprivation induced injury to condylar cartilage. Thus, LIPUS can serve as an effective non-invasive treatment modality in the management of TMJ OA.

Advantages and Disadvantages of US

The practice of ultrasound therapy for temporomandibular joint disorders has various advantages including cost efficiency, ease of the technique, non-invasive nature of the procedure and active ability to provide significant pain relief[3,4,11]. Ultrasound phonophoresis has an added advantage of minimizing the risk of hepatic and renal injury by drug elimination as it eliminates the need for systemic drugs and it is also well tolerated by the patients[30]. Rashid et al. conducted a national survey among oral and maxillofacial surgery consultants of United Kingdom (UK) in which 52% of consultants reported ultrasound as an effective electro-physical modality in TMD management[38]. One of the major disadvantages of ultrasound therapy is that it requires multiple visits.

Bezbednosna razmatranja

Terapeutski ultrazvuk kao modalitet fizikalne terapije za poremećaje TMZ-a obično ima nizak rizik od povrede pacijenta onda kada ga koristi kvalifikovano osoblje. Ne preporučuje se ultrazvučna terapija aplikovana na mesto infektivne regije[15]. Postoji dovoljno dokaza u literaturi da su metalni implantati za ultrazvučnu terapiju bezbedni i da ne izazivaju pojačano zagrevanje[39]. Upotreba neodgovarajuće visoke frekvencije i intenziteta može izazvati prekomerno zagrevanje ciljnog tkiva, kao i susednih zdravih tkiva. Upotreba fonoforeze za isporuku lekova kroz kožu može uticati na poroznost kože i izazvati neke histološke promene na koži nakon izlaganja ultrazvuku, ali se koža vraća u normalu kada izlaganje ultrazvuku prestane[3]. Određeni lokalni lekovi koji se koriste za fonoforezu mogu izazvati alergijske reakcije na koži, pa se uvek preporučuje patch test pre početka terapije[30]. Efikasna dezinfekcija sonde neophodna je za sprečavanje bolničkih infekcija. Transduktore treba očistiti nakon upotrebe kvaternarnim amonijumom (sredstvo za dezinfekciju niskog nivoa), sprejevima ili maramicama. Transduktori moraju biti isključeni sa ultrazvučnog skenera.

Održavanje i kontrola infekcija

Oprema za ultrazvučnu terapiju je tehnički složena i zahteva redovnu proveru kvaliteta radi bezbednog rada i provere odgovarajućih ultrazvučnih polja[15]. Upotreba sterilnih sredstava za spajanje i efikasna dezinfekcija sonde od suštinskog su značaja za sprečavanje bolničkih infekcija. Prema Centru za kontrolu i prevenciju bolesti (CKB), terapijski ultrazvuk, koji se koristi za fizikalne terapije, jeste uređaj koji ne dolazi u direktan kontakt sa mukoznim površinama ili neoštećenom kožom. Ovi uređaji zahtevaju nizak nivo dezinfekcije. Sonde se moraju odvojiti od opreme i treba ih očistiti dezinfekcionim sredstvom niskog nivoa nakon svake upotrebe. Prema CKB-u, za efikasnu kontrolu infekcije preporučuje se dezinfekcija niskog nivoa korišćenjem agenasa kao što su 70% do 90% etil alkohola, fenolni germicidni deterdženti, 5,25% do 6,15% natrijum-hipohlorit ili kvaternarni amonijum germicidni rastvor, za vreme izlaganja duže od jednog minuta[40,41].

Safety considerations

Therapeutic ultrasound as a modality of physical therapy for TMJ disorders usually possess a low risk of harm to the patient, when operated by a skilled operator. Ultrasound therapy over an infectious site and open wound is not recommended[15]. There are sufficient literature evidences that claim that ultrasound therapy metal implants are safe and they do not cause increased heating[39]. Use of inappropriate high frequency and intensity may cause excessive heating of the target tissue as well the adjacent normal tissues. Use of phonophoresis for delivery of drugs through the skin can affect the porosity of the skin and can produce some histological changes in skin following ultrasound exposure, but the skin reverts to normal once exposure to ultrasound has stopped[3]. Certain topical drugs used for phonophoresis can cause allergic skin reactions, hence a patch test is always recommended before the start of the therapy[30]. Effective disinfection of the transducer is essential to prevent nosocomial infections. Transducers should be cleaned after use with quaternary ammonium (a low-level disinfectant) sprays or wipes. The transducers must be disconnected from the ultrasound scanner for anything more than wiping or spray cleaning.

Maintenance and Infection control

The ultrasound therapy equipment is technically complex and require quality check on a regular basis for safe operation and verification of appropriate ultrasound fields[15]. Use of sterile coupling agents and effective disinfection of the transducer is essential to prevent nosocomial infections.

According to the Center for Disease Control and Prevention (CDC), therapeutic ultrasound used inphysical therapy is a noncritical device that does not directly contact the mucosal surfaces or non-intact skin. These devices require low-level disinfection. The transducers must be disconnected from the equipment and should be cleaned with a low-level disinfectant after each use. According to CDC, low-level disinfection using agents such as 70–90% ethyl alcohol, phenolic germicidal detergents, 5.25–6.15% of sodium hypochlorite or quaternary ammonium germicidal solution for an exposure time greater than one minute is recommended for effective infection control[40,41].

Zaključak

Terapijski ultrazvuk je dobro poznat elektrofizički modalitet u lečenju poremećaja temporomandibularnog zgloba. Iako je ovaj modalitet široko prihvaćen među kliničarima, fizioterapeutima i pacijentima, nedostaju standardizacija, ultrazvučna dozimetrija i trajanje lečenja. Uz aktivno istraživanje i razvoj, u bliskoj budućnosti mogu se razviti različiti novi terapijski modaliteti zasnovani na ultrazvuku.

Zahvalnica: Nema

Sukob interesa: Nema

Conclusion

Therapeutic ultrasound is a well-known electrophysical modality in the management of temporomandibular joint disorders. Though the modality is a widely accepted among the clinicians, physical therapists and patients, there is a lack of standardization, ultrasound dosimetry, and treatment duration. With active research and development various new ultrasound based therapeutic modalities can evolve in the near future.

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BENIGNI MEŠOVITI TUMOR MALE PLJUVAČNE ŽLEZDE

BENIGN MIXED TUMOUR OF THE MINOR SALIVARY GLAND

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Sažetak

Uvod: *Najčešća velika neoplazma pljuvačne žlezde je pleomorfni adenom. Samo 10% pleomorfnih adenoma javlja se u malim pljuvačnim žlezdama. U 42,8% do 68,8% slučajeva nepce predstavlja intraoralnu lokalizaciju ovog tumora. Ovde je predstavljen redak slučaj pleomorfnog adenoma koji je ličio na leziju odontogenog porekla.*
Prikaz slučaja *je pacijent koji se javlja sa glavnim tegobama u vidu otoka u predelu gornjeg levog molara koji je trajao 3 meseca pre javljanja lekaru. Na ortopan snimku bila je dijagnostikovana promena mekog tkiva u levoj zadnjoj maksilarnoj regiji sa destrukcijom i resorpcijom alveolarnog nastavka. Razmatrana je radiografska diferencijalna dijagnoza benignih odontogenih/neodontogenih cista ili tumora, benignih malih tumora pljuvačne žlezde.Urađena je eksciziona biopsija i lezija je uklonjena u potpunosti do periosta poslata na histopatološki pregled, koji je potvrdio dijagnozu pleomorfnog adenoma.*
Zaključak: *Pleomorfni adenom je benigna neoplazma koja ima odličnu prognozu sa stopom izlečenja većom od 95%. Međutim, periodično dugotrajno praćenje je obavezno.*

Ključne reči: *Pleomorfni adenom, tumor pljuvačne žlezde*

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Abstract

Introduction: *The most common major salivary gland neoplasm is the Pleomorphic adenoma. Only 10% of the pleomorphic adenoma occur in minor salivary glands. 42.8% to 68.8% of cases with intraoral lesion occurs in the palate. Here we present a rare case of a pleomorphic adenoma masquerading as a lesion of odontogenic origin.*
Case report *presents a male patient who reported with a chief complaint of swelling in the upper left tooth region since 3 months. Panoramic radiograph revealed shadow of a soft tissue swelling in the left maxillary posterior region with destruction and resorption of the alveolar process. Radiographic differential diagnosis of benign odontogenic/non-odontogenic cysts or tumours, benign minor salivary gland tumours were considered. Excisional biopsy was carried out and the lesion was removed in total up to the periosteum and the overlying mucosa and sent for histopathologic examination, which suggested pleomorphic adenoma.*
Conclusion: *Pleomorphic adenoma is a benign neoplasm which has excellent prognosis with a cure rate of more than 95%. However, periodic long term follow up is mandatory.*

Key words: *pleomorphic adenoma, salivary gland tumour*

Uvod

Pleomorfni adenom je benigna neoplazma, koja je u većini slučajeva tipično neprimetna, sporastuća masa čvrste konzistencije. Malo je češća njegova pojava kod osoba ženskog pola. U većini slučajeva javlja se u velikim pljuvačnim žlezdama; međutim, nepce je takođe uobičajeno mesto za pojavu manjih pleomorfnih adenoma pljuvačnih žlezda[1].

Prikaz slučaja

Na Odeljenje oralne medicine i radiologije javio se pacijent sa glavnom tegobom u vidu otoka u predelu gornjeg levog poslednjeg zuba, prisutnog u poslednja tri meseca. Anamneza je otkrila da je pacijent uočio veoma mali otok u tom predelu pre tri meseca, koji je postepeno narastao do sadašnje veličine. Dva meseca pre toga, odnosno pre pet meseci, posetio je stomatologa radi vađenja gornjeg levog zadnjeg zuba. Nepuna dva meseca nakon ekstrakcije, pacijent je počeo da primećuje mali otok u pomenutoj regiji. Ovaj sporastući otok bio je praćen tupim bolom, bez većih promena u intenzitetu i nije zračio u susedne regije. Dve nedelje po pojavi otoka, pacijent je primetio mali čir na levoj strani promene. On je povezivao čir sa oštrim kvržicama donjih zuba, koje su gotovo uvek imale kontakt sa nastalim otokom u toku mastikacije. Pacijent nije primetio iscedak ili krvarenja iz otoka. Inače, pacijent je od ranije poznat klinici, jer boluje od dijabetesa melitusa tipa 2, koji je kontrolisao antidijabetičnom terapijom poslednjih pet godina.

Kliničkim pregledom evidentiran je usamljeni otok kupastog oblika leve strane maksile u distalnioj regiji, dimenzija približno 2 cm x 2 cm. Lezija se protezala anteriorno od zadnjeg kraja tubera maksile, zahvatajući meko nepce , medijalno nekoliko milimetara udaljeno od srednje linije , bočno zahvatajući bukalni vestibulum i posteriorno 2 cm udaljeno od tubera. Bočna strana otoka pokazala je prisustvo solitarnog tumefakta bez drenaže ili krvarenja. Prilikom palpacije, otok je bio čvrste konzistencije i neosetljiv (Slika 1). Razmatrana je diferencijalna dijagnoza rezidualne ciste u levoj zadnjoj maksilarnoj regiji, pošto je pacijent ukazao na istoriju ekstrakcije zuba iz tog predela.

Introduction

Pleomorphic adenoma is a benign neoplasm which is typically a non tender, slow growing mass and firm in consistency in majority of the cases. It has a slight female predilection. Although majority of the cases are associated with major salivary glands, palate is the common site for minor salivary gland pleomorphic adenomas[1].

Case Report

A patient presented to the Department of Oral Medicine and Radiology with a chief complaint of swelling in the upper left back tooth region lasting 3 months. History revealed that the patient had visited a dentist for extraction of the upper left back tooth 5 months previously. Two months after the extraction, the patient noticed a very small swelling in that region which gradually during 3 months grew to the present size. This slow-growing swelling was associated with a dull, aching kind of pain which was intermittent and was non-radiating, with no aggravating and relieving factors associated with the pain. Two weeks prior to presenting to the Department of Oral Medicine and Radiology, the patient noticed a small ulcer in the left side of the swelling. He associated the ulcer with the sharp cusp of the lower teeth which would always come in contact with the swelling while chewing. There was no history of discharge or bleeding from the swelling. The patient was a known case of Type 2 Diabetes Mellitus with 5 years of medication use.

