Stom Glas S COBISS. SR-ID 8417026 UDC 616.31 ISSN 0039-1743

STOMATOLOŠKI GLASNIK SRBIJE

SERBIAN DENTAL JOURNAL

Vol. 67 • Number 4 • October-December 2020

http://www.stomglas.org.rs

Stom Glas S COBISS. SR-ID 8417026 UDC 616.31 ISSN 0039-1743

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www.stomglas.org.rs

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Časopis izlazi četiri puta godišnje.
The journal is published four times a year.

Cene pretplate za 2020. godinu su: 2.400 dinara za pojedince, 4.800 dinara za ustanove i 50 evra za čitaoce van Srbije. Pretplata se može uplatiti Srpskom lekarskom društvu, ul. Džordža Vašingtona 19, 11000 Beograd, na tekući račun 205-8041-21 (Komercijalna banka AD, Beograd), sa pozivom na broj 04/1710, imenom časopisa i godinom za koju se pretplata uplaćuje.
Sve dodatne informacije mogu se dobiti na telefon 011/3245-149.

Subscriptions prices for the year 2020 are: 2,400 RSD for individuals, 4,800 RSD for institutions, and 50 Euros for readers outside Serbia. Subscription order: Serbian Medical Society, Džordža Vašingtona 19, 11000 Belgrade; details of payment: bank account number 205-8041-21 (Komercijalna banka AD, Belgrade), invoice number 04/1710, with the name of the journal and the year for which you subscribe; beneficiary: Serbian Medical Society.
For further information, please contact us on stomglas@bvcom.net.

Finansijsku podršku izdavanju časopisa pruža Ministarstvo prosvete, nauke i tehnološkog razvoja Republike Srbije i Stomatološka komora Srbije.

The publishing of the Journal is financially supported by the Ministry of Education, Science and Technological Development of the Republic of Serbia and Serbian Dental Chamber.

ISSN 0039-1743
ISSN Online 1452-3701
COBISS. SR-ID 8417026
UDC 616.31

www.stomglas.org.rs

Stomatološki glasnik Srbije
Serbian Dental Journal

Izdavač Srpsko lekarsko društvo
Publisher Serbian Medical Society

Osnivač Stomatološka sekcija Srpskog lekarskog društva
Founder Dental Section of the Serbian Medical Society

Prelom teksta i priprema za štampu
Layout & Prepress
Jasmina Živković

Štampa
Printed by
JP „Službeni glasnik", Beograd

Broj primeraka
Number of copies
300

Contents / Sadržaj

Serbian Dental Journal, vol. 67, N° 4, 2020

„Šta vredi galopirati, ako se
krećemo u pogrešnom pravcu“
Radjard Kipling

Naša „aktuelna“ svakodnevica i „zlatno doba“ koje živimo je u stvari „iščašena normalnost“ i pogled u stvarnost kroz zatamnjene naočare u maglovitom danu. Život u ikonografiji laži i primitivizaciji „svega postojećeg“ je najoriginalnije ruganje svemu što je normalno, moralno i etično. Agresija laži i „medijska imitacija“ aktuelnog trenutka su u stvari ogoljena metodologija „društvene lobotomije“ zaodenute primitivnom patetikom i lažnim moralisanjem, koja pri tome uspešno zasejava „korov nemorala“ i dodatno pospešuje „kolaps dostojanstva“.

Ovakav društveni kontekst i revija prostakluka na svim nivoima su osnovna premisa „filozofije besmisla“ koja nadkriljuje našu realnost. Naša svakodnevica je „osenčena jezom“ gde svaki dan počinje i završava se strahom, a medijski linč i svakojako zastrašivanje su vrhunski domet i najveća „vrednost“ onih koji nam oblikuju život. Sluganski odnos aktuelnih ZP individua (čitaj podoban, poltron, poslušan) prema onima koji su ih odabrali, i bahat odnos prema onima kojima bi trebalo da služe, najčešće vode ka kolapsu dostojanstva i obično se završavaju trajnim posrnućem i tonjenjem u najdublji ambis. Otrovne informacije, manipulacije i pogane laži često su ubojitije i efikasnije nego teška bolest, samoća „akutni virus“ (o kome ne znamo ništa) ili mržnja o kojoj možda znamo sve, ali nas uvek iznenadi svojom oštrinom i žestinom.

U društvu razorenih institucija i bahatog odnosa onih na funkcijama, protagonisti su uglavnom „mali, neobrazovani i nestručni“ (odabrani prema partijskim a ne stručnim i moralnim kvalitetima). U takvoj realnosti svaka normalnost je prilično izvitoperena, a put u posrnuće i najdublji ambis sasvim izvesni. Zato je i moguće da se važne odluke za sopstveni narod donose na osnovu „nerelevantnih podataka“ i „posebne statistike“ i na osnovu „izopštene“ istine. Lažni narativ o napretku i poštenju i lažno moralisanje su aktuelna formula za „provizorijum“ i „kontinuirano vanredno stanje“ koje živimo u simbiozi sa virusom, ali i „nesuvisni“ izgovor za civilizacijski sunovrat jednog naroda.

Da bismo izbegli potonuće iz bezizlaza kojim se krećemo, neophodno je biti slobodan, čestit, hrabar, svoj, iskren i nadasve odgovoran i prema sebi i prema drugima. Važno je iskoračiti iz „društvene kaljuge“ i prostotu i laž zameniti odgovornošću, istinom i neodustajanjem od borbe za svetlo i izlaz iz „besprizorne praznine“ našeg beznađa.

Unutrašnja hrabrost, odgovornost, naučna čestitost i stručnost su najsvetliji zadaci u borbi za bolje sutra i izbegavanje puta u nestajanje.

Urednički komentar ću završiti citatom velikog i slobodoumnog Borislava Pekića: „Treba gledati pravo, jer da se htelo gledati iza sebe, imali bismo oči na potiljku“, jer je to jedini put u ispravno i najsvrsishodniji iskorak iz vremena gde su laži „duboko cementirane“ u fasadu trenutka suspendovanog razuma.

Prof. dr Slavoljub Živković

ORIGINAL ARTICLE
ORIGINALNI RAD
DOI: https://doi.org/10.2298/SGS2004185A
UDC: 616.314-77

Biological complications in patients with implant-supported dental restorations

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SUMMARY

Introduction Biological complications are the most common type of complications around dental implants. They appear in two forms, peri-mucositis and peri-implantitis. The aim of our research was to analyze the above-mentioned complications regarding the time elapsed from implantation and implant loading, as well as regarding the type of dental restoration.

Material and methods 18 patients with self-reported complications were examined at the Department of Periodontology and Oral medicine, School of Dental medicine, University of Belgrade. Each patient filled an anamnestic questionnaire. Clinical examination, including photographic and radiographic documentation have been performed.

Results Clinical examination included 18 patients and 97 implants in total (70% female patients and 30% male patients). The average time elapsed from implants placement was 7.5 years and the average from final dental restoration was 7 years. Periodontitis was diagnosed in 85% of the patients. Complications were more common among the patients with cement-retained restorations.

Conclusions Due to the limitation of our study, we can assume that periodontal disease and cement-retained restorations are the risk factors for genesis and development of the complications around dental implants. The results of our study are in consent with data found in the literature, but in order to confirm these results it is necessary to perform analysis on a larger sample and with longer follow-up.

Keywords: dental implants; peri-implantitis; peri-mucositis

INTRODUCTION

Biological complications are the most common complications around dental implants. They present as *peri-implant mucositis* and *peri-implantitis*. New classification of periodontal and peri-implant diseases and conditions was the result of the meeting of The American Academy of Periodontology and The European Federation of Periodontology in 2017. Finally, new and uniform definitions of peri-implant health, peri-implant mucositis and peri-implantitis were adopted [1].

- The main criterion for distinction between healthy and inflammatory mucosa is bleeding on probing (BoP).
- The main criterion for distinction between peri-mucositis and peri-implantitis is deterioration in the bone supporting the dental implant.

In the period of healing, after implant placement, soft tissues and hard tissues are forming. The formation of a new bone on the implant surface is the process called *osseointegration*. The development of masticatory mucosa and connective tissue around the new implant, and formation of peri-implant mucosa is the process known as *mucointegration* [2].

Peri-implant health is characterized by the absence of the clinical signs of the inflammation in the peri-implant complex. It is marked as absence of swelling, redness and bleeding on probation. Hence, there is no precisely defined range of probing depths that is compatible with peri-implant health, because peri-implant probing depth depends on thickness of the peri-implant tissues, type and position of the implant, as well as the type of dental replacement. In addition, peri-implant health can exist around implants with reduced bone support. It can be established after successful treatment of peri-implantitis.

The characteristics of the peri-implant tissues in health are:

- The absence of clinical signs of inflammation
- The absence of bleeding or suppuration on mild probation
- The absence of increased probing depth
- The absence of bone loss

We can diagnose peri-mucositis with first discrete signs of soft tissue inflammation, but without peri-implant bone loss. The common cause is accumulated dental plaque around the neck of a dental implant. Dental plaque in peri-implant region is generally the most common cause of peri-mucositis.

The main clinical sign of peri-mucositis is bleeding on mild probation, but we can also notice redness and swelling. Sometimes, there can be increased probing depth due to swelling. It is important to point out that the main

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inflammatory process is located exclusively in epithelial tissue, while the junction between connective tissue and epithelium is not affected.

There is evidence that biofilm is the main etiological factor of peri-mucositis. It is proven that adequate plaque control therapy reduce inflammation. That means that in peri-mucositis changes are most probably reversible.

- Clinical signs of peri-mucositis:
- Bleeding or suppuration on mild provocation
- Absence of bone loss

Inadequate peri-mucositis therapy leads to the spread of inflammation from soft to hard tissues. There is apical migration of pathologically changed masticatory epithelium and bone resorption. Defect in alveolar bone is developing, known as peri-implant pocket that can be diagnosed with probing or radiography. Afterword we can put diagnosis of peri-implantitis. The peri-implantitis is characterized by inflammation of peri-implant soft tissues and progressive bone loss. All clinical signs of infections are presented (redness, swelling) as well as bleeding and suppuration on probing.

The main etiological factor is the same as in peri-mucositis, bacterial infection and the influence of dental plaque microorganisms. The connection between peri-implantitis and accumulated dental plaque is confirmed by many studies that showed in patients with inadequate oral hygiene and rare control checkups lay higher risk for the development of the inflammation of soft tissue and bone around the implant. The frequency of this disease is about 20% in regard to the patients, and about 10% in regard to the implants [3].

Clinical signs of peri-implantitis:

- Bleeding and/or suppuration on mild provocation
- Increased probing depth on each control
- Probing depth ≥ 6mm
- Bone loss (bone level ≥ 3mm apically from the most coronal bone level)

There is clear evidence that patients with positive medical history of the periodontal disease have increased risk for the development of peri-implantitis. Risk factors that are important are some systemic disorders like diabetes, osteoporosis, bad habits (inadequate oral hygiene and smoking), and iatrogenic factors (inadequately planned oral and prosthodontic procedures that lead to many mistakes that can result with occlusal overload, that latter accelerate marginal bone loss and lead to contact loss between bone and implant neck) [4].

It is important to pay attention to risk factors during preparation, planning, patient motivation, implantation and dental restoration, since consequences may be very delicate. Also it is very important to have frequent and regular oral hygiene checkups of patients with implants and also treatment evaluation [5].

The bone destruction has faster pattern around dental implant than around natural tooth, hence peri-implantitis progression can be very aggressive. It is of a great importance to mark probing depth values measured around newly placed implant, as well as to make control radiograms, since they will represent referent values for discovering pathological changes in early stadium [4].

MATERIAL AND METHODS

In the period of October 2019 to March 2020 at the Department of Periodontology and Oral medicine at the Faculty of Dental medicine at the University of Belgrade, 18 patients with dental implant difficulties were examined.

In each patient, anamnestic questionnaire was filled, clinical examination was performed, and clinical photos and control radiograms were taken, in order to set up adequate diagnosis and treatment.

Anamnestic data:

- General health condition (presence of systemic disorders)
- History of periodontal diseases
- Medication consumption
- Allergies
- Bad habits – cigarettes consumption (if the patient is smoker- data about quantity and frequency) and parafunctions
- Frequency and quality of oral hygiene (how often, methods, resources)

Data about frequency of check-ups and changes in general health condition after implant placement were also collected.

Data from previous medical reports:

- Time elapsed from implant placement
- Type of implant
- Implant dimensions
- Implant placement protocol (immediate, early, delayed, monophasic, biphasic)
- Implant loading protocol (immediate, late, early, conventional)
- Augmentation (if it was performed and when-before, during or after implant placement)
- Abutment type (screw/cement; platform switched/non platform switched)
- Time elapsed from dental restoration completion
- Type of dental restoration
- Type of restoration retention (cement retained, screw retained)

Clinical examination included the following parameters:

- Probing depth (PD), the measured distance from the free end of the gingival margin to the bottom of the peri-implant space.
- Attached gingiva level (AGL), the measured distance from the top of the implant to the bottom of peri-implant space
- Bleeding on probing (BoP), bleeding 30s after probing, with score 1 if the bleeding is present and score 0 if there is no bleeding at all
- Silness-Loe plaque index, defined by scores from 0 to 3 based on recording dental plaque around dental implant
- Modified gingival index (GI), score 0 – no signs of inflammation, 1-mild inflammation, minimal color

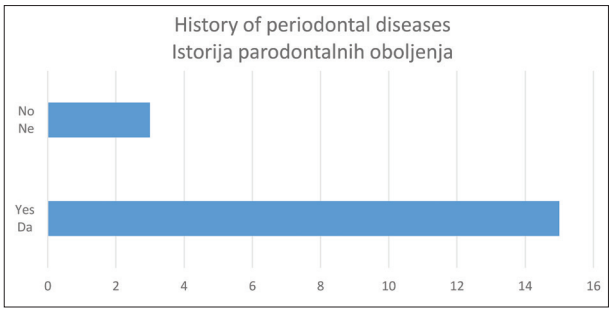

Figure 1. Ratio of patients with/without history of periodontal diseases
Slika 1. Odnos pacijenata sa prethodnom istorijom parodontalnih oboljenja i bez nje

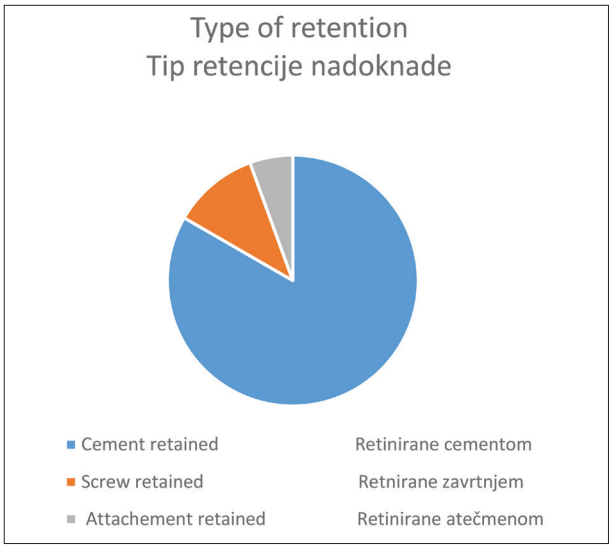

Figure 2. Type of restoration retention
Slika 2. Tipovi retencije protetskih nadoknada