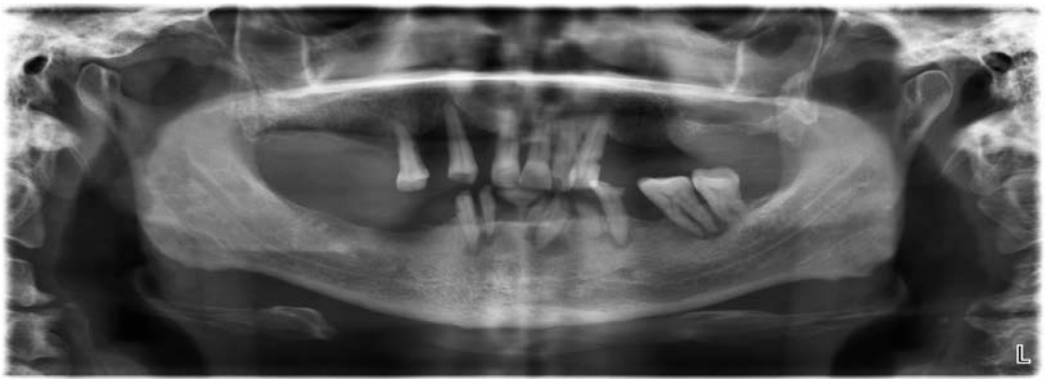
On clinical examination, a solitary dome-shaped swelling was evident in the left posterior maxillary region beyond the left maxillary tuberosity measuring ap-proximately 2 cm x 2 cm. The lesion extended anteriorly from the posterior end of the left maxillary tuberosity involving the soft palate, medially a few millimetres away from the midline, laterally involving the buccal vestibule and posteriorly 2 cm away from the tuberosity. The lateral side of the swelling showed the presence of solitary ulcer with no discharge or bleeding.The swelling was firm in consistency and non-tender on palpation (Figure 1). A provisional diagnosis of residual cyst in the left posterior maxilla was considered as the patient gave the history of having the tooth extraction done in the same region.

Slika 1. Usamljeni otok kupastog oblika leve distalne maksilarne regije

Figure 1. A solitary dome-shaped swelling was evident in the left posterior maxillary region

Na panoramskom rendgen snimku uočeno je rasvetljenje u levoj zadnjoj maksilarnoj regiji sa destrukcijom i resorpcijom alveolarnog nastavka. Radiografija je takođe otkrila generalizovanu apikalnu migraciju interdentalne kosti do apikalne trećine korena, što ukazuje na teški parodontitis. Uočeno je prisustvo loše definisane radiolucencije oko vrhova korenova zuba 31, 32, 33, 34, 36, 42 i 46, što ukazuje na hronične periapikalne apscese (Slika 2). Razmatrana je radiografska diferencijalna dijagnoza benignih odontogenih/ neodontogenih cista ili tumora, benignih malih tumora pljuvačnih žlezdi. Tumori mekog tkiva poput fibroma takođe su bili smatrani mogućom diferencijalnom dijagnozom.

Panoramic radiograph revealed a shadow of a soft tissue swelling in the left maxillary posterior region with destruction and resorption of the alveolar process. The radiograph also revealed generalised apical migration of the interdental bone up to the apical third of the roots suggestive of severe periodontitis. There was the presence of ill-defined radiolucency surrounding the apex of 31, 32, 33, 34, 36, 42 and 46 suggestive of chronic periapical abscesses (Figure 2). Radiographic differential diagnosis of benign odontogenic/non-odontogenic cysts or tumours, benign minor salivary gland tumours were considered. Soft tissue tumours like fibroma were also considered as a possible differential diagnosis.

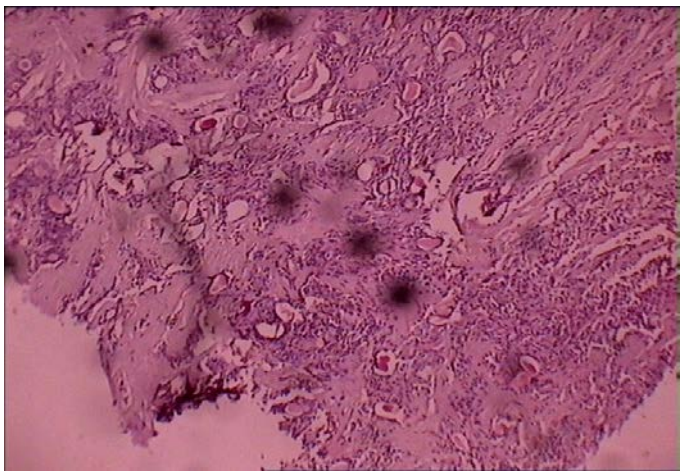


Slika 2. Panoramski rendgenski snimak koji otkriva senku otoka mekog tkiva u levoj zadnjoj maksilarnoj regiji sa destrukcijom i resorpcijom alveolarnog nastavka

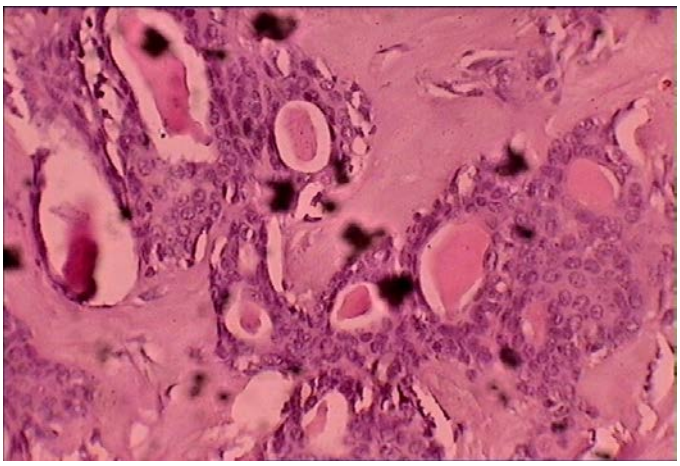
Figure 2. Panoramicradiographrevealing a shadow of a soft tissue swelling in the left maxillary posterior region with destruction and resorption of the alveolar process

Urađena je eksciziona biopsija i lezija je uklonjena u celini do periosta , a zatim je defekt potpuno prekriven sluzokožom. Uzorak je poslat na histopatološki pregled . Histopatološki pregled obojenih preseka pokazao je uglavnom ćelijske i hijalinizovane oblasti. Ćelije su bile epitelnog porekla, uglavnom okruglog oblika, sa nekoliko ćelija u obliku vretena , što je ukazivalo na to da su mioepitelnog porekla. Okrugle ćelije sadržale su vezikularna jedra. Uočene su strukture slične kanalima, koje sadrže eozinofilni koagulum ili mukoidni materijal. Neke oblasti koje okružuju vretenaste ćelije sastoje se od rastresite ili miksoidne strome. Vlakna kolagena, koja okružuju samu leziju primećena su u nekoliko oblasti , što ukazuje na fibroznu kapsulu. Uočena su i žarišta mukoznih acinusa, krvnih sudova, neurovaskularnog snopa i žarišta površinskog epitela. Ove karakteristike upućivale su na pleomorfni adenom (Slika 3 i Slika 4).

Excisional biopsy was carried out and the lesion was removed in total up to the periosteum and the overlying mucosa. The sample was sent for histopathological examination. Histopathological examination of the H and E stained sections showed mainly cellular and hyalinized areas. The cells were epithelial in origin, mainly round in shape with few spindle shaped cells suggesting their myoepithelial origin. The round cells contained vesiculated nuclei. Duct like structures containing eosinophilic coagulum or mucoid material were seen. Some areas surrounding the spindle cells consisted of loose or myxoid stroma. Collagen fibres surrounding the lesion proper were seen in a few areas, suggesting it to be the fibrous capsule. Foci of mucous acini, blood vessels, neurovascular bundle and foci of surface epithelium were also seen. These features were suggestive of Pleomorphic adenoma (Figure 3 and 4).



Slika 3. Histopatološki prikaz biosiranog materijala
Figure 3. Photomicrograph of H and E stained sections



Slika 4. Histopatološki prikaz biopsiranog materijala
Figure 4. Histopathological presentation of biopsied material

Diskusija

Pleomorfni adenom je tipično asimptomatski, spororastući tumor, uglavnom solidne konzistencije. Žene su unekoliko podložnije razvoju ove promene. U našem slučaju pacijent je muškog pola. U studiji Pitagaro i sar.[2] navodi se da je tumor detektovan kod 16 žena starosti između 16-30 god. i kod samo 4 osobe muškog pola, od ukupno 20 uključenih u studiju. Iako se u većini slučajeva javlja u velikim pljuvačnim žlezdama, smatra se da je nepce takođe predilekciono mesto za manje pleomorfne adenome pljuvačnih žlezda. Ovaj tumor je obično glatke površine, kupastog oblika, dobro ograničen i inkapsuliran[1].Ovakva lokalizacija je prisutna i u našem prikazu slučaja. Postojala je oteklina u obliku kupole koja je takođe pokazivala znake ulceracije. Patigaroo i sar.[2] su primetili da je samo 15% otoka pokazalo ulceraciju, 85% je pokazalo normalnu prekrivenu sluzokožu, 90% je imalo glatki otok, a 10% je pokazalo lobulirane otoke. Pored toga, nijedan slučaj nije pokazao recidiv u periodu praćenja[2].

Tumor je mešavina žlezdanog epitela i mioepitelnih ćelija unutar mezenhimalne pozadine. Hirurška ekscizija je tretman izbora. Ako tumori zahvataju tvrdo nepce, kao u našem sadašnjem slučaju, lezija se potpuno uklanja do periosta, sa uključivanjem sluznice koja pokriva leziju.

Pleomorfni adenom ima veoma dobru prognozu i beleži stopu izlečenja veću od 95%. Tumori malih pljuvačnih žlezda imaju veoma nisku stopu recidiva. Kada je hirurška resekcija urađena u potpunosti, skoro da ne postoji mogućnost recidiva. Recidiv se javlja kao posledica neadekvatne hirurške ekscizije[3]. Pleomorfni adenomi sa pretežno miksoidnim izgledom podložniji su recidivu[4,5].

Zaključak

Pleomorfni adenom je retko stanje. Rana dijagnoza i pravovremeni tretman su sinonimi za odličnu prognozu . Iako su stope niske, ne mogu se isključiti recidivi i maligna transformacija u dužem vremenskom periodu, posebno oni sa miksoidnim izgledom. Stoga je periodično dugoročno praćenje izuzetno obavezno za sve slučajeve.

Zahvalnica: Nema

Sukob interesa: Nema

Discussion

Pleomorphic adenoma is typically a non-tender slow-growing mass which is firm in consistency in majority of the cases. It is a benign neoplasm with slight female preponderance. In our case, the patient affected is a male, despite the female predilection stated in literature. In a study conducted by Patigaroo et al., 16 males were affected, predominantly in the age group of 16-30 years, and there were only 4 females out of the 20 people included in the study[2]. Although it occurs in the major salivary glands on most occasions, palate is considered to be a common site for minor salivary gland pleomorphic adenomas. This tumour is usually smooth surfaced, dome-shaped, well-circumscribed and encapusalated[1]. Further, in our case, the palate was the affected site. There was a dome-shaped swelling which also showed signs of ulceration. Patigaroo et al. observed that only 15% of the swelling showed ulceration, 85% showed normal overlying mucosa, 90% had a smooth swelling and 10% showed lobulated swellings. Additionally, no cases showed recurrence in the follow up period[2].

This tumour is a mixture of glandular epithelium and myoepithelial cells within the mesenchymal background. Surgical excision is the treatment of choice. If the tumours involve the hard palate as in our present case, the lesion is completely excised down to the periosteum with the inclusion of the overlying mucosa.

Pleomorphic adenoma has a very good prognosis and records a cure rate of more than 95%. Tumours of the minor salivary glands have very low recurrence rates. If the surgical excision is adequate, chances of recurrence are minimal. Recurrence can be associated with inadequate surgical excision[3]. Pleomorphic adenomas with predominantly myxoid appearance are more susceptible to recurrence[4,5].

Conclusion

Pleomorphic adenoma is a rare condition. Early diagnosis and prompt treatment are synonymous with an excellent prognosis. Although the rates are low, recurrence and malignant transformation over a long period of time cannot be ruled out, especially the ones with myxoid appearance. Hence periodic long term follow up is extremely mandatory for all cases.

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Conflict of interest: Nil

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KALCIJUM-SILIKATNI CEMENTI U ENDODONCIJI

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Sažetak

Uvod: *Endodontske paste za punjenje kanala korena služe da obezbede opturaciju nepropusnu za tečnost, opturaciju pomoćnih kanala i multiplih foramena, potpuno ograničavajući prodor bakterija. U poslednje vreme, umesto potrebe za hermetičkim zatvaranjem kanala korena, veći značaj daje se biološkoj strani, pri čemu se paste za punjenje kanala korena razlažu, kako bi stvorile interakciju sa dentinom korena, što aktivira njihovu bioaktivnost. Trikalcijum-silikatne paste pokreću bioaktivnost na površini materijala nakon kontakta sa tkivnim tečnostima.*
Cilj *ovog rada jeste da sagleda svojstva kalcijum-silikatnih pasta za punjenje kanala korena i njihovu kliničku primenu.*
Rezultati: *Nasuprot cementima na bazi smole, cementi na bazi kalcijum-silikata poseduju slaba i, ispod standarda, fizička svojstva, ali pokazuju obećavajuća svojstva – biokompatibilnost, antimikrobni potencijal zajedno sa sklonošću ka biološkoj aktivnosti.*
Zaključak: *Korisna svojstva cementa na bazi kalcijum-silikata čine ih pogodnim za dugoročni uspeh u lečenju kanala korena. S obzirom na to da se noviji kompetentni cementi redovno pojavljuju na tržištu, neophodno je proučiti njihova svojstva, kako bi se pojednostavio izbor endodontskih cemenata stomatolozima, u slučaju da je indikovana upotreba cementa.*

Ključne reči: *antimikrobna aktivnost, bioaktivnost, biokompatibilnost, kalcijum-fosfat, kalcijum-silikat, jačina veze, dentin kanala korena, cement*

Abstract

Introduction: *Endodontic root canal sealers serve the purpose of providing a fluid-tight seal, sealing off accessory canals and multiple foramina, while comprehensively confining the bacteria. Of late, rather than seeking a hermetic seal of the root canal, a more biological perspective is being tackled in which, sealers resolve to interact with root dentin, resulting in bioactivity. Tricalcium silicate sealers set the bioactivity in motion on the material surface after contacting the tissue fluids.*
The Aim: *The purpose of this paper is to review the properties of calcium silicate sealers in addition to the recent advances of the same and their clinical applications.*
Results: *Although calcium silicate sealers possess subpar physical properties in comparison to resin-based sealers, they manifest promising properties like biocompatibility, antimicrobial potential along with their propensity for bioactivity.*
Conclusion: *Beneficial properties of calcium silicate sealers render these sealers beneficial in the long-term success of root canal treatment. With newer competent sealers being put forth in the market on a regular basis, it is imperative to study their properties to simplify the clinician's selection of sealer, where indicated.*

Key words: *antimicrobial activity, bioactivity, biocompatibility, calcium phosphate, calcium silicate, push-out bond strength, root canal dentin, sealers.*

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Uvod

Prednost upotrebe osnovnih materijala i endodontske paste igra ključnu ulogu u konkretnom ostvarivanju hermetičke opturacije nakon terapije kanala korena, pored toga što eliminišu mogućnost prodora bakterija koje uzrokuju oboljenje.

Značajnost endodontskih cemenata za punjenje kanala pripisuje se njihovoj sklonosti da obezbede opturaciju nepropusnu za tečnost, kao i formiranje veze između materijala za opturaciju i zidova kanala korena dok potpuno ograničavaju prodor bakterija[1]. Od samog početka, endodontski cementi poboljšani su tako da odgovaraju zahtevima koje je naveo Grossman. Napredak u ovom pravcu delovanja doveo je do najsavremenijih kalcijum-silikatnih cemenata[2].

Ovaj pregledni rad zasnovan je na istraživanju pomenutih pasta kako bi se procenila njihova različita svojstva.

Pregled literature

Kalcijum-silikatne paste se u širem smislu dele na paste na bazi kalcijum-fosfata, paste na bazi MTA i paste na bazi kalcijum-silikata. Sastav pomenutih pasta naveden je u Tabeli 1.

Cementi na bazi kalcijum-fosfata

Apatitni cementi kanala korena (ARCS - tip I, II i III)

Proučavajući jedan od štetnih efekata cemenata kanala korena, Partovi i sar. zaključili su da je ARCS tip III izazvao najmanje prebojavanja u poređenju sa drugim testiranim cementima[3].

Ne samo da je utvrđeno da ARCS nije citotoksičan zajedno sa drugim kalcijum-silikatnim cementima kao što su iRoot SP i MTA Fillapex, već je, takođe, efikasno indukovao aktivnost alkalne fosfataze (ALP) i povećanje osteoblastnih markera i faktora transkripcije[4].

Capseal I i II

U poređenja sa ARCS i Sealapex[5], Capseal I i II cementi pokazali su najveći alkalizirajući potencijal, kao i poboljšano otpuštanje jona kalcijuma.

Bae i sar. zaključili su da su od svih testiranih endodontskih pasta Capseal I i II bili najmanje citotoksični; osim toga, pojačali su bioaktivnost povećanjem lučenja osteokalcina (OCN) i ALP[6].

Introduction

The preference of core material and endodontic sealer plays a pivotal role in concretizing the attainment of a hermetic seal following root canal therapy Besides erasure of disease-causing bacteria.

The momentousness of endodontic sealers is attributed to their propensity for engineering a fluid-tight seal also bond formation between the obturation material and root canal while comprehensively confining bacteria[1]. From the outset, sealers have been ameliorated to match the requirements connoted by Grossman. A furtherance following this course of action led to the state-of-the-art Calcium silicate sealers[2].

This review is based on the exploration of these sealers for assessing different properties.

Review of Literature

Calcium silicate sealers are broadly divided into calcium phosphate-based, MTA-based and calcium silicate-based sealers. The compositions of these sealers are listed in Table 1.

Calcium Phosphate-based Sealers

Apatite Root Canal Sealer (ARCS- Type I, II and III)

While studying one of the adverse effects of root canal sealers, Partovi et al. concluded that ARCS Type III caused the least amount of discoloration in comparison to the other sealers tested[3].

Not only was ARCS found to be non-cytotoxic along with other calcium silicate sealers like iRoot SP and MTA Fillapex, but it also efficiently induced alkaline phosphatase (ALP) activity and the upregulation of osteoblastic markers and transcription factors[4].

Capseal I and II

Both, Capseal I and II sealers showed the highest alkalizing potential in addition to enhanced calcium ion leaching when compared to ARCS and Sealapex[5].

Bae *et al.* concluded that of all the sealers tested, Capseal I and II were least cytotoxic, additionally, boosted bioactivity by increasing the expression of Osteocalcin (OCN) and ALP[6].

Tabela 1: Klasifikacija i sastav kalcijum-silikatnih cementa
Table 1: Classification and composition of calcium silicate sealers

OSNOVA MATERJALA MATERIAL BASE	PROIZVOD PRODUCT	PROIZVOĐAČ MANUFACTURER	SASTAV COMPOSITION
Na bazi kalcijum fosfata/ Calcium phosphate-based	Apatitni cement kanala korena Tip I / Apatite Root Canal Sealer Type-I	Sankin Kogyo, Tokyo, Japan	**Prah:** 80% Alfa trikalcijum fosfat, 20% Hidroksiapatit; **Powder:** 80% Alpha tricalcium phosphate, 20% Hydroxyapatite; **Tečnost: :** 25%Poliakrilna kiselina, 75% Voda 25% **Liquid:** Polyacrylic acid, 75% Water.
	Apatitni cement kanala korena Tip II / Apatite Root Canal Sealer Type-II		**Prah:** 56% Alfa trikalcijum fosfat/ 14% Hidroksiapatit, 30% jodoform; **Powder:** 56% Alpha tricalcium phosphate, 14% Hydroxyapatite, 30% Iodoform; **Tečnost:** 25% Poliakrilna kiselina, 75% Voda **Liquid: :** 25% Polyacrylic acid, 75% Water.
	Apatitni cement kanala korena Tip III/ Apatite Root Canal Sealer Type-III		**Prah:** 80% Alfa trikalcijum fosfat, 14% Hidroksiapatit, 5% Jodoform, 1% Bizmut subkarbonat; **Powder: :** 80% Alpha tricalcium phosphate, 14% Hydroxyapatite, 5% Iodoform, 1% Bismuth subcarbonate; **Tečnost: :** 25% Poliakrilna kiselina, 75% Voda. **Liquid: :** 25% Polyacrylic acid, 75% Water.
	Capseal I	-	**Prah:** Tetrakalcijum fosfat (TKF) i dikalcijum fosfat dehidrirani/ (DKFD) Portland cement, cirkonijum oksid **Powder:** Tetracalcium phosphate (TTCP) and dicalcium phosphate anhydrous (DCPA), Portland cement, zirconium oxide **Tečnost:** Hidroksi apatit metal celuloza u rasstvoru natrijum sulfata **Liquid** :Hydroxypropyl methyl cellulose in sodium phosphate solution.
	Capseal II		**Prah:** Tetrakalcijum fosfat (TKF) **i** dikalcijum fosfat dehidrirani/ (DKFD), beli Portland cement i cirkonijum oksid **Powder:** Tetracalcium phosphate (TTCP) i Tetracalcium phosphate (TTCP) and dicalcium phosphate anhydrous (DCPA), white Portland cement, zirconium oxide; **Tečnost:** Hidroksilapatit metal celuloza u rastvoru natrijum fosfata **Liquid:** Hydroxypropyl methyl cellulose in sodium phosphate solution.
Na bazi mineral-tri-oksida (MTA) /MTA based	MTA Fillapex	Angelus, Londrina, PR, Brazil	**Pasta A:** Silikatna smola, bizmut troksid, silikatni dim **Paste A:** Salicylate resin, bismuth trioxide, fumed silica; **Pasta B:** Silikatni dim, titanijum dioksid, MTA(40% trikalcijum silikat, dikalcijum silikat, kalcijum oksid, trikalcijum aluminat), baza od smole (pentaeritritol, rozinat, p-toluensulfonamida) **Paste B:** Fumed silica titanium dioxide, MTA (40%, tricalcium silicate, dicalcium silicate, calcium oxide, tricalcium aluminate), base resin (pentaerythitol, rosinate, p-toluenesulfonamide).
	Endo CPM	EGEO S.R.L., Buenos Aires, Argentina	Silicijum dioksid, kalcijum karbonat, bizmut trioksid, barijum sulfat, propilen glikol alginat, natrijum citrat, kalcijum hlorid, aktivni sastojci. Silicon dioxide, calcium carbonate, bismuth trioxide, barium sulfate, propylene glycol alginate, sodium citrate, calcium chloride, active ingredients.
	MTA-Angelus	Angelus, Londrina, PR, Brazil	Trikalcijum silikat, dikalcijum silikat, trikalcijum aluminat, tetrakalcijum aluminoferit, bizmut oksid, gvožđe oksid, kalcijum karbonat, magnezijum oksid, kristalni silicijum dioksid i ostaci Tricalcium silicate, dicalcium silicate, tricalcium aluminate, tetracalcium aluminoferrite, bismuth oxide, iron oxide, calcium carbonate, magnesium oxide, crystalline silica, and residues.
	ProRoot Endo	Dentsply, Tulsa Dental, Tulsa, OK, USA	**Prah:** Trikalcijum silikat, dikalcijum silikat, kalcijum sulfat, bizmut oksid i mala količina trikalcijum aluminata; **Powder:** Tricalcium silicate, dicalcium silicate, calcium sulfate, bismuth oxide, and a small amount of tricalcium aluminate; **Tečnost:** Viskozni vodeni rastvor polimera rastvorljivog u vodi **Liquid:** Viscous aqueous solution of a water-soluble polymer.
	ProRoot MTA	Dentsply Maillefer, Ballaigues, Switzerland	Trikalcijum silikat, trikalcijum aluminat, trikalcijum oksid, bizmut oksid. Tricalcium silicate, tricalcium aluminate, tricalcium oxidate, bismuth oxide.
	EndoSeal MTA	Maruchi, Wonju, Korea	Kalcijum silikat, kalcijum aluminati, kalcijum aluminoferit, kalcijum sulfati, radiopacifififikator, sredstvo za zgušnjavanje. Calcium silicate, calcium aluminates, calcium aluminoferrite, calcium sulfates, radiopacifier, thickening agent.
	MTA Plus	Avalon Biomed Inc., Bradenton, Florida, USA	Trikalcijum silikat, dikalcijum silikat, trikalcijum aluminat, bizmut oksid, kalcijum sulfat, silicijum dioksid Tricalcium silicate, dicalcium silicate, tricalcium aluminate, bismuth oxide, calcium sulphate, silica
Na bazi kalcijum silikata/ Calcium silicate-based	iRoot SP	Innovative Bioceramix, Vancouver , BC, Canada	Cirkonijum oksid, kalcijum silikati, kalcijum fosfat monobazni, kalcijum hidroksid, punioci, sredstvo za zgušnjavanje. Zirconium oxide, calcium silicates, calcium phosphate monobasic, calcium hydroxide, fillers, thickening agent.
	EndoSequence BC	Brasseler, Savannah, GA, USA	Cirkonijum oksid 35%-45%, Dikalcijum silikat 7%-15%, Trikalcijum silikat 20%-35%, Kalcijum hidroksid 1%-4%, punila.. Zirconium oxide 35%–45%, Dicalcium silicate 7%–15%, Tricalcium silicate 20%–35%, Calcium hydroxide 1%–4%, fillers.
	TotalFill BC	FKG Dentaire, La Chaux-deFonds,	Cirkonijum oksid 35%–45%, Dikalcijum silikat 7%–15%, Trikalcijum silikat 20%–35%, Kalcijum hidroksid 1%–4%, punila

		Switzerland	Zirconium oxide 35%–45%, Dicalcium silicate 7%–15%, Tricalcium silicate 20%–35%, Calcium hydroxide 1%–4%, fillers.
	BioRoot RCS	Septodont, Saint-Maur-desFossés, France	**Prah:** Trikalcijum silikat, cirkonijum oksid i ekscipijenti; **Powder:** Tricalcium silicate, zirconium oxide and excipients; Vodeni rastvor: Kalcijum hlorid i pomoćne supstance. **Aqueous solution:** Calcium chloride and excipients.
	Sealer Plus BC	MK Life, Porto Alegre, Brazil	Kalcijum disilikat, nanočestica kalcijum trisilikat, cirkonijum oksid. Calcium disilicate, nanoparticulate calcium trisilicate, zirconium oxide.
	CeraSeal	Meta Biomed, South Korea	Kalcijum silikati, cirkonijum oksid, sredstvo za zgušnjavanje. Calcium silicates, zirconium oxide, thickening agent.
	Bio-C Sealer	Angelus, Londrina, PR, Brazil	Trikalcijum silikat, dikalcijum silikat, trikalcijum aluminat, kalcijum oksid, cirkonijum oksid, silicijum oksid, polietilen glikol, gvožđe oksid. Tricalcium silicate, dicalcium silicate, tricalcium aluminate, calcium oxide, zirconia oxide, silicon oxide, polyethylene glycol, iron oxide.