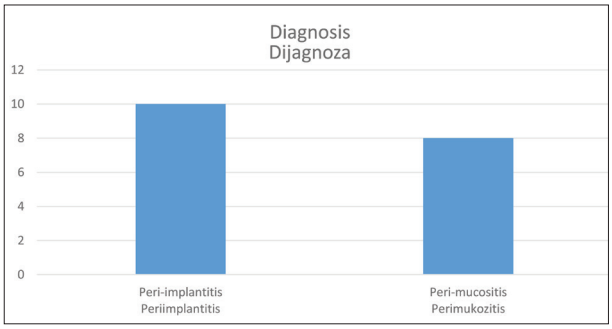

Figure 3. Distribution of complications
Slika 3. Zastupljenost komplikacija

change, minimal swelling, absence of BoP, 2-mild inflammation, redness, swelling, BoP, 3- modern inflammation, modern redness, severe swelling, ulceration, spontaneous bleeding
- Gingival recession (GR) on the buccal side – the measured connection implant-abutment distance
- Width of the keratinized gingiva (WKG), the measured distance from the free gingival margin to the mucogingival junction

The measuring was performed with periodontal probe in 4 points around each implant.

RESULTS

Our research included 18 patients, 13 females and 5 males. Clinical examination was performed around 97 implants and data were collected.

One third of patients (33%) were cigarettes consumers, defined as heavy smokers (10 cigarettes or more per day). 85% of all patients affirm having history of periodontal disease, while 15% clinically have not presented any problem with periodontal health (Figure 1).

Findings from anamnestic questionnaires revealed that more than half of the patients had some systemic disease: 56% of the patients stated systemic disease (40% hypertension, 30% asthma, 10% rheumatic disease, 10% migraine, 10% other disease). While discussing their habits associated with mechanical plaque control, all patients confirmed brushing at least 2 per day, while only 50% of them were using additional tools for interdental hygiene. 20% of the patients used Waterpik device. None of the patients have experienced any changes of the general health condition after implant placement.

While summarizing data about surgical and prosthodontics rehabilitation of the patients, we found out that average time elapsed from implants placement was 7.5 years, while average time elapsed from completion of dental restoration was 7 years. Out of 18 examined patients 15 had cement retained implant restoration, 2 screw retained and only one patient had attachment retained restoration (Figure 2). Data acquired by clinical examination around implants are summed in Table 1.

The diagnoses were based on anamnesis, clinical examination and additional diagnostic procedures. Data are presented in Figure 3.

According to diagnosis, specific treatment plan was prepared:

- In patients with peri-mucositis:
  - In 88% causal therapy was indicated
  - In 12% beside causal therapy, additional therapy was necessary

- In patients with peri-implantitis:
  - In 40% explantation and another implant placement
  - In 30% surgical therapy
  - In 20% causal therapy with antibiotics
  - In 10% causal therapy without antibiotics

DISCUSSION

Peri-implant disease develops gradually. It starts with peri-mucositis, when inflammation appears in peri-implant soft tissues, but without changes on supporting alveolar bone. It is assumed that with progression of untreated peri-mucositis, the inflammation spreads from mucosa to connective tissue and bone, leading to peri-implantitis [4].

The main etiological factor is bacterial infection i.e. bad oral hygiene that causes plaque accumulation around the implant. Peri-implant diseases were more common among patients without adequate oral hygiene, or usage

Table 1. Clinical parameters around implants
Tabela 1. Klinički parametri oko implantata

BoP around implant (mean value) KNP* oko implantata (srednja vrednost)	0.65 (65%)	
PD around implant (mean value) NPE* oko implantata (srednja vrednost)	3.8 mm	
WKG around implant (mean value) ŠKG* oko implantata (srednja vrednost)	1.8 mm	
Restoration Vrsta protetske nadoknade	Single crown Pojedinačna kruna	1
	Fixed dental prosthesis Fiksni protetski rad (most)	27
	Removable dental prosthesis	5
Loading protocol Protokol opterećenja	Immediate Imedijatno	5%
	Early Rano	0%
	Delayed Odloženo	95%
Retention Retencija	Cement retained Retencija cementom	83%
	Screw retained Retencija zavrtnjem	11%
	Attachment retained Retencija atačmentom	6%
Augmentation Augmentacija	Prior Pre ugradnje	8%
	Simultaneously Tokom ugradnje	5%
	Non Bez augmentacije	87%
Implant system Sistem implantata	Straumann AstratechDentsply Biohorizons Bredent	

BoP – bleeding on probing, PD – probing depth, WKG - width of keratinized gingiva
KNP – krvarenje na provokaciju, NPE – nivo pripojnog epitela, ŠKG – širina keratinizovane gingive

Inadequately planned dental restorations (usually full arch bridge or cantilever bridge) with unstable position or inadequate number of placed implants cannot enable good stabilization, and usually lead to occlusal overload and inadequate pressure transmission from implants to supporting bone. That causes loss of connection between implant and marginal bone and development of peri-implantitis. Poorly manufactured restoration (enlarged, inadequately planned) can make difficult to maintain oral hygiene and indirectly influence development of peri-implant disease. The choice of retention of the restoration is also very important since it is known that biological complications are more often around restoration retained with cements. The reason for that is probably accidentally extruded cement in subgingival region. Considering that our research was conducted on a limited sample, the presence of complications was more common in patients with cement-retained restorations and with extended restorations.

Many studies were focused on research of incidence and prevalence of the peri-implant disease. Hence, they showed different results. The reason for that is the lack of consensus about definition of peri-implant disorder, which significantly complicates the comparison of different studies. With publication of a new classification, this deficiency was solved [1, 3].

of indicated hygiene tools for elimination of dental plaque around implants. It is necessary to support interdental hygiene in the implant retained dental restorations with interdental toothbrushes like 'Superfloss' etc. Inadequate oral hygiene maintenance is in correlation with infrequent professional plaque control (at least 2 per year). It is noticed that patients with implant retained dental restorations that don't come to regular checkups, are more prone to develop any kind of complications [5].

Many studies showed correlation of peri-implantitis with history or presence of periodontal disease. The frequency of peri-implantitis (PD ≥ 5mm, with BP, and bone loss >2mm annual) was higher in patients with anamnestic data of positive periodontal disease history. One study showed that the therapy of peri-implantitis required longer time in patients with positive periodontal disease history than in healthy patients. Also, complications of peri-mucositis into peri-implantitis were more common in patients with present periodontal disease than in those without positive periodontal disease history [6]. One of the important periodontal measures that were in relation with peri-implant complications was the width of keratinized gingiva, i.e. existence of functional attached gingiva.

Iatrogenic factors, as inadequate dental restoration, can also influence the development of peri-implantitis.

CONCLUSION

Within this study, on a limited sample, we analyzed patients with implant retained dental restoration completed mostly 7 years ago. In that period we can expect the development of complications. The existence of periodontal diseases was significant risk factor for the development of peri-implant complications. This statement is in consent with data found in literature. Besides, low levels of WAG potential can influence development and progression of complications. Also, many restorations were retained with cement so it was reasonable to expect complication if cement is accidentally extruded apically.

In prevention of peri-implant complication, it is important to have adequate treatment plan, previous treatment of periodontal diseases, adequate restoration, and maintain the results with frequent control checkups. In order to confirm results from our research, it is necessary to have larger sample.