Cementi na bazi mineralnog trioksida agregata

Mineral trioksid agregat (MTA) Filappex

Kalcijum-silikatnim cementima generalno nedostaju fizička svojstva dobrog zaptivanja, tako da ne ispunjavaju ISO specifikacije. MTA Fillapex pokazao je svojstva apsorpcije vode, rastvorljivost i vreme vezivanja niže od onog kod BioRoot RCS, ali veće od onog kod cemenata na bazi smole[7]. Suprotno tome, MTA Fillapex pokazao je veću rendgenkontrastnost od drugih kalcijum-silikatnih cemenata[7,8]. Iako je pokazao najveću fluidnost[9], debljina filma bila je najmanja u poređenju sa ostalim testiranim kalcijum-silikatnim cementima[10]. U poređenju sa AH Plus i drugim testiranim pastama, MTA Fillapex pokazao je najveći protok[9,11], iako je imao veću debljinu filma od AH plus[10]. Ovaj endodontski cement pokazao je najniži kapacitet alkalizacije među ostalim testiranim cementima na bazi kalcijum-silikata, nakon dvadeset-osmodnevnog potapanja u destilovanu vodu, Hankov balansirani rastvor soli (HBSS) i Dulbeccoov modifikovani medijum Eagle (DMEM; Gibco, SAD)[10]. Osim toga, MTA Filappex cement pokazao je najveće otpuštanje jona kalcijuma u poređenju sa cementima na bazi smole[12], ali najniže među cementima na bazi kalcijum-silikata[13]. Pored jona kalcijuma, MTA Fillapex takođe je pokazao oslobađanje jona bizmut-oksida[13], natrijuma i kalijuma[14], kao i apsorpciju jona fosfora[13]. Kada je potopljen u fiziološki rastvor sa fosfatnim puferom (PBS), MTA Fillapex demonstrirao je najveći gubitak zapremine i procentualne zapreminske širine[15].

Nakon tople vertikalne kompakcije posle sedam dana, MTA Fillapex pokazao je veće mikrocurenje od cemenata na bazi smole; međutim, nakon četiri nedelje, rezultati su bili obrnuti[16]. MTA Fillapex takođe je pokazao manje prebojavanje u poređenju sa cementom na bazi cink-oksida-eugenola (ZOE)[17].

Mineral Trioxide Aggregate-based Sealers

MTA Fillapex

Calcium silicate sealers in general lack physical properties of a good sealer thus not meeting the ISO specifications. MTA Fillapex has been reported to have water sorption, solubility, and setting time lower than that of BioRoot RCS but higher than that of resin-based sealers[7]. Contrastingly, MTA Fillapex showed greater radiopacity than other calcium silicate sealers[7,8]. Though it showed the highest flow[9], it had the lowest film thickness amongst other calcium silicate sealers tested[10]. Similarly, as opposed to AH Plus and other sealers tested, MTA Fillapex showed the highest flow[9,11], albeit had a greater film thickness than the former[10]. This sealer demonstrated the lowest alkalizing capacity amongst the other tested calcium silicate sealers, following a 28-day immersion period into distilled water, Hank's Balanced Salt Solution (HBSS) and Dulbecco's Modified Eagle Medium (DMEM; Gibco, USA)[10]. Moreover, MTA Fillapex has shown the highest calcium ion release when compared with resin-based sealers[12], but the lowest amongst calcium silicate sealers[13]. In addition to calcium ions, MTA Fillapex has also displayed the leaching of bismuth[13], sodium and potassium ions[14], and uptake of phosphorus ions[13]. When immersed into Phosphate Buffered Saline (PBS), MTA Fillapex showed the highest volume loss and percentage volume of extrusion[15].

Following warm vertical compaction after seven days, MTA Fillapex demonstrated greater microleakage than a resin-based sealer, however at 4 weeks, the results were vice-versa[16]. MTA Fillapex also reported lower discoloration in comparison to a Zinc Oxide Eugenol-based (ZOE) sealer[17].

MTA Fillapex demonstrated thrice the cytotoxicity of iRoot SP and BioRoot RCS but lower than that of resin-based sealers[18].

MTA Fillapex je pokazao tri puta veću citotoksičnost od iRoot SP i BioRoot RCS, ali nižu od cemenata na bazi smole[18]. Antimikrobni efekat i bioaktivnost koje ima MTA Fillapex inferiorni su kada se uporede sa BioRoot RCS[7,19]. Siboni i sar. naveli su da su površine i MTA Fillapex i BioRoot RCS cementi izazivaju taloženje sloja kalcijum-fosfata i kalcijum-apatita nakon potapanja u HBSS[7]. DCT je zaključio da TotalFill BC i EasySeal imaju bolji antimikrobni potencijal nego MTA Fillapex[19].

Endo CPM

Endo CPM pokazao je rastvorljivost sličnu rastvorljivosti AH Plus (Dentsply, Nemačka) i nižu rendgenkontrastnost, iako je njegova alkalizirajuća sposobnost bila veća od one koju ima AH Plus[20]. Takođe, Endo CPM pokazao je veći alkalni pH i oslobađanje jona kalcijuma u poređenju sa MTA i ZOE[21].

Za razliku od MTA Fillapex, Endo CPM pokazao je znatan prodor boje apikalno[22], iako ima veću jačinu veze otpornosti (POBS) nakon monokonusne tehnike i lateralne kondenzacije[23]. Pored toga, Endo CPM pokazao je lošiju adaptaciju na zidove kanala od AH Plus nakon lateralne kondenzacije[20].

Endo CPM nije, za razliku od MTA Fillapex[24] pokazao zonu inhibicije prilikom testiranja antimikrobne aktivnosti, bez obzira na primenjenu metodu testiranja.

MTA Angelus

Ispostavilo se da je rastvorljivost MTA Angelus najmanja među testiranim kalcijum-silikatnim endodontskim cementima, bez statističke razlike u odnosu na AH Plus[14]. Bez obzira na blagu citotoksičnost nakon 24 sata, MTA Angelus nije imao nikakve štetne efekte na vijabilnost ćelija[25].

ProRoot MTA

U poređenju sa EndoSeal MTA i AH Plus, ProRoot MTA pokazao je nisku rastvorljivost[26], rendgenkontrastnost[26] i povećanje zapremine[26], a veći potencijal alkalizacije[26] i potencijal za promenu boje od AH Plus[27]. ProRoot MTA pokazao je veće oslobađanje jona kalcijuma nego EndoSequence BC, ali manje nego Biodentine[28]. Za ProRoot MTA utvrđeno je da je najmanje citotoksični endodontski cement u poređenju sa iRoot SP i AH Plus[29].

The antimicrobial effect and bioactivity of MTA Fillapex was reported to be inferior to BioRoot RCS[7,19]. Siboni et al. stated that both, MTA Fillapex and BioRoot RCS sealer surfaces had deposition of calcium phosphate and apatite layer following HBSS immersion[7]. DCT concluded that TotalFill BC and EasySeal have better antimicrobial potential than MTA Fillapex[19].

Endo CPM

Endo CPM displayed solubility similar to that of AH Plus (Dentsply, Germany) and radiopacity lower than the latter, although its alkalizing ability was reported greater than that of AH Plus[20]. Also, Endo CPM displayed a higher alkaline pH and calcium ion release when compared to MTA and ZOE[21].

As opposed to MTA Fillapex, Endo CPM has reported significantly greater apical dye leakage[22], albeit has a higher push-out bond strength (POBS) following single cone and lateral compaction techniques[23]. Additionally, Endo CPM demonstrated poor adaptation to the canal walls compared to AH Plus following lateral compaction[20].

No inhibition zone was produced by Endo CPM when its antimicrobial effect was tested, regardless of the test method implemented, unlike MTA Fillapex[24].

MTA Angelus

The solubility of MTA Angelus was reported to be the least amongst the calcium silicate sealers tested, with no statistical difference to that of AH Plus[14]. Regardless of being slightly cytotoxic after 24 hours, MTA Angelus did not have any adverse effects on the cell viability[25].

ProRoot MTA

In comparison to EndoSeal MTA and AH Plus, ProRoot MTA has demonstrated low solubility[26], radiopacity[26], and volume gain[26], albeit, a higher alkalizing[26], and discoloration potential than the latter[27]. ProRoot MTA showed a greater calcium ion release than EndoSequence BC but lower than that of Biodentine[28]. ProRoot MTA was reported to be the least cytotoxic sealer when compared to iRoot SP and AH Plus[29].

EndoSeal MTA

U pogledu apsorpcije vode i rendgenkontrastnosti, EndoSeal MTA pokazao je veće vrednosti od BioRoot RCS[10]. U pogledu rastvorljivosti, rezultati EndoSeal MTA bili su uporedivi sa BioRoot RCS, iako su bili veći od AH Plus[10]. Međutim, EndoSeal MTA demonstrirao je kraće vreme vezivanja od BioRoot RCS nakon potapanja u HBSS i DMEM[9]. EndoSeal MTA pokazao je otpuštanje jona aluminijuma i bizmuta zajedno sa jonima kalcijuma i fosfora[10]. Kada je testiran na 37 °C, EndoSeal MTA pokazao je veću fluidnost nego ProRoot MTA[26]. Pored toga, ovaj endodontski cement pokazao je veće povećanje zapremine od AH Plus nakon tridesetodnevnog perioda potapanja u destilovanu vodu[9].

Rezultati prodora bakterija pri korišćenju EndoSeal MTA i AH Plus podudarali su se kada su mereni na jedan, dva i tri mm od apeksa[30]. Studija koja je upoređivala jačinu veze otpornosti EndoSeal MTA i MTA Fillapek zaključila je da je prvi imao veću jačinu (i POBS)[31]. Pored toga, zapreminski procenat praznine EndoSeal MTA primenom monokone tehnike obturacije bio je uporediv sa onim kod AH Plus sa toplom vertikalnom kompakcijom[32].

Što se biokompatibilnosti tiče, EndoSeal MTA i ProRoot MTA pokazali su veću vijabilnost ćelija i niži inflamatorni odgovor u poređenju sa AH Plus[26]. DCT rezultati ukazali su na visoku antimikrobnu aktivnost EndoSeal MTA pre postavljanja endodontske paste, premda su pokazali smanjenu aktivnost nakon postavljanja cementa[33]. Yoo i sar. proučavajući bioaktivni potencijal EndoSeal MTA i ProRoot MTA, zaključili su da sam EndoSeal MTA dovodi do niže intratubularne kristalizacije apatita i kalcijum-fosfata[34].

MTA Plus

Nakon lateralne kompakcije, kod MTA Plus primećeno je manje otpuštanje boje nego kod AH Plus, ali veće od onog kod EndoSekquence BC[35]. Kada je u pitanju POBS, MTA Plus pokazao je niži POBS od oba gorenavedena, bez obzira na korišćeni metod opturacije[36].

Endodontski cementi na bazi kalcijum-silikata

iRoot SP

iRoot SP pokazao je veću stopu apsorpcije vode od AH Plus, a njihova rastvorljivost u destilovanoj vodi bila je komparabilna[37].

EndoSeal MTA

In terms of water sorption and radiopacity, EndoSeal MTA has displayed higher values than those by BioRoot RCS[10]. In terms of solubility, the results of EndoSeal MTA were comparable to BioRoot RCS, albeit, were greater than AH Plus[10]. However, EndoSeal MTA displayed a lower setting time as opposed to BioRoot RCS, following immersion into HBSS and DMEM[9]. EndoSeal MTA demonstrated the leaching of aluminium and bismuth ions along with calcium and phosphorus ions.10 When tested at 37°C, EndoSeal MTA reported a greater flow than ProRoot MTA[26]. In addition, this sealer displayed a volume gain greater than AH Plus, following a 30-day immersion period into distilled water[9].

The results of bacterial leakage of EndoSeal MTA and AH Plus were analogous when measured at one, two and three mm from the apex[30]. Comparing the push-out bond strengths of EndoSeal MTA and MTA Fillapex, the study concluded that the former had a greater POBS[31]. In addition, the void volume percentage of EndoSeal MTA using single-cone obturation technique was comparable to that of AH Plus with warm vertical compaction[32].

In terms of biocompatibility, EndoSeal MTA and ProRoot MTA demonstrated higher cell viability and lower inflammatory response in comparison to AH Plus[26]. DCT results showed a high antimicrobial activity of EndoSeal MTA prior to sealer setting, albeit demonstrated a diminished activity after the sealer set[33]. On studying the bioactive potential of EndoSeal MTA and ProRoot MTA, Yoo et al. concluded that EndoSeal MTA alone resulted in a lower intratubular crystallization of apatite and calcium phosphate[34].

MTA Plus

Following lateral compaction, MTA Plus has demonstrated a lower dye leakage than AH Plus, but higher than that of EndoSequence BC[35], whereas in terms of POBS, MTA Plus displayed a lower POBS than both, regardless of the obturation method utilized[36].

Calcium Silicate-based Sealers

iRoot SP

While iRoot SP showed a higher water sorption rate than AH Plus, their solubility in distilled water was comparable[37].

Kada je podvrgnut temperaturi od 140°C, iRoot SP pokazao je smanjenu fluidnost u poređenju sa AH Plus, dok su u pogledu vremena vezivanja rezultati bili obrnuti[38]. iRoot SP pokazao je manji kapacitet alkalizacije od MTA Fillapex, ali veći od ostalih testiranih cemenata na bazi smole[39]. Otpuštanje jona kalcijuma nakon potapanja u destilovanu vodu[40] bilo je pak veće sa iRoot SP nego sa MTA Fillapex.

Za iRoot SP uočena su inferiorna svojstva prodora paste, uz neadekvatnu opturaciju lateralnih kanala, u poređenju sa cementima na bazi smole, bez obzira na primenjenu tehniku opturacije[41]. Međutim, u drugoj studiji iRoot SP i AH Plus imali su iste rezultate u pogledu mikrocurenja, odnosno znatno niže u odnosu na Sealapek (Sibron–Kerr, SAD) i EndoREZ (Ultradent Products Inc., SAD)[37]. iRoot SP i MTA Fillapex pokazali su manje prebojavanje strukture zuba nego AH Plus nakon tri meseca; rezultati nakon šest meseci bili su pak obrnuti[42].

Ne samo da je iRoot SP bio necitotoksičan, već je takođe pokazao bioaktivnost, evidentno na ekspresiju mRNA dentin sialofosfoproteina (DSPP), COL1A i ekspresije ALP[43]. Sveže zamešan iRoot SP pokazao je antimikrobnu efikasnost veću nego kod drugih cemenata na bazi smole i dao je sličan rezultat nakon tri dana, mada je pokazao samo blagu antimikrobnu aktivnost nakon šest dana[39].

EndoSequence BC

EndoSekquence BC je, u poređenju sa MTA Filapex i drugim proučavanim cementima, pokazao slabe fizičke osobine – visoka rastvorljivost[44], niska rendgen-kontrastnost[9] i vreme vezivanja[44]. Pored toga, ovaj cement je pokazao duže vreme vezivanja od AH Plus[45]. Uprkos tome, u pogledu fluidnosti EndoSequence BC ispunjava ISO zahteve, iako ima manju fluidnost nego MTA Filapex[44]. EndoSekquence BC nadmašuje EndoSeal MTA i MTA Fillapex, pokazujući veći alkalizirajući potencijal[9]. Ovaj cement ima manju debljinu filma od MTA Fillapex, ali veću od AH Plus i Pulp Canal Sealer[44]. Lopez-Garcia i sar. otkrili su da EndoSequence BC pokazuje veće otpuštanje jona kalcijuma nego EndoSeal MTA, ali manje nego CeraSeal[46].

Pri poređenju sa cementima na bazi smole EndoSequence BC je pokazao izvesna štetna svojstva (niži POBS[47] i veće curenje endotoksina[48]), bez obzira na korišćene tehnike obturacije.

When subjected to 140°C, iRoot SP displayed decreased flow in comparison to AH Plus, but in terms of setting time, the results were vice-versa[38]. iRoot SP exhibited a reduced alkalizing capacity as opposed to MTA Fillapex but higher than the other resin-based sealers tested[39]. Contrastingly, the leaching of calcium ions was higher with iRoot SP than MTA Fillapex following immersion into distilled water[40].

iRoot SP displayed inferior sealer penetration properties along with inadequately obturated lateral canals when compared to a resin-based sealer, regardless of the obturation technique employed[41]. Whereas, in another study, iRoot SP and AH Plus had analogous results in terms of microleakage, significant lower as opposed to Sealapex (Sybron-Kerr, USA) and EndoREZ (Ultradent Products Inc., USA)[37]. Both, iRoot SP and MTA Fillapex showed discoloration of tooth structure, lesser than AH Plus after three months but vice-versa after six months[42].

Not only was iRoot SP non-cytotoxic, but also exhibited bioactivity, evident on mRNA expression of Dentin Sialophosphoprotein (DSPP), COL1A and ALP expression[43]. Freshly mixed iRoot SP displayed highest antimicrobial efficacy in comparison to other resin-based sealers, and had similar results after three days, albeit showed only slight antimicrobial activity after six days[39].

EndoSequence BC

EndoSequence BC has exhibited subpar physical properties like high solubility[44], low radiopacity[9], and setting time[44], in comparison to MTA Fillapex and other sealers studied. Additionally, this sealer has demonstrated a greater setting time than AH Plus[45]. Even so, in terms of flow, EndoSequence BC meets the ISO requirements, albeit has a decreased flow compared to MTA Fillapex[44]. EndoSequence BC surpasses EndoSeal MTA and MTA Fillapex by demonstrating a greater alkalizing potential[9]. This sealer has a lesser film thickness than MTA Fillapex but greater than AH Plus and Pulp Canal Sealer[44]. López-García et al. found that EndoSequence BC showed a higher calcium ion release as opposed to EndoSeal MTA but lesser than that of CeraSeal[46].

EndoSequence BC displayed detrimental properties like lower POBS[47], and higher endotoxin leakage[48], in comparison to resin-based sealers, regardless of the obturation techniques used.

Broj otvorenih pora koji je nakon monokonusne obturacije imao EndoSequence BC bio je veći nego kod AH Plus[49]. Ipak, oba cementa su pokazala analogne rezultate u pogledu izmerenih zatvorenih pora[49].

Studija o biokompatibilnosti EndoSequence BC otkrila je da je blago citotoksičan, ali manje nego AH Plus[50]. Međutim, dve druge studije o istom zaključile su da je EndoSequence bio najkompatibilniji cement među svim testiranim cementima[45,51]. Antimikrobnim testiranjem sa Agar Diffusion Testom (ADT) zaključeno je da EndoSequence BC ima veću antimikrobnu aktivnost nego AH Plus, dok je test direktnog kontakta (DCT) dao komparabilne rezultate za oba cementa. Dokazano je da je ekspresija[50] mRNA ALP i OCN veća kod EndoSequence nego kod MTA Fillapex i AH Plus[51].

TotalFill BC

U poređenju sa AH Plus, TotalFill BC pokazao je veću stopu rastvorljivosti, povećanje zapremine za sedam dana i gubitak zapremine za 30 dana[19]. Pored toga, ovaj cement imao je veću rastvorljivost od BioRoot RCS i MTA Fillapex[19]. Što se tiče fluidnosti, TotalFill BC pokazao je najveću fluidnost kada se upoređivao sa AH Plus i GuttaFlow Bioseal (Coltene Whaledent, Švajcarska)[52]. TotalFill BC bio je manje rendgenkontrastan od AH Plus, ali više nego GuttaFlow Bioseal[52]. Kada je testiran u odnosu na BC-RRM-Putty (FGK, Švajcarska), TotalFill BC pokazao je nižu rendgenkontrasnost, ali duže vreme vezivanja, uporedo[53]. U drugoj studiji zabeležen je veći potencijal alkalizacije kod TotalFill BC i BioRoot RCS nego kod MTA Fillapex, AH Plus i Sealapex[19].

TotalFill BC pokazao je veći POBS nego AH Plus i EndoREZ[54], imao je i veći broj pora između cementa i gutaperke nego AH Plus[55].

Među testiranim cementima na bazi biokeramike i smole, biokompatibilnost TotalFill BC bila je uporediva sa BioRoot RCS, iako su imali blage citotoksične efekte; s druge strane, MTA Fillapex bio je visoko citotoksičan[19].

BioRoot RCS

Kada je potopljen u destilovanu vodu, BioRoot RCS je imao nižu stopu rastvorljivosti od MTA Fillapex, iako je imao suprotne rezultate pri potapanju u PBS[56].

The number of open pores reported by EndoSequence BC, following single cone obturation, were higher than those of AH Plus[49]. However, both sealers displayed analogous results in case of closed pores measured[49].

The study of biocompatibility of EndoSequence BC revealed it to be slightly cytotoxic, however, lesser in comparison to AH Plus[50]. Whereas, two other studies on the same concluded EndoSequence to be the most biocompatible sealer amongst all sealers tested[45,51]. Antimicrobial testing with Agar Diffusion Test (ADT) concluded AH Plus to have a higher antimicrobial ability as opposed to AH Plus, while Direct Contact Test (DCT) gave comparable results of both sealers[50]. mRNA expression of ALP and OCN have been proved to be higher with EndoSequence when compared to MTA Fillapex and AH Plus[51].

TotalFill BC

In comparison to AH Plus, TotalFill BC demonstrated a higher rate of solubility, volume gain at 7 days and volume loss at 30 days[19]. Additionally, this sealer had higher solubility than BioRoot RCS and MTA Fillapex[19]. In terms of flow, TotalFill BC recorded the highest flow rate as opposed to AH Plus and GuttaFlow Bioseal (Coltene Whaledent, Switzerland)[52]. TotalFill BC was less radiopaque than AH Plus, but more than GuttaFlow Bioseal[52]. When tested in relation to BC-RRM-Putty (FGK, Switzerland), TotalFill BC displayed lower radiopacity but a higher setting time, comparatively[53]. In another study, TotalFill BC and BioRoot RCS recorded the highest alkalizing potential in comparison to MTA Fillapex, AH Plus and Sealapex[19].

TotalFill BC demonstrated a higher POBS as opposed to AH Plus and EndoREZ[54], but reported the highest number of gaps between the sealer and gutta percha than AH Plus[55].

Amongst the bioceramic sealers and resin sealers tested, the biocompatibility of TotalFill BC was comparable to BioRoot RCS, although they had mild cytotoxic effects, whereas MTA Fillapex was highly cytotoxic[19].

BioRoot RCS

When immersed into distilled water, BioRoot RCS showed a lower rate of

Rendgenkontrasnost koju je pokazao BioRoot RCS bila je niža od one kod AH Plus[57]; međutim, Prullage i sar. naveli su drugačije rezultate, prema kojima je rendgenkontrasnost ovog endodontskog cementa komparabilna sa AH Plus i MTA Fillapex[56]. Na 37 °C, BioRoot RCS pokazao je brzinu protoka analognu onoj koju ima EndoSeal MTA, ali nižu od one koju poseduje MTA Fillapex[57]. Benezra i sar. objavili su da je BioRoot RCS imao veći protok nego AH Plus[10], dok su Khalil i sar. došli do suprotnog zaključka – AH Plus pokazao je veći protok od BioRoot RCS[57]. Zapaženo je da je BioRoot RCS imao nižu debljinu filma od Bio MM, a višu od AH Plus[57]. Ova studija je pokazala da BioRoot RCS ima duže vreme vezivanja od AH Plus[56]; u drugoj studiji, međutim, došlo se do drugačijeg zaključka[57]. Kada je potopljen u HBSS, BioRoot RCS je pokazao veći kapacitet alkalizacije[57], otpuštanje jona kalcijuma[7,57] i uzimanje jona fosfora od AH Plus[57].

Prodor ovog endodontskog cementa u dentin kanala korena bila je najveća u srednjoj trećini korena, što je komparabilno sa AH Plus, manja u koronarnom delu, za razliku od AH Plus, a najmanja u apikalnom delu, što se podudara sa EndoSeal MTA[58]. BioRoot RCS pokazao je niži POBS nego TotalFill BC i AH Plus, ali viši od Endo CPM[59]. Kada je podvrgnut temperaturi od 250°C, sa ciljem stimulisanja efekta vertikalne kompakcije, BioRoot RCS pokazao je gubitak težine od 15%[60].

U studijama koje su procenjivale biokompatibilnost BioRoot RCS, zajedno sa drugim endodontskim cementima na bazi kalcijum-silikata i smole, zaključeno je da je ovaj cement citotoksičan i bez štetnog uticaja na vijabilnost i morfologiju humanih PDL ćelija[61,62]. ADT nakon kontakta sa EDTA dokazao je da je antimikrobni potencijal BioRoot RCS i AH Plus analogan, ali veći od onog koji ima MTA Fillapex[63]. Međutim, nakon upotrebe destilovane vode i PBS, ovi endodontski cementi nisu uspeli da proizvedu zonu inhibicije[63]. Test intratubularne infekcije, izveden nakon kontakta sa svim rastvorima, pokazao je da je, u poređenju sa MTA Filapek i AH Plus[63], BioRoot RCS imao najveću antimikrobnu aktivnost. Delotvorna bioaktivnost BioRoot RCS dokazana je u studiji Camps i sar.; tu je ekspresija koštanog morfogenog proteina-2 i transformišućeg faktora rasta-2 bila veća sa BioRoot RCS nego sa Pulp Canal Sealer, iako su oni pokazali komparabilne rezultate u ekspresiji vaskularnog endotelnog faktora rasta[61].

solubility than MTA Fillapex, albeit had contrasting results on immersion into PBS56. Radiopacity displayed by BioRoot RCS was lower than that of AH Plus[57], but Prüllage et al. reported dissimilar results that this sealer's radiopacity was comparable to AH Plus and MTA Fillapex[56]. At 37°C, BioRoot RCS demonstrated a flow rate analogous with EndoSeal MTA but lower than that of MTA Fillapex[57]. Benezra et al. reported that BioRoot RCS had a higher flow than AH Plus[10], whereas Khalil et al. had a contrasting conclusion, that AH Plus displayed a higher flow than BioRoot RCS[57]. In case of film thickness, BioRoot RCS had a lower film thickness than Bio MM but greater than that of AH Plus[57]. A study reported BioRoot RCS to have a greater setting time than AH Plus[56], while another study concluded vice versa[57]. When immersed in HBSS, BioRoot RCS showed the greatest alkalizing capacity[57], leaching of calcium ions[7,57], and phosphorus ions uptake than AH Plus[57].