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Received: 26.08.2020 • Accepted: 11.12.2020

Biološke komplikacije kod pacijenata sa implantno nošenim zubnim nadoknadama

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KRATAK SADRŽAJ

Uvod Najčešće komplikacije oko dentalnih implantata su biološke komplikacije koje se javljaju u dve forme – kao peri-mukozitis i kao peri-implantitis. Cilj ovog rada bio je analiza navedenih komplikacija u odnosu na vreme proteklo od ugradnje i opterećenja implantata, kao i u odnosu na tip protetske rekonstrukcije.

Materijal i metode Na Klinici za parodontologiju i oralnu medicinu Stomatološkog fakulteta Univerziteta u Beogradu pregledano je 18 pacijenata koji su se javili zbog tegoba oko dentalnih implantata. Kod svakog pacijenta ispunjen je anamnestički upitnik, obavljen je klinički pregled, napravljene su kliničke fotografije, kao i kontrolni rendgenski snimci.

Rezultati Kliničkim pregledom obuhvaćeno je 18 pacijenata i 97 implantata (od toga je 70% ugrađenih implantata kod ženskih, a 30% kod muških ispitanika). Prosečno vreme od ugradnje implantata iznosilo je 7,5 godina, a prosečno vreme od predaje protetskog rada 7 godina. Kod 85% ispitanika ustanovljeno je prisustvo parodontitisa. Komplikacije su bile češće kod nadoknada retiniranih cementom.

Zaključci Imajući u vidu ograničenja ove studije, može se pretpostaviti da su prisustvo parodontalnog oboljenja i nadonkade retinirane cementom faktor rizika za nastanak i razvoj komplikacija oko dentalnih implantata. Rezultati ove studije su u saglasnosti s podacima iz literature. Potrebani su veći uzorak i duže vreme praćenja kako bi navedeni nalazi bili potvrđeni.

Ključne reči: dentalni implantat; peri-implantitis; peri-mukozitis

UVOD

Najčešće komplikacije oko dentalnih implantata su biološke komplikacije koje se predstavljaju kao peri-implantatni mukozitis i peri-implantitis. Na zajedničkoj radionici Američke akademije za parodontologiju i Evropske federacije za parodontologiju, koja je održana 2017. godine, oformljena je nova klasifikacija parodontalnih i peri-implantnih oboljenja i stanja i predstavljene su uniformne definicije peri-implantnog zdravlja, peri-implantnog mukozitisa i peri-implantitisa [1].

- Osnovni kriterijum za razlikovanje zdrave od inflamirane mukoze je krvarenje na provokaciju.
- Osnovni kriterijum za razlikovanje peri-mukozitisa i peri-implantitisa je gubitak kosti oko implantata.

Meka i čvrsta peri-implantna tkiva se formiraju posle ugradnje implantata, u toku zarastanja rane. Na površini implantata dolazi do stvaranja nove kosti i taj proces se naziva oseointegracija, a izgradnjom pripojnog epitela i vezivnog tkiva u kontaktu sa delovima implantata stvara se peri-implantna mukoza i taj proces se naziva mukointegracija [2].

Peri-implantno zdravlje se jednostavno može definisati kao odstustvo inflamacije u peri-implantnom kompleksu. Karakteriše se izostankom kliničkih znakova zapaljenja, kao što su otok, crvenilo i krvarenje na provokaciju. Međutim, ne postoji tačno definisan raspon dubine sondiranja koji je kompatibilan sa zdravljem peri-implantnih tkiva, zato što dubina peri-implantnog sulkusa zavisi od debljine okolnih tkiva, tipa i pozicije implantata, kao i vrste protetskog rada. Pored toga, peri-implantno zdravlje može postojati i oko implantata koji imaju slabiju koštanu potporu, tj. može se uspostaviti nakon uspešne terapije peri-implantitisa.

Klinički znaci peri-implantnog zdravlja:

- Odsustvo kliničkih znakova inflamacije
- Odsustvo krvarenja ili supuracije na blagu provokaciju
- Nema povećanja dubine sondiranja u odnosu na prethodna ispitivanja
- Nema gubitka kosti

Peri-mukozitis se može dijagnostikovati već kada se uoče diskretni znaci inflamacije mekog tkiva, ali bez gubitka potporne peri-implantne kosti. Najčešće se oko vrata implantata uočava akumulirani dentalni plak, ujedno i glavni uzročnik peri-mukozitisa.

Glavna klinička karakteristika peri-mukozitisa je krvarenje na blagu provokaciju, mada se mogu pojaviti i drugi znaci inflamacije kao što su crvenilo i otok. Nekada se, zbog otoka, kod peri-mukozitisa može javiti povećana dubina sondiranja. Važno je istaći da je inflamatorna komponenta locirana isključivo u epitelu, dok vezivno-tkivni pripoj nije zahvaćen.

Postoje dokazi da je biofilm glavni etiološki faktor peri-mukozitisa. Takođe, evidentno je da se zapaljenje povlači nakon adekvatne kontrole plaka, što znači da su promene kod peri-mukozitisa najverovatnije reverzibilne prirode.

Klinički znaci peri-mukozitisa:

- Krvarenje ili supuracija na blagu provokaciju
- Nema gubitka kosti

Ukoliko izostane pravovremena terapija peri-mukozitisa, inflamacija se širi sa mekih na čvrsta tkiva. Dolazi do apikalne migracije patološki izmenjenog pripojnog epitela, kao i do resorpcije koštanog tkiva i stvara se defekt u alveolarnoj kosti – peri-implantni džep, koji se može dijagnostikovati sondiranjem ili radiografijom. Tada se postavlja dijagnoza peri-implantitisa. Karakteriše se inflamacijom peri-implantne mukoze i progresivnim gubitkom potporne kosti. Prisutni su svi klinički znaci infekcije (crvenilo, otok) i pojava krvarenja i/ili supuracije prilikom sondiranja.

Kao i kod peri-mukozitisa, glavni etiološki faktor peri-implantitisa jeste bakterijska infekcija, odnosno uticaj mikroorganizama dentalnog plaka. Povezanost peri-implantitisa i akumuliranog dentalnog plaka potvrđena je studijama koje su pokazale da kod pacijenata sa nedovoljnom ili slabom oralnom higijenom, koji ne dolaze redovno na kontrolne preglede, postoji

veći rizik za pojavu inflamacije u mekom tkivu i kosti oko implantata. Učestalost ovog oboljenja iznosi oko 20% na nivou pacijenata i oko 10% na nivou implantata [3].

Klinički znaci peri-implantitisa:

- Krvarenje i/ili supuracija na blagu provokaciju
- Povećanje dubine sondiranja u odnosu na prethodnu kontrolu
- Dubina sondiranja ≥ 6 mm
- Gubitak kosti (nivo kosti ≥ 3 mm apikalnije od najkoronarnijeg nivoa kosti okolnih struktura)

Postoje jasni dokazi da je kod pacijenata koji su ranije imali parodontitis povećan rizik za razvoj peri-implantitisa. Pored toga, utvrđeni su još neki potencijalni faktori rizika, kao što su određena sistemska oboljenja (dijabetes, osteoporoza), loše navike (nedovoljna oralna higijena i pušenje), ali i jatrogeni faktori (loše planiranje, kako hirurške procedure, tako i protetske nadoknade, dovodi do niza grešaka koje mogu rezultirati preteranim okluzalnim opterećenjem koje ubrzava gubitak marginalne kosti i dovodi do gubitka kontakta kosti sa vratom implantata) [4].

S obzirom na delikatnost mogućih posledica, faktorima rizika se posvećuje posebna pažnja tokom pripreme i planiranja, motivacije pacijenta, zatim samog hirurškog zahvata – implantacije, kao i tokom izrade zubne nadonade. Od posebnog su značaja i stalna kontrola oralne higijene pacijenta s implantatima kao i procena uspeha terapije [5].