Dentinal penetration of this sealer was highest in the middle third portion of the root, comparable to AH Plus, lesser in the coronal portion as opposed to AH Plus, and the least in the apical portion, matching EndoSeal MTA[58]. BioRoot RCS demonstrated the lowest POBS amongst TotalFill BC and AH Plus but higher than that of Endo CPM[59]. When subjected to a temperature of 250°C to stimulate the effect of vertical compaction, BioRoot RCS showed a 15% loss of weight[60].

Studies evaluating the biocompatibility of BioRoot RCS along with other calcium silicate and resin-based sealers, concluded this sealer to be the cytotoxic with no detrimental effect on human PDL cell viability and morphology[61,62]. ADT following contact with EDTA proved the antimicrobial potential of BioRoot RCS and AH Plus to be analogous, but greater than MTA Fillapex[63]. However, after using distilled water and PBS, these sealers failed to produce an inhibition zone[63]. Intratubular Infection Test performed after contact with all the solutions, concluded BioRoot RCS to have the highest antimicrobial activity as opposed to MTA Fillapex and AH Plus[63]. The beneficial bioactivity of BioRoot RCS was proved in a study by Camps et al., where the expression of Bone Morphogenic Protein-2 and Transforming Growth Factor-2 was higher with BioRoot RCS than Pulp Canal Sealer, although they showed comparable results in expression of Vascular Endothelial Growth Factor[61].

Sealer Plus BC

Ispostavilo se da je Sealer Plus BC, jedan od novijih endodontskih cemenata na bazi kalcijum-silikata, imao rastvorljivost veću nego AH Plus[64,65], sličnu sa TotalFill BC i nižu od Bio-C Sealer[65]. Ovaj endodontski cement je manje rendgen-kontrastan i ima nižu brzinu protoka od AH Plus[64]. Sealer Plus BC je takođe pokazao veće vreme vezivanja, sposobnost alkalizacije i otpuštanje jona kalcijuma od poslednjeg pomenutog[64]. Međutim, Sealer Plus BC nije pokazao nikakvo povećanje zapremine pri potapanju u PBS i destilovanu vodu, za razliku od AH Plus[65]. Pored toga, njegov zapreminski gubitak bio je uporediv sa TotalFill BC i Bio-C Sealer[65].

Analizom intratubularne penetracije endodontskog cementa korišćenjem fluorofora, Sealer Plus BC pokazao je komparabilne rezultate sa EndoSequence BC i AH Plus, bez obzira na metodu opturacije[66,67].

Silva i sar. naveli su da Sealer Plus BC i Bio-C Sealer nisu pokazali inhibiciju vijabilnosti ćelija, pa su zato bili biokompatibilni[68]. Bioaktivnost ovog enodontskog cementa potvrđena je prisustvom naslaga kalcijuma i nepravilnih struktura nakon bojenja po Von Kossi[68].

CeraSeal

Prilikom procene fizičkih osobina, CeraSeal je pokazao veću stopu rastvorljivosti i fluidnosti nego BioRoot RCS[69]. Nasuprot tome, ovaj endodontski cement pokazao je manju apsorpciju vode i otpuštanje jona kalcijuma, nakon potapanja u destilovanu vodu[69]. Lopez-Garcia i sar. zaključili su da je nakon uranjanja u Milli-Q vodu pH koji ima CeraSeal alkalniji nego pH EndoSequence BC, a niži kada se uporedi sa EndoSeal MTA[46]. Slično tome, Kharouf i sar. naveli su da je BioRoot RCS imao alkalniji pH od CeraSeal kada je potopljen u destilovanu vodu[69].

Kombinacija CeraSeal sa gutaperka poenima obloženim biokeramikom doprinela je većim vrednostima POBS od monokone obturacije sa AH Plus u svim delovima kanala korena[70]. Nakon monokone obturacije, CeraSeal je imao manji procenat praznine na 2 mm i 8 mm od apeksa, pri čemu su rezultati bili analogni sa BioRoot RCS, 5 mm od vrha[69].

Utvrđeno je da su CeraSeal i EndoSequence BC biokompatibilniji od

Sealer Plus BC

One of the newer calcium silicate sealers, Sealer Plus BC has been reported to have a higher solubility in comparison to AH Plus[64,65], but analogous with TotalFill BC and lower than that of Bio-C Sealer[65]. This sealer is less radiopaque and has a lower flow rate than AH Plus[64]. Contrastingly, Sealer Plus BC displayed a higher setting time, alkalizing ability, and calcium ion release than the latter[64]. However, Sealer Plus BC did not display any volume gain on immersion into PBS and distilled water, unlike AH Plus[65]. Additionally, it's volumetric loss was comparable to TotalFill BC and Bio-C Sealer[65].

On analysis of intratubular sealer penetration using fluorophore, Sealer Plus BC demonstrated comparable results with EndoSequence BC and AH Plus, regardless of the method of obturation[66,67].

Silva et al. stated that Sealer Plus BC and Bio-C Sealer did not show inhibition of cellular viability, hence were biocompatible[68]. This sealer's bioactivity was confirmed on presence of calcium deposits and irregular structures following von Kossa staining[68].

CeraSeal

On evaluation of physical properties, CeraSeal demonstrated a higher rate of solubility and flow in comparison to BioRoot RCS[69]. Contrastingly, this sealer showed lesser water sorption and calcium ion leaching, after being immersed into distilled water[69]. López-García et al. concluded that, when subjected to immersion into Milli-Q water, the pH of CeraSeal is more alkaline than that of EndoSequence BC but lesser in comparison to EndoSeal MTA[46]. Similarly, Kharouf et al. stated that the BioRoot RCS had a higher alkaline pH than CeraSeal when immersed into distilled water[69].

The combination of CeraSeal with bioceramic-coated gutta percha points yielded higher POBS values than single-cone obturation with AH Plus in all portions of the root canal[70]. Following single cone obturation, CeraSeal reported a lower percentage of voids at 2 and 8 mm from the apex, whereas the results were analogous with BioRoot RCS, 5 mm from the apex[69].

CeraSeal and EndoSequence BC were found to be more biocompatible than EndoSeal MTA, which was reported to be slightly cytotoxic to human periodontal

EndoSeal MTA, za koji se navodi da je blago citotoksičan za matične ćelije humanog parodontalnog ligamenta (hPDLSC) od prethodnih endodontskih pasta[46]. Oh i sar. su zaključili da je CeraSeal najbiokompatibilniji endodontski cement kada se uporedi sa AH Plus i EndoSeal TCS (Maruchi, Koreja)[71]. Tokom procene antimikrobne aktivnosti, ADT nije pokazao formiranje zona inhibicije od strane CeraSeal i BioRoot RCS, iako je DCT pokazao iste rezultate za oba[69]. CeraSeal, EndoSekuence BC su pokazali veću ekspresiju ALP, katabolitnog aktivatorskog proteina), proteina-1 iz cementoblastoma nego EndoSeal MTA, tokom procene njihove bioaktivnosti[46]. U drugoj studiji u vezi sa ispitivanjem bioaktivnosti, koju ima CeraSeal navedeno je da ima bolji osteogeni potencijal nego AH Plus, ali manji od EndoSeal TCS[71].

Bio-C Sealer

Bio-C Sealer je, u odnosu na TotalFill BC i AH Plus[72], zabeležio najveću stopu rastvorljivosti i protoka, premda je u pogledu rendgenkontrasnosti ovaj endodontski cement pokazao iste rezultate kao TotalFill BC, ali niže u odnosu na AH Plus[72]. U istoj studiji, Bio-C endodontski cement pokazao je najbrže vreme vezivanja među testiranim endodontskim cementima[72]. Kada je potopljen u dejonizovanu vodu i DMEM, alkalizirajući potencijal Bio-C endodontskog cementa bio je komparabilan sa TotalFill BC i Bio-C Repair (Angelus, Brazil), ali značajno veći od AH Plus[72,73]. Bio-C endodontski cement pokazao je veću stopu otpuštanja jona kalcijuma nego Bio-C Repair, nakon potapanja u DMEM[73]. Slično drugim endodontskim pastama na bazi kalcijum-silikata, Bio-C endodontski cement pokazao je veći gubitak zapremine od AH Plus, nakon stavljanja u destilovanu vodu[72].

Procenom sposobnosti zaptivanja, Bio-C Sealer pokazao je najmanju penetraciju boje u poređenju sa AH Plus i MTA Fillapex[74]. Pored toga, Bio-C Sealer i AH Plus pokazali su sličan procenat praznina kao u srednjem i apikalnim delovima kanala korena, nakon monokone opturacije[75].

Bio-C Repair pokazao je bolju biokompatibilnost nego Bio-C Sealer, mada nije prijavljena citotoksičnost ni za jedan materijal prema Lopez-Garcia i sar[73]. Sveže zamešani Bio-C Sealer pokazao je antimikrobni efekat na sve bakterije, izuzev na bakteriju S. mutans, premda su, nakon vezivanja, svi testirani endodontski cementi pokazali analogne rezultate na bakteriju E. faecalis[76].

ligament stem cells (hPDLSCs) than the former sealers[46]. Oh et al. concluded CeraSeal to be the most biocompatible sealer as opposed to AH Plus and EndoSeal TCS (Maruchi, Korea)[71]. During evaluation of antimicrobial ability, ADT revealed no formation of inhibition zones by CeraSeal and BioRoot RCS, although, DCT reported analogous results with both[69]. CeraSeal, EndoSequence BC demonstrated an increased expression of ALP, Catabolite Activator Protein, Cementoblastoma-derived Protein-1 than EndoSeal MTA, during the evaluation of their bioactivity[46]. In another study evaluating bioactivity of CeraSeal stated that it had a better osteogenic potential than AH Plus but lesser than EndoSeal TCS[71].

Bio-C Sealer

Bio-C Sealer recorded the highest rate of solubility and flow, when evaluated against TotalFill BC and AH Plus[72]. Although, in terms of radiopacity, this sealer showed results analogous with TotalFill BC, but lower than AH Plus[72]. In the same study, Bio-C sealer demonstrated the fastest set, amongst the sealers tested[72]. When immersed into deionized water and DMEM, the alkalizing potential of Bio-C sealer is comparable with TotalFill BC and Bio-C Repair (Angelus, Brazil), but significantly greater than AH Plus[72,73]. Bio-C Sealer when subjected to DMEM immersion, displayed a higher rate of calcium ion release as opposed to Bio-C Repair[73]. Mimicking other calcium silicate sealers, Bio-C sealer has also demonstrated a higher volume loss than AH Plus, after being placed into distilled water[72].

On evaluation of sealing ability, Bio-C Sealer showed the least dye penetration in comparison to AH Plus and MTA Fillapex[74]. Additionally, Bio-C Sealer and AH Plus demonstrated similar percentage of voids in the middle and apical portions of root canal, following single-cone obturation[75].

Bio-C Repair displayed better biocompatibility than Bio-C Sealer, although, no cytotoxicity was reported by any of the materials according to López-García et al.[73] Freshly mixed Bio-C Sealer, exhibited an antimicrobial effect against all bacteria, excluding S. mutans, although, following setting, all the tested sealers displayed analogous results against E. faecalis[76].

Zaključak

Endodontske paste za punjenje kanala korena služe da obezbede zaptivanje koje je nepropusno za tečnost, prilagođeno tako da fizička blokada koju stvaraju ne ometa komunikaciju između prostora kanala korena i okolnih tkiva, istovremeno sprečavajući rast mikroorganizama. Stoga, ishod obturacije kanala korena u velikoj meri zavisi od fizičkih i bioloških karakteristika materijala za opturaciju kanala korena.

Na stabilnost dimenzija endodontskih cemenata utiče hidrofilno okruženje, što zauzvrat utiče na njihova fizička svojstva. Iako endodontski cementi na bazi kalcijum-silikata pokazuju fizička svojstva koja su inferiorna ili analogna svojstvima cementa na bazi smole, zaključeno je da su biokompatibilni i bez ikakvih citotoksičnih ili genotoksičnih efekata. Bioaktivni potencijal endodontskih pasta na bazi kalcijum-silikata, zajedno sa njihovim antimikrobnim svojstvima, pojačava njihovu sposobnost da formiraju jaču fizičku barijeru koja zatvara bakterije, čime se sprečava ponovna infekcija, što je prednost njihovog korišćenja.