Razaranje kosti oko implantata je znatno brže nego oko prirodnih zuba, te je progresija peri-implantitisa veoma agresivna. Od velike je važnosti da se zabeleže vrednosti dubine sondiranja oko tek ugrađenih implantata, kao i da se naprave kontrolni radiogrami, jer će oni predstavljati referentnu vrednost za otkrivanje patoloških promena u ranom stadijumu bolesti [4].

MATERIJAL I METODE

U periodu od oktobra 2019. do marta 2020. godine na Klinici za parodontologiju i oralnu medicinu Stomatološkog fakulteta Univerziteta u Beogradu pregledano je 18 pacijenata koji su se javili zbog tegoba oko dentalnih implantata.

Kod svakog pacijenta, ispunjen je anamnestički upitnik, obavljen je klinički pregled, napravljene su kliničke fotografije i kontrolni rendgenski snimci u cilju postavljanja adekvatne dijagnoze i izrade plana terapije.

Anamnestički su od pacijenata prikupljeni podaci o:

- opštem zdravstvenom stanju (postojanju sistemskih oboljenja)
- istoriji parodontalnih oboljenja
- upotrebi lekova
- postojanju alergija
- prisustvu loših navika – prvenstveno konzumiranje cigareta (ukoliko je pacijent pušač – podaci o količini cigareta koje konzumira i koliko dugo) i prisustvu parafunkcija
- učestalosti i načinu održavanja oralne higijene (koliko puta dnevno, koja sredstva koristi)

Od pacijenata su prikupljani i podaci o tome koliko često dolaze na kontrolne preglede, kao i da li je došlo do promene zdravstvenog stanja nakon ugradnje implantata.

Takođe, ekstrahovani su podaci iz prethodnih implantoloških izveštaja o:

- vremenu proteklom od ugradnje implantata
- tipu implantata
- dimenzijama implantata
- protokolu ugradnje (imedijatna/rana/odložena, zatim jednofazna/dvofazna)
- protokolu opterećenja (imedijatno/rano/konvencionalno)
- augmentaciji (ukoliko je sprovedena, vreme: pre, u toku ili nakon ugradnje)
- tipu abatmenta (retiniran zavrtnjem/cementom; *platform switched/non platform switched*)
- vremenu proteklom od predaje protetske nadoknade
- tipu protetske nadoknade i
- vrsti retencije nadoknade (cement/šraf)

Kliničkim pregledom obuhvaćeni su sledeći klinički parametri:

- Dubina sondiranja (DS), mereno rastojanje u milimetrima od ivice gingive do dna peri-implantnog prostora.
- Nivo pripojnog epitela (NPE), mereno rastojanje u milimetrima od konekcije tj. vrha implantata do dna peri-implantnog prostora.
- Krvarenje na provokaciju (KNP), postojanje krvarenja 30 s. nakon sondiranja, dodeljivanjem ocene 1 ukoliko je krvarenje prisutno, a ocene 0 ukoliko nije prisutno.
- Plak indeks Silness-Loe, kojim se dodeljuju ocene od 0 do 3 u odnosu na prisustvo dentalnog plaka oko dentalnog implantata.
- Modifikovani gingivalni indeks (GI) (Lobene, 1986): s ocenama 0 – bez znakova inflamacije; 1 – umerena inflamacija, minimalna promena boje, minimalan otok, nema KNP; 2 – umerena inflamacija, crvenilo, otok, KNP; 3 – izražena inflamacija, markirano crvenilo, jasno uočljiv otok, ulceracije, tendencija ka spontanom krvarenju.
- Gingivalna recesija (GR) na bukalnoj strani – mereno rastojanje u milimetrima od veze implantat–abutment.
- Širina keratinizovane gingive (ŠKG) – mereno rastojanje u milimetrima od ivice gingive do mukogingivalne linije.

Merenja su izvršena primenom parodontalne sonde u četiri tačke oko svakog implantata.

REZULTATI

U toku istraživanja pregledano je 18 pacijenata, 13 žena i pet muškaraca. Kliničkim pregledom potrebni parametri su ispitivani za oko 97 implantata (od toga je 70% ugrađenih implantata kod ženskih, a 30% kod muških ispitanika).

Trećina pacijenata (33%) navela je da svakodnevno konzumira 10 cigareta ili više, a 85% pacijenata već ima istoriju parodontalnih bolesti, dok 15% nema (Slika 1).

Sumirajući rezultate ekstrahovane iz anamnestičkih upitnika, zanimljivo je izdvojiti da je kod preko polovine pacijenata bilo prisutno neko od sistemskih oboljenja: 56% pacijenata (40% hipertenzija, 30% astma, 10% reumatska oboljenja, 10% migrena, 10% ostala oboljenja). Razgovarajući o navikama vezanim za mehaničku kontrolu plaka, svi ispitanici naveli su da najmanje dva puta dnevno koriste četkicu i pastu za održavanje oralne higijene, dok samo 50% pacijenata navodi da pored osnovnih, koristi i sredstva za interdentalnu higijenu, a 20% pacijenata navodi da svakodnevno koristi i Waterpik aparat kao dodatno sredstvo za održavanje oralne higijene.

Ni kod jednog pacijenta nije došlo do promene zdravstvenog stanja posle ugradnje implantata.

Sumirajući dostupne izveštaje o hirurško-protetskoj rehabilitaciji pacijenata, ustanovljeno je da je prosečno vreme proteklo od ugradnje iznosilo 7,5 godina, dok je prosečno vreme proteklo od predaje protetskog rada 7 godina. Od 18 ispitanih pacijenata sa implantatima 15 je imalo protetsku nadoknadu retiniranu cementom, 2 pacijenta zavrtnjem retiniranu a samo 1 pacijent protetsku nadoknadu retiniranu atačmenom (Slika 2).

Podaci dobijeni kliničkim pregledom oko implantata sumirani su u Tabeli 1.

Na osnovu anamneze, kliničkog pregleda i dopunskih dijagnostičkih metoda kod pacijenata je uspostavljena dijagnoza, koja je takođe prikazana grafički (Slika 3).

Na osnovu postavljene dijagnoze, postavljen je sledeći plan terapije.

- Kod pacijenata sa perimukozitisom:
  - u 88% slučajeva indikovana je kauzalna terapija.
  - u 12% slučajeva, pored kauzalne, neophodno je bilo sprovesti i dodatnu terapiju.

- Kod pacijenata sa peri-implantitisom:
  - u 40% slučajeva – eksplantacija i ugradnja implantata na drugom mestu
  - u 30% slučajeva – hirurška terapija
  - u 20% slučajeva – kauzalna terapija uz primenu antibiotika
  - u 10% slučajeva – kauzalna terapija

DISKUSIJA

Razvoj peri-implantnih oboljenja je postepen, ali nelinearnog toka. Promene najčešće počinju peri-mukozitisom, kada u peri-implantnoj mukozi dolazi do inflamacije, ali bez promena na potpornoj kosti. Međutim, pretpostavlja se da progresijom (nelečenog) peri-mukozitisa inflamacija iz mukoze prelazi na vezivno tkivo i kost, dovodeći do peri-implantitisa [4].

Smatra se da je glavni etiološki faktor bakterijska infekcija, tj. loša oralna higijena koja uzrokuje akumulaciju plaka oko implantata. Nalaz peri-implantnih oboljenja češći je kod pacijenata koji nisu održavali adekvatnu oralnu higijenu niti su koristili preporučena sredstva za uklanjanje naslaga oko implantatno nošenih nadoknada. Naime, oko protetskih radova na implantatima neophodna je primena i sredstava za održavanje interdentalne higijene – interdentalne četkice, „*Superfloss*“ itd. Loše održavanje oralne higijene je uglavnom u korelaciji sa neredovnim dolaskom na kontrolne preglede (barem dva puta godišnje), a samim tim i neredovnom profesionalnom kontrolom plaka. Uočeno je da pacijenti koji su zbrinuti nadoknadama na implantatima a ne dolaze na redovne kontrolne preglede, imaju veću učestalost komplikacija [5].

Brojne studije dokazale su vezu peri-implantitisa sa istorijom ili trenutnim postojanjem parodontalnih oboljenja kod pacijenata. Pokazano je da je učestalost peri-implantitisa (DS ≥ 5 mm, prisutno KNP, gubitak kosti > 0, 2 mm godišnje) veća kod pacijenata koji su anamnestički navodili prethodno postojanje parodontalnih oboljenja. Jednom studijom dokazano je da terapija peri-implantitisa zahteva više vremena kod pacijenata sa istorijom parodontitisa nego kod zdravih. Takođe, verovatnije je da će peri-mukozitis progredirati u peri-implantitis kod pacijenata sa parodontitisom nego kod onih koji anamnestički ne navode prethodna parodontalna oboljenja [6]. Još jedan od parodontalnih parametara koji se dovodi u vezu s razvojem peri-implantnih komplikacija jeste širina keratinizovane gingive, odnosno postojanje zone funkcionalne pripojne gingive.

Jatrogeni faktori, kao što je neadekvatna izrada protetskog rada, takođe mogu uticati na razvoj peri-implantitisa. Loše isplanirane protetske nadoknade (uglavnom semicirkularni ili viseći mostovi) kojima pozicija ili broj ugrađenih implantata ne pružaju odgovarajuću potporu, vremenom dovode do okluzalnog preopterećenja i loše transmisije pritiska preko implantata na potpornu kost. Tako dolazi do gubitka veze između implantata i marginalne kosti i razvoja peri-implantitisa. Loše izrađene nadoknade (predimenzionirane, neadekvatno izmodelovane) mogu otežati održavanje oralne higijene i indirektno pospešiti razvoj peri-implantnih oboljenja. Izbor retencije nadoknade je takođe važan, jer je utvrđeno da se biološke komplikacije češće javljaju oko nadoknada koje su retinirane cementima. Razlog za to jeste mogućnost zaostatka cementa subgingivalno. Na ograničenom uzorku pacijenata u našoj studiji, prisutvo komplikacija bilo je učestalije kod nadoknada retiniranih cementom, kao i kod predimenzioniranih nadoknada.

Mnogobrojne studije bavile su se određivanjem incidence i prevalence peri-implantnih oboljenja, međutim pokazivale su različite rezultate. Razlog za to jeste nedostatak konsenzusa o definicijama peri-implantnih oboljenja, što značajno otežava međusobno upoređivanje različitih studija. S publikovanjem nove klasifikacije, ovaj nedostatak je prevaziđen [1, 3].

ZAKLJUČAK

U okviru ove studije, na ograničenom uzorku pacijenata, analizirani su pacijenti kojima je implantatno-protetska terapija okončana, u najvećem broju slučajeva, pre sedam godina, što predstavlja period u kome se prva komplikacija i očekuje.

Postojanje parodontalnog oboljenja pokazalo se kao značajan faktor rizika za nastanak i razvoj peri-implantnih komplikacija. Ovaj zaključak je u saglasnosti s literaturnim podacima.

Osim toga, niske srednje vrednosti širina keratinizovane gingive potencijalno mogu imati uticaja na nastanak i progresiju komplikacija.

Takođe, imajući u vidu da je najveći broj nadoknada naših pacijenata cementom retiniran, logično je očekivati veću stopu komplikacija usled potencijalnog zaostatka cementa.

Za prevenciju peri-implantnih komplikacija od ključnog značaja su adekvatan plan terapije i prethodna sanacija parodontalnog oboljenja, korektna implantatno-protetska rehabilitacija i održavanje postignutih rezultata redovnim kontrolnim pregledima. Potrebne su studije na većem uzorku kako bi se potvrdili nalazi ovog istraživanja.

REVIEW ARTICLE
PREGLED LITERATURE
DOI: https://doi.org/10.2298/SGS2004193M
UDC: 616.314-77

Basics of navigation implant prosthetics planning

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SUMMARY

Due to the development of digital technologies, the modern concept of prosthetic-guided implantology is based on non-invasive surgical and restorative techniques. Computer-aided planning, computer-guided workup and computer-guided surgery have largely ensured the predictability of the therapeutic outcome. This is supported by research data related to the frequency of implant therapy, according to which in the first half of 2020 there was an increase of 9.7%. However, anatomical limitations remain a challenge for the implant team. The most common problem related to implant therapy in edentulous patients is limited edentulous space in one or more spatial planes. Improving the design of surgical guides facilitates implantation in spatially limited and complex cases. By introducing interactive computed tomography into the field of implantology, a three-dimensional approach to every aspect of planning and implantation has become possible.

Keywords: prosthetic-guided implantology; computer-aided planning; computer-guided surgery

INTRODUCTION

Positioning implants according to the requirements of prosthetics, while respecting the capacity of bone structures and anatomical risk zones, requires detailed analysis and radiological visualization of a three-dimensional implant projection [1]. In order to ensure the optimal position of the implant, the procedure of "backward planning" is used in practice, i.e. implant placement according to prosthetic needs [2]. As the part of pre-surgical treatment, a clinician takes medical history, performs clinical examination, makes diagnosis, and plans the type and design of prosthetic restoration with an emphasis on the transmission of occlusal forces, as it dictates the number, type and position of implants. When creating a treatment plan, the clinician pays special attention to the quality of the remaining hard and soft tissue, which directs surgical positioning of the implants and subsequent bone remodeling. Clinical examination requires detailed extraoral, intraoral and radiographic analysis.

It is known that radiological diagnostics is the basis for planning implant therapy. *The American Academy of Oral and Maxillofacial Radiology* recommends conventional radiological methods as a starting point for planning [3]. Orthopantomography is used as part of the initial assessment of the patient, while intraoral radiograms are an additional element for a more accurate presentation of a particular segment. The main disadvantages of orthopantomography are: image deformation, which is 20-30% vertically and as much as 60-70% horizontally, supraposition of anatomical structures in the frontal region, lack of "third dimension", as well as lack of information on bone quality [4, 5]. This implies that the precise creation of a surgical plan is not possible with two-dimensional radiographic methods and requires the use of cone beam computed tomography (Cone Beam Computer Tomography-CBCT). One of the most significant achievements in CBCT technology is interactive computed tomography (ICT) [6]. Most therapists agree that a correct diagnosis is the foundation of therapeutic success. In implant prosthetics, the foundations are defined by the precision of implant position. Ideal position of the implant is precisely planned spatial orientation in relation to the adjacent anatomical structures and / or the adjacent implant. Data on the comparison of the precision of the implant placement using conventional method of free-hand surgery and computer-guided implantation are available in the literature [7–9]. Table 1 shows the results of the research by Sun et al. [7].

According to the results, to meet these requirements, different static and dynamic navigation systems are available to clinicians. Due to the high costs of dynamic navigation, surgical templates are more widely used in practice as the main representatives of statically guided implant placement. Guides can be categorized according to different parameters. Based on the supporting tissues, they can be supported by teeth, bone or soft tissue structures, determined for toothless fields or edentulous jaws, depending on the indication [10]. The second division, based on materials for making surgical guides, refers mainly to self-bonding / light-curing acrylate resins, although they can be made of an alloy of CoCr and titanium. The third division of the guide refers to the design and can be open or closed [11, 12].

The aim of this paper is to present chronologically procedural planning steps in implant prosthetics with reference to the pre-prosthetic aspect of planning.