U suštini, upotreba cemenata na bazi kalcijum-silikata u endodonciji izuzetno je poboljšana nakon decenija razvoja, sve do sadašnjeg vremena. Ovi endodontski cementi su procvetali, pokazujuci niz korisnih svojstava; s pravom su bili odskočna daska u budućnost endodoncije, čekajući da budu dalje istraženi.

Zahvalnica: Nema

Sukob interesa: Nema

Conclusion

Endodontic root canal sealers serve the purpose of providing a fluid-tight seal, tailored such that the physical blockade imparted by them hampers the communication between the root canal space and surrounding tissues simultaneously impeding growth of micro-organisms. Hence, the outcome of a root canal obturation is significantly dependent on the physical and biological characteristics of a root canal sealer.

The dimensional stability of sealers is affected by the hydrophilic surroundings which in turn affect their physical properties. Even though calcium silicate sealers display physical properties that are inferior or analogous to those of resin-based cements, they have been concluded as biocompatible without any cytotoxic or genotoxic effects. The bioactive potentiality of calcium silicate sealers along with their antimicrobial properties amplify their ability to form a stronger physical barrier entombing the bacteria, thus preventing re-infection, adding to their advantages.

Essentially, the use of calcium silicate sealers in endodontics is at a high state of refinement, having had decades of development, up to the present time. These sealers have blossomed to display an array of advantageous properties, and rightfully, have been the stepping-stone into the future of endodontics, waiting to be explored.

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IZLOŽENOST ŽIVI U STOMATOLOGIJI: PITANJE SIGURNOSTI

EXPOSURE TO MERCURY IN DENTISTRY: A SAFETY CONCERN

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Sažetak

Uvod: *Živa spada u teške metale, a prekomerno izlaganje živi može imati toksično delovanje na nervni sistem, bubrežni sistem, reproduktivni sistem, imuni sistem i na motoričku aktivnost. U stomatologiji se živa koristi zajedno sa metalima u amalgamskim restauracijama. Istraživanja su pokazala da se živa konstantno oslobađa iz amalgamskih restauracija. Postoji kontroverza u vezi sa tim da li ova oslobođena živa ima bilo kakav toksični učinak na ljudski organizam.*
Cilj *ovog rada je da se istakne štetni efekat srebrnih amalgamskih restauracija i stvori svest o tome u javnosti.*
Zaključak: *Amalgam se još uvek često koristi kao restaurativni materijal zbog svojih odličnih fizičkih svojstava. Zbog uticaja na životnu sredinu, upotrebu žive trebalo bi smanjiti i u stomatologiji.*

Ključne reči: *živa, toksičnost, restauracije, amalgam, stomatologija*

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Abstract

Introduction: *Mercury is a heavy metal and overexposure to mercury may have a toxic effect on the nervous system, renal system, reproductive system, immune system and on motor activity. In dentistry, mercury is used along with metals in amalgam restorations. Studies have shown that mercury consistently releases from amalgam restorations. There is a controversy regarding this released mercury having any toxic effect on human beings.*
The aim: *The aim of this work was to highlight the adverse effect of silver amalgam restoration and create awareness among all.*
Conclusion: *Amalgam is still widely used as restorative material due to its excellent physical properties. Because of its environmental impact, mercury must be kept away from all users, including dentistry.*

Key words: *mercury, toxicity, restorations, amalgam, dentistry*

Uvod

Budući da je pružanje bezbedne zdravstvene zaštite veoma komplikovan proces, potrebno je uzeti u obzir mnoge faktore prilikom brige o zdravlju. Glavni cilj po pitanju sigurnosti pacijenata u stomatološkom sistemu zdravstvene zaštite tiče se smanjenja pojave neželjenih događaja, koji se mogu sprečiti adekvatnim merama prevencije takvih događaja[1].

Privatni praktičari obavljaju stomatološku negu u mnogim delovima sveta, a u javnosti se misli da mnogi stomatolozi ne znaju da prate bezbednost pacijenata tokom stomatološkog lečenja.

Živa je teški metal; smatra se da je neurotoksična i da utiče na razvoj nervnog sistema kod dece. Prekomerna izloženost živi može izazvati neurodegenerativne bolesti kod odraslih[2]. Niska koncentracija žive može uzrokovati oksidativni stres, ćelijsku citotoksičnost i toksično delovanje na bubrežni sistem, reproduktivni sistem, imuni sistem i motoričku aktivnost[3].

Cilj ovog rada je da se istakne štetni efekat srebrnih amalgamskih restauracija i stvori svest o tome u javnosti.

U stomatologiji, živa se koristi za restauracije. Dentalni amalgam je popularan za restauracije na bočnim zubima već duže vreme. Amalgam se bira zbog izuzetne čvrstine, dugostrajnosti i stabilnosti[4]. Sada se upotreba amalgama smanjuje zbog zabrinutosti oko njegovih efekata na zdravlje, zagađenje okoline, i estetske neeprihvatljivosti, ali mnogi stomatolozi širom sveta, još uvek ga upotrebljavaju[4].

Amalgam iz plombi se konstantno oslobađa u oralnu šupljinu uporedo sa ostalim metalima[5], a svojstva su joj potencirana usled prisustva žvakanja, četkanja zuba i upotrebe toplih napitaka; mada količina žive koja se na ovaj način oslobodi i njen uticaj na zdravlje su kontraverzni. Studije su kontradiktorne, i mnogi veruju da postoji preterivanje od strane naučne zajednice u pogledu amalgamskih plombi.

Rade se brojna istraživanja sa ciljem da kvantifikuju živu koja se oslobađa iz amalgamskih plombi, ispitaju njenu povezanost sa količinom žive u usnoj duplji i to da li ona prelazi sigurnosne granice. Istraživači su koristili različite metode i parametre za prikupljanje i procenu pod različitim fiziološkim uslovima, što je činilo komplikovanim[4]. Istraživanja su dokazala da se živa oslobađa iz amalgamskih ispuna i da se apsorbuje u telu[5], kao i da postoji pozitivna korelacija između broja amalgamskih restauracija i koncentracije žive u urinu, ali nije

Introduction

Provision of safe health care is a very complicated event, and many factors need to be considered during health management. The main intention of patient safety in both medical and dental health care system is to facilitate the avoidance of preventable adverse events during health management and the impact of specific adverse events[1].

Private practitioners undertake dental care in many parts of the world, and public perception is that many dental practitioners are ignorant of following patient safety during dental treatment.

Mercury is a heavy metal and considered to be neurotoxic and affect the development of Nervous system in children. Excess exposure to mercury may induce neurodegenerative diseases in adults[2]. Low concentration of mercury can cause oxidative stress, cellular cytotoxicity, and toxic effect on the renal system, reproductive system, immune system and motor activity[3].

The aim of this work is to highlight the adverse effect of silver amalgam restoration and create awareness among all.

In dentistry, mercury is used along with metals as amalgam restorations. Dental amalgam restorations are popular posterior restorative material over a long period. Amalgam is preferred for its excellent strength, durability and stability[4]. Now,the usage of amalgam restorations is decreasing due to concerns for its effecton health, environment pollution and aesthetic non-acceptability[4], however many dentists still use amalgam restorations all over the world.

Amalgam restorations constantly release mercury into the oral cavity[5], and it is enhanced by the abrasive action of chewing, brushing and ingestion of hot beverages; whether the amount of mercury released is adequate to cause health risk is controversial. Studies are contradicting, and many believe it is an overreaction of the scientific community towards dental amalgam.

Many studies are done to quantify the mercury released from dental fillings and relating the measured quantity of mercury in the oral cavity and whether it exceeds the safety limits. However, these investigators have used different methods and parameters for collection and evaluation under various physiological assumptions, thus making it complicated. Studies have proved that mercury is released from amalgam restorations and absorbed by the body[5] and also a positive correlation between the number of amalgam restorations to mercury

primećeno da živa utiče na zdravstveno stanje ispitanika koji su učestvovali u studiji. Druga slična studija takođe je pokazala značajnu razliku u nivou žive u urinu pronađenom kod dece u Nemačkoj starosti od tri godine do pet godina, sa amalgamskim ispunima i bez njih[6].

Istraživanja sprovedena na majmunima pokazala su da se živa oslobođena iz amalgamskih restauracija apsorbuje u unutrašnjim organima, kao što su bubrezi, mozak, pluća, jetra i egzokrine žlezde[7], a pokazalo se i da živa prolazi kroz krvno-moždanu i placentnu barijeru[8]. Međutim, u mnogim studijima pominje se da se živa možda neće akumulirati u tkivu na duži period i da se obično izlučuje iz organizma u roku od 55 dana[9]; takođe, veruje se da nema dokaza da živa koja se oslobađa iz amalgamskih restauracija ima štetan uticaj na javno zdravlje. Veliki broj istraživača veruje da je količina žive koja se oslobađa iz restauracija manja od trenutnog zdravstvenog standarda i da ne predstavlja nikakav zdravstveni rizik, osim alergijskih reakcija[10]. Studije su pokazale da se lokalni lihenoidni tip reakcija retko viđa kao posledica amalgamskih restauracija[11].

U mnogim delovima sveta stomatolozi zamenjuju stare amalgamske nadoknade; to je preventivna mera za smanjenje ili ograničavanje izloženosti organizma živi. Uklanjanje amalgama vrši se turbinama sa vodenim mlazom uz upotrebu sisaljki; tako se živi iznova izlažu i stomatološko osoblje i pacijenti[12]. Potrebno je strogo se pridržavati odgovarajućih higijenskih mera uz upotrebu zaštitne opreme tokom uklanjanja amalgama, kako bi se izlaganje živi minimalizovalo[12]. Mnogi sugerišu da zamena restauracija može dovesti do skidanja nepotrebne količine zdrave zubne supstance. Brojna istraživanja su pokazala da je izloženost živi nakon uklanjanja stare plombe kratkotrajna i da je izloženost ispod vrednosti trovanja živom[13]. Studije koje ukazuju na to da je stomatološko osoblje uključeno u postavljanje i uklanjanje amalgama izloženo živi u većoj meri nego pacijenti takođe izazivaju zabrinutost[14].

Sada je potražnja za amalgamskim restauracijama opala uglavnom zbog njihovog lošeg estetskog kvaliteta, a ne zbog izloženosti živi, usled nedostatka svesti šire javnosti o tome.

Uprkos kontroverzi u vezi sa izloženošću živi, amalgam se i dalje često koristi, jer amalgamska restauracija još uvek nije bila direktno povezana ni sa jednom bolešću.

concentration of urine, and no noticeable health effect found on this study group. Another similar study also showed a significant difference in urine mercury level found in German children between the age of 3 to 5 years with and without amalgam restorations[6].

Research on monkeys has shown that mercury released from the amalgam restoration is absorbed and indifferent organs such as kidney, brain lung liver and exocrine glands[7] and also showed that it crossed blood-brain and placental barrier[8]. However, many studies have mentioned that mercury may not store in tissue for a long period in the body and is usually excreted from the body within 55 days[9], and there is no evidence that mercury released from amalgam restorations has adverse health effects in the general public.

A large number of researchers believe that the amount of mercury released from restorations are for less than the current health standard and does not pose any health risk other than allergic reactions[10]. Studies indicated local lichenoid type of reactions is seen rarely to amalgam restorations[11].

Recently new in many parts of the world dentist remove old amalgam restorations as a preventive measure to reduce or limit the mercury exposure. Removal of amalgam is done by drilling with water spray and high suction, creating a situation of mercury exposure to both dental staffs as well as to the patient[12]. Strict adherence to appropriate occupational hygiene protective equipment during amalgam removal is needed to be followed to avoid mercury exposure[12]. Many suggest that restoration replacement may lead to removing the unnecessary amount of sound tooth structure prone to fracture during removal may end up in RCT. Many studies have shown that the exposure to mercury after removal of old filling is of a short duration and exposure may be below the value of mercury poisoning[13]. Studies indicating that dental staff who are involved in placement and removal of amalgam are exposed to mercury at a higher level than the patients is also a matter of concern[14].

Now the demand for amalgam restoration has come down mainly due to its poor aesthetic quality rather than mercury exposure due to the lack of awareness among the general public on mercury.

Despite the controversy over mercury exposure, amalgam is still widely used as the restoration and has not yet been linked directly to any disease process.

Istraživači se i dalje bave preispitivanjem kontroverzi zbog izvrsnih fizičkih osobina amalgamskih ispuna.

Zaključak

Odgovornost svakog pojedinca je da spreči zagađenje i zaštiti živu planetu za buduće generacije; stoga, stomatolog mora imati odgovornu ulogu. Mada su amalgamske restauracije sigurne, s obzirom na štetan uticaj žive na zemlju, njenu upotrebu bi trebalo smanjiti zbog zaštite okoline od okoline.

Zahvalnica: Nema

Sukob interesa: Nema

And also few investigators are in favour of re-evaluating this controversy due to the excellent physical property of the amalgam restorations.

Conclusion

It is the responsibility of every individual to prevent pollution and to protect the living planet for future generations; hence, the dentist needs to play a more responsible role. Considering the effect of mercury on the earth even if amalgam restorations are safe, mercury needs to be kept away from the environment.

Acknowledgement: Nil

Conflict of Interest: Nil

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UPUTSTVA AUTORIMA

Acta Stomatologica Naissi je naučni časopis Klinike za dentalnu medicinu, Medicinskog fakulteta Univerziteta u Nišu, koji publikuje radove iz svih oblasti stomatologije i srodnih medicinskih grana.