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Table 1. Deviations of the longitudinal and angular position of implants comparing free hand guided and computer guided surgery
Tabela 1. Odstupanja uzdužnog i ugaonog položaja implantata ugrađenih tradicionalnom i kompjuterski navođenom hirurgijom

	Jaw Vilica	Longitudinal error (mm) Greška u vertikalnom položaju (mm) Mean ± SD Aritmetička sredina ± SD	Angular error (degree) Greška u angulaciji (stepeni ugla) Mean ± SD Aritmetička sredina ± SD
Eksperimental group (computer guided surgey) Eksperimentalna grupa (kompjuterski navođena hirurgija)	Maxilla Gornja	0.63 ± 0.24	3.07 ± 0.99
	Mandible Donja	0.88 ± 0.22	3.59 ± 0.99
Control group (traditional free hand surgery) Kontrolna grupa (tradicionalna hirurgija vođena slobodnom rukom hirurga)	Maxilla Gornja	1.21 ± 0.09	6.02 ± 0.04
	Mandible Donja	1.63 ± 0.17	6.22 ± 0.09

(CONE BEAM COMPUTERIZED TOMOGRAPHY) CBCT

CBCT provides the possibility of volumetric imaging of bones and preoperative collection of large amounts of information, of which the most important in toothless and edentulous jaws are: available bone volume and quality, position of anatomical structures and the presence of pathological changes [13]. Having in mind the oldest ethical principle of ancient medicine "primum non nocere (do not harm)", with the advent of modern methods of radiography, and in connection with the radiation dose, the so-called ALARA principle (As Low As Reasonable Achievable) was introduced, i.e. the application of the lowest possible radiation dose to obtain the characteristics of anatomical structures of interest [13]. The American Academy of Periodontology (AAP), by consensus in 2017, made recommendations for the rational use of CBCT radiography in oral and maxillofacial surgery [13]. As CBCT images have a high diagnostic capacity, the radiation dose for CBCT imaging per jaw is equal to 2 to 10 orthopantomograms. There are different sizes of fields of view depending on the indication. In the basic categorization, three types of fields of view are distinguished: limited (small), medium and large. The large field of view, which covers a wider anatomical region, requires a higher dose of radiation, creating an image of lower resolution. The limited field of view captures a small region, up to 15 cm, applying a lower effective dose of radiation, and provides a higher resolution image [14]. Reducing the radiation dose is achieved by choosing smaller recording volume, i.e. smaller FOV (Field Of View) [14]. Bornstein et al. [14] provided data for effective radiation doses (Table 2). Table 2 is provided with modifications from "Cone Beam Computed Tomography in Implant Dentistry: A Systematic Review Focusing on Guidelines, Indications, and Radiation Dose Risks" [14].

ANALOG AND DIGITAL PLANNING

The preoperative segment of analog planning begins with the development of a diagnostic cast (Figure 1). Preliminary tooth placement on the diagnostic cast can be realized through the use of a set of fabricated PMMA teeth (set up) or by modeling the teeth in wax (wax up). The choice is a matter of the clinician's choice. However, there is a recommendation that factory-made teeth be used in edentulous patients, while wax modeling is easier to implement in cases of minor edentulousness [15]. Preliminary tooth placement on diagnostic model is the basis for making a radiological guide.

In a narrower sense, digital planning encompasses the domain of software tools of CBCT and CAD-CAM machines. The image created during the volumetric recording of the anatomical structures of the face and jaws is processed in the software program of the device in Digital Imaging and

Table 2. Values of effective dose of CBCT radiation and panoramic radiography
Tabela 2. Vrednosti efektivnih doza zračenja izraženih u mikrosivertima za CBCT i panoramsko radiografisanje

Study Studija	Radiographic technique Radiografska terapija	Field of view Polje pregleda	Effective dose Efektivna doza (μSv)
Theodorakou et al. 125 ref	CBCT **(< 40 cm²)**	4 × 4 cm²	32
Pauwels et al. Ref 127	CBCT **(< 40 cm²)**	5 × 3.7 cm²	40 40
Suomalainen et al. REF 119	CBCT **(< 40 cm²)**	6 × 6 cm²	91
Jeoung et al.	CBCT	8 × 5 cm²	83
Pauwelset al.	CBCT **(40–100 cm²)**	10 × 5 cm²	54
Koivisto et al.	CBCT **(40–100 cm²)**	8 × 8 cm²	153
Qu et al.	CBCT **(40–100 cm²)**	8 × 8 cm² Mala/velika/ standardna doza zracenja	30/306/197
Ludlow et al	CBCT **(40–100 cm²)**	16 × 6 cm²	74 74
Ludlow et al.	CBCT **(> 100 cm²)**	10 × 10 cm²	283
Pauwels et al.	CBCT (> 100 cm²)	15 × 15 cm²	194 194
Okano et al.	CBCT (> 100 cm²)	15 × 15 cm²	511
Ludlow et al.	CBCT (> 100 cm²)	20 × 20 cm²	1073
Theodorakou et al.	Panoramic Ortopan tomografija	15 × 10 cm²	6
Silva et al.	Panoramic Ortopan tomografija	15 × 11 cm²	10
Carrafiello et al.	Panoramic Ortopan tomografija	15 × 23 cm²	50
Grünheid et al.	Panoramic Ortopan tomografija	15 × 30 cm²	21.5

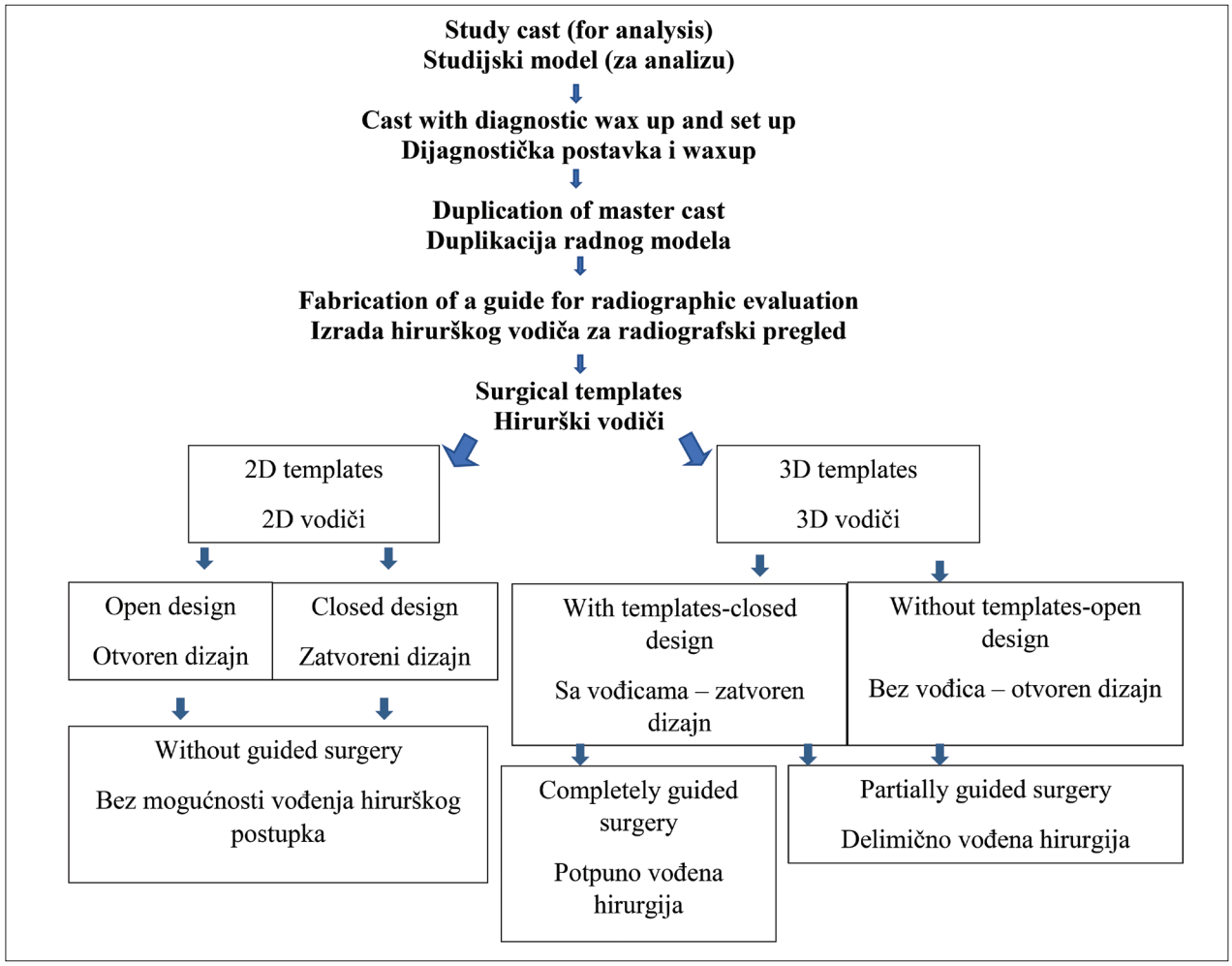

Figure 1. Chronological procedures from analog planning to implant surgery.
Slika 1. Postupci prikazani hronološkim redom od analognog planiranja to implantacije

Communications in Medicine (DICOM) format [16]. The data thus obtained are combined with the data on the modeled wax-up. An important segment of planning includes the analysis of intermaxillary relations. With the introduction of the so-called Bari techniques the transfer of intermaxillary and occlusal relationships in all three spatial planes is enabled, and that in a digital environment. The method is based on the fabrication of a prosthetic stent that aims to transmit occlusal relations recorded by a temporary diagnostic prosthesis within the final prosthetic restoration on the implants [17]. Based on the above data, the therapist has clearly defined requirements for the prosthetic component and approaches virtual implant position planning including the length, diameter, inclination and depth of the implant. This is followed by the design of a surgical guide. Technological procedures for making surgical guides are divided into additive and subtractive (stereolithographic) methods [15].

RADIOLOGICAL GUIDE FOR SUCCESSFULLY DESIGNED SURGICAL TEMPLATE

The purpose of radiological guide is to enable the transfer of information about the position of the crown part of future restoration to the CBCT image. Good guide stability on supporting tissues is mandatory. Any imprecise fit can result in the conductor moving during radiography, resulting in displacement of the reference object. If the surgical guide is based on the information obtained that way, the clinician will find difficult to place the surgical guide and the entire procedure can be compromised [15]. In order to fulfill radiological visualization of prosthetic part of the dental compensation successfully, various radiopaque materials can be put within the radiographic guide. Numerous authors [15, 18] have compared opacity of the materials most commonly used for that purpose. The research results have shown that the biggest opacity has barium sulfate ($BaSO_4$), gutta-percha and the materials used for fixing the crowns based on zinc oxide. The radiological stent is most often made on a base of a master cast. The templates are made of hard vacuum foil of 1 mm in diameter. When it comes to edentulous patients, the old denture, if retained well on the supporting tissues, can also be used for the purpose of the radiographic guide. It is advised that adhesives should be applied on the mucosal side of the prosthesis before radiography as well. Perforations, in which the radiopaque materials are placed, are formed within acrylic teeth [19, 20]. The other option is fabricating the master cast based on complete denture.

The master cast represents the working cast for making the radiographic guide, most often of the vacuum foil [15].

DYNAMIC AND STATIC NAVIGATION

Dynamic navigation is computer-guided implant placement. This method refers to applying the intraoperative navigational system which constructional solution is usually based on the optical tools for measuring the position of the implants. Some of the currently available on the market are: Blue Sky Bio Plan Software, Fusion Nobel Biocare, CoDiagnostic software, M-Guide, DentalWings, Simplant Software, SMOP Swisseda etc. As indications for applying the dynamic navigation, Block and Emery have named mostly all those situations where relative or absolute restrictions to applying the surgical guide are possible: the patients with limited mouth opening, the implantation in hardly accessible regions of the side segments of the jaws, where mesiodistal dimension of toothless space does not allow placing the static guide due to the cylinder width [21]. The clinician follows on the computer screen moving of the surgical drill during the intervention [22]. The dynamic navigation advantages are: the cost-effectiveness procedure for the patient, the possibility of constant irrigation of the surgical area and more possibilities for the clinician to lead the surgical drill intraoperatively. The high expenses of tools are stated as the main disadvantage. The dynamic navigation is not advised as a part of the edentulous patient treatment [21]. The static navigation is based on applying the surgical template. The main function of the template is to enable transferring the analogous or digital therapeutic plan into three-dimensional intraoral surrounding. The vacuum foils, identical to those applied to the radiological templates, were used as the first guides. Such guide provides the insight into the future crown position, so, according to that, the surgeon can map the implantation place. Further implantation course is guided by the clinician and depends on his experience and skills.

Speaking of the contemporary static template, the implantation of virtually planned installation of the implants can be realized through semi-guided or fully guided and depending on the design of the sleeves (cylinders) which are integrated into the guide [15, 23, 24]. Fully guided surgery refers to applying the surgical template which design provides precisely planned position, angulation, diameter and implants' depth. The template is placed in the patient's mouth during the entire surgical procedure, not allowing the therapist to intraoperatively lead the drill to any other position apart from the one defined by the cylinders integrated within the guide. Due to the properties of the materials from which the templates are made (polymethyl methacrylate or metal alloys), as well as sleeves, which can be made from metal alloys or zirconium, rigidity of the guide is insured and therefore the greater safety for the clinician [15]. In order to provide greater safety during the procedure, the template should be retained well on the supporting tissues. This is also the reason why it is not justified to use poorly retained and old complete denture as the surgical template.

The term of semi-guided surgery refers to the templates that are in favor of the therapist only during the first implantation phases. These guides use cylindrical sleeves that can accept the first, and perhaps second surgical drill. When there is no enough space in the mesiodistal direction, the preference should be given to the sleeves for the semi-guided surgery since the cylinders have narrower diameter compared to fully guided surgery sleeves [15].

Fully guided approach has the advantage in cases of weak quality of the bone, considering that the light arm movement during the placement of the implants can result in greater deviation for the semi-guided surgery [24]. Considering the advantages and disadvantages of the both systems, the authors [24] who have analyzed the difference between fully and semi-guided surgery precision, have concluded that the statistically significant difference in accuracy is evident only in the position of the apical third of implants. The advantages of the fully guided surgery are: lower risk of anatomic structure damages, performing the surgical procedure without opening the flap (flapless surgery) and therefore shortening the postsurgical period of recovery, the possibility of individualization of the abutment design according to the surgical guide position etc [15]. However, even if the concept of applying the surgical guide considers simple protocol, these solutions contain certain disadvantages. Major ones are: insufficient surgical area visibility, impossibility of applying the surgical guide in case of the little inter-occlusal space, the risk of damaging or contaminating the drill when it passes through sleeve [23]. In order to compensate these disadvantages, nowadays the method of placing the implants applying the open guide has been considerably developing (TWIN-Guide®, 2Ingis, Brussels, Belgium). The open design compensates the mentioned disadvantages of the closed system of the guide, and it is compatible with all dental implant systems. Besides, surgical procedure is performed with continuous irrigation of the osteotomy site. The guide uses the pattern of the open frame, giving the clinician the guidelines for the implantation in the form of two reference cylindrical bushings places on the vestibular and oral sides of the surgical guide [23, 25].

CONCLUSION

Ideal position of the implants implies the spatial orientation in relation to adjacent anatomic structures and/or adjacent