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JEZIK

Svi predati radovi za štampanje moraju biti napisani na srpskom i engleskom jeziku. Apstrakti treba da budu pripremljeni pored srpskog i na preciznom i gramatički ispravnom engleskom jeziku (US engleski stil) (videti niže). Izbegavati korišćenje latinskih izraza; ako su potrebni staviti ih u zagrade.

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Kada se radi o eksperimentima na humanom materijalu ili pacijentima, ukazati da li je primenjeni postupak u skladu sa etičkim standardima odgovornog komiteta za ljudske eksperimente ili sa Deklaracijom iz Helsinkija (1964, amandmani iz 1975 i 1983) Svetske medicinske asocijacije.

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Radovi treba da budu napisani na A4 formatu sa duplim proredom, obezbeđujući 25 mm margine. Samo jedna kopija rada treba da sadrži prezime i prvo slovo autorovog imena u gornjem desnom uglu. Broj stranica rada počinje sa naslovnom stranom kao strana 1 i nastavlja se sa redanjem.

NASLOVNA STRANA

Gornji deo naslovne strane treba da sadrži: a) puni naslov rada (velikim slovima), b) puna imena (prvo ime, srednje slovo ako je primenljivo i poslednje ime) svih autora bez akademskih titula, c) nazivi institucija i d) radni naslov od ne više od 10 reči. Na dnu naslovne strane molimo da ukažete na ime autora odgovornog za korespondenciju, sa akademskim zvanjem, poštanskom adresom, telefonskim i fax brojevima i E-mail adresom.

Sledeća strana počinje samo sa naslovom, i dalje se nastavlja sa tekstom. Tekst treba da bude podeljen u delove sa naslovima: uvod, pacijenti/materijal i metod rada, rezultati, diskusija, zaključci, zahvalnost i literatura. Za tabele, figure (slike) i legende vidi deo Tabele i Figure.

Poželjno je da se koriste reči prikladne za indeksiranje i pretraživanje. Ako takvih reči nema u naslovu, poželjno je da se naslovu doda podnaslov.

Ako je članak u prethodnoj verziji bio izložen na skupu u vidu usmenog saopštenja (pod istim ili sličnim naslovom) podatak o tome treba da bude naveden u posebnoj napomeni pri dnu prve strane članka.

APSTRAKT I KLJUČNE REČI

Originalni radovi moraju da sadrže strukturni apstrakt od 250 reči, podeljenih na sledeća 4 paragrafa:

Uvod: opisuje problem o kome se radi u radu

Materijali i metode: opisuje kako je istraživanje sprovedeno

Rezultati: opisuje primarno rezultate

Zaključak(ci): saopštenje autora o zaključcima proisteklim iz rezultata, i implicira njihovu kliničku primenljivost.

Strukturni apstrakti nisu potrebni kod uvodnika i pisma. Ispod apstrakta stoje ključne reci i to tri do pet. Ključne reči mogu biti uzete samo iz Medical Subjects Headings (MeSH).

Apstrakt treba da bude preveden i na engleski jezik (US style), sa naslovom, imenima autora, institucija i ključnim recima.

Za pisanje radova u formi prikaza slučaja, treba uraditi strukturirani apstrakt, na sledeći način:

Osnova problema: (opisati problem ili pojavu u nekoliko rečenica),

Metode rada: (opisati kako je obrađen i dijagnostikovan pacijent i koja bolest ili poremećaj je u pitanju),

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Zaključak: (1-3 rečenice koja može da služi i kao opis celog postupka koji je rađen i napisan u radu).

TABELE I FIGURE

Svaka tabela sa jasnim naslovom na srpskom i engleskom treba da bude otkucana sa duplim proredom na odvojenom papiru. Obeležiti brojevima tabele jednu za drugom kako nailaze posle prvog navođenja u tekstu (obeležavaju se arapskim brojevima). Dati svakoj kolumni kratko ili skraćeno zaglavlje. Staviti objašnjenja u legendama svih nestandardnih skraćenica korišćenih u tabeli. Za jedinice i merenja vidi odeljak niže. Ne koristiti unutrašnje horizontalne i vertikalne linije. Staviti sve tabele na kraju vaseg fajla. Uvek odvojiti posebne kolumne upotrebom tabulatora, a ne upotrebom razmaknice, tabele moraju biti u tekst formatu.

Linijski prikazani dijagrami i ilustracije (fotografije, fotomikrografije itd.), trebaju biti osmišljene kao figure. Oni takođe treba da budu smešteni na odvojenom listu papira i numerisani jedan za drugim arapskim brojevima u saglasnosti sa prvim koji je citiran u tekstu. Figure treba da budu profesionalno nacrtane i fotografisane. Svaka figura treba da bude etiketirana pozadi ukazujući broj figure, prezime i prvo slovo imena autora, i vrh figure. Fotografije treba da se daju u dva primerka. Kolor fotografije ce se štampati samo u dogovoru sa urednikom ili ako autor sam snosi troškove. Fotomikrografije moraju imati obeleženu unutrasnju razmeru, i simbole, i strelice ili slova treba da su u kontrastu sa pozadinom. Na fotografijama pacijenata mora se sakriti identitet, osim ako se pacijenti u pismenoj formi slože sa objavljivanjem njihovih fotografija sa identitetom. Ukoliko ste pozajmili ili već publikovali negde fotografije priložite i pismenu dozvolu za reprodukovanje. Naslovi i detaljna objašnjenja fotografija treba da budu data u legendama. Ako su korišćeni simboli, strelice, brojevi ili slova za identifikaciju delova slike objasniti svaku jasno u legendi.

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Priznanja i zahvalnosti prethode literaturi specificirajući generalnu podršku kao i odeljenje i ime šefa odeljenja, priznanja tehničkoj pomoći i konačno finansijskoj i materijalnoj pomoći. Navesti naziv i broj projekta, odnosno naziv programa u okviru koga je nastao članak i naziv institucije koja je finansirala projekat, u posebnoj napomeni pri dnu prve strane članka.

LITERATURA

Autori su odgovorni za tačnost literaturnih podataka. Reference treba da budu na posebnom listu i delu odmah iza teksta. Samo reference bitne za studiju mogu biti citirane. Kada je citiranje literature neophodno primeniti Vankuver stil. Na posebnom listu se navode citati referenci koji su označeni rednim brojevima po redosledu u kome se pojavljuju u tekstu i svaki citat odgovara brojevima koji sadrži navedenu referencu. Primeri tačnih oblika referenci :

RADOVI U ČASOPISIMA

1. Standardni članak u časopisu (lista svih autora, ali ako je broj veći od šest citirati tri i dodati et al): Glass DA, Mellonig JT, Towle HJ. Histologic evaluation of bone inductive proteins complexed with coralline hydroxyapatite in an extraskeletal site of the rat. J Periodontol 1989; 60:121-125.

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The title page should contain: a) the full title of the article (in upper case); b) first name, middle initial, and last name of each author without the academic degree; c) name of department and institutional affiliation for each author; d) running title of no more than 10 characters. At the bottom of the page, please indicate the name, academic degree and address (including E-mail, telephone and fax number) of the author responsible for correspondence.

It is recommendable to use the words appropriate for indexing and searching. If there are not such words in the title, then subtitle should be added.

If the article in the previous version has been orally exposed (under the same or similar title), such information should be separately noted at the bottom of the first page ofthe article.

Abstract and Key words

All original abstracts should be submitted with a structured abstract, consisting of no more than 250 words, and the following 4 paragraphs:

Background: Describes the problem being addressed.

Material and Methods: Describes how the study was performed.

Results: Describes the primary results.

Conclusion: Reports what authors have concluded from these results, and notes their clinical implications.

Key words: A maximum of 5 key words drawn from MeSH documentation. Abstract should be translated into English (US style), with the title, name(s) of author(s), institutional affiliation and key words.

To write papers in the form of a case report, a structured abstract should be done, as follows:

Basis of the problem: (describe the problem or occurrence in a few sentences),

Methods of work: (describe how the patient was treated and diagnosed and which disease or disorder is in question),

Results: (describe the results of the work and the final outcome),

Conclusion: (1-3 sentences that can also serve as a description of the whole procedure that was done and written in the paper).

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TABLES AND FIGURES

Each table with a brief title (on Serbian and English) should be typed double-spaced on a separate sheet of paper. Number tables consecutively (with Arabic numbers) in the order of their first citation in the text. Give each column a short or abbreviated heading. Place explanations in legends of all nonstandard abbreviations which are used in table. For units and measurements see paragraph below. Do not use internal horizontal and vertical rules. Place all tables at the end of your file. Always separate the individual columns using tabulators, not using space bar, i.e. tables must be in text format. Line drawings diagrams and halftone illustrations (photographs, photomicrographs, etc.) should be designated as figures. They should be listed on separate sheet and numbered consecutively with Arabic numerals according to the order in which they have been first cited in the text. Figures should be professionally drawn (not simply typewritten) and photographed. Each figure should be labeled on its back indicated the number of the figure, last name and the first letter of the author, and the topside of the figure. Photographs should be supplied in two copies. Color photographs are published only in case if author himself bears expenses. Photomicrographs must have internal scale markers, and symbols, arrows or letters should contrast with the background. Photographs of patients must conceal their identity unless patients approve the publishing of the photograph in written form. If you borrow or use already published photographs please submit a written permission for reproduction. Permission is not required for the documents in the public domain. Figures will not be returned unless requested. Captions and detailed explanations of the figures should be given in the legends. If symbols, arrows, numbers, or letters are used to identify parts of the figure identity and explain each one clearly in the legend.

ACKNOWLEDGEMENTS

Acknowledgements are positioned before the reference list specifying general support by department chairman, acknowledgements of technical as well as financial and material support. Acknowledgement includes the title and number of the project, i.e. the title of the programme within which the article was composed and the title of the institution funding the project; it should be written as a separate notification at the bottom ofthe first page of the article.

REFERENCES

Authors are responsible for accuracy of literature data. References should be listed in a separate section immediately following the text. Only references important for the study should be cited. It is necessary to apply Vancouver style. Citations are numbered consecutively in the order in which they appear in the text and each citation corresponds to a numbered reference containing publication information about the source cited in the reference list at the end of the publication. Examples of references are given bellow:

Journals:

1. Standard journal reference. (Note: list all authors if six or less; when seven or more, list only first three and add et al): Glass DA, Mellonig JT, Towle HJ. Histologic evaluation of bone inductive proteins complexed with coralline hydroxyapatite in an extraskeletal site of the rat. J Periodontol 1989;60:121-125.

2. Corporate author: Federation Dentaire Internationale. Technical Report No.28. Guidelines for antibiotic prophylaxis of infective endocarditis for dental patients with cardiovascular disease. Int Dent J 1987;37:235.

3. No author given: Coffee drinking and cancer of the pancreas (editorial). BMJ 1981;283:628.

4. Volume with supplement: Magni R, Rossoni G, Berti R, BN52021 protect guinea pig from heart anaphylaxis. Pharmacol Res Commun 1988; 20 Suppl 5:75-8.

Books or other monographs:

5. Personal author(s): Tullman JJ, Redding SW. Systemic Disease in Dental Treatment. St. Louis: The CV Mosby Company; 1983:1-5.

6. Chapter in a book: Rees TD. Dental management of the medically compromised patient. In: McDonald RE, Hurt WC, Gilmore HW, Middleton RA, eds. Current Therapy in Dentistry, vol. 7. St. Louis: The CV Mosby Company; 1980:3-7.

7. Dissertations and thesis: Teerakapong A. Langerhans Cells in human periodontally healthy and diseased gingiva. (Thesis). Houston, TX: University of Texas; 1987.92 p.

Other published material:

8. Newspaper article: Shaffer RA.Advances in chemistry are starting to unlock mysteries ofthe brain. The Washington Post 1989Ang 7; Sect.A:2 (col. 5).

References - electronic quotations:

9. Online journals without volume and page information. Berlin JA, Antman EM. Advantages and limitations of metaanalytic regressions of clinical trials data. Online J Curr Clin Trials (serial online). June 4; doc 134. Accessed July 20, 2000.

10. Online journals with volume and page information. Fowler EB, Breault LG. Ridge augmentation with a folded acellular dermal matrix allograft: A case Report. J Contemp Dent Pract (serial online). 2001;2(3):31-40. Available from: Procter&Gamble Company, Cincinnat, OH. Accessed December 15, 2001.

11. World Wide Web.Centers for Disease Control and Prevention. Preventing emerging infectious diseases: Addressing the problem of antimicrobial resistance. Available at: http://www.cdc.gov/ncidod/emergplan/antiresist/. Accessed November 5, 2001.

UNITS OF MEASUREMENTS

All measurements should be reported in terms of the International System of Units (SI)

ABBREVIATIONS AND SYMBOLS

Avoid abbreviations in the text but whenever possible use standard abbreviations. However, if nonstandard abbreviations are used, the full term of which and abbreviation stands for should precede its first use in text. Names of symptoms, signs and diseases, as well as anatomic and histologic characteristics cannot be abbreviated.

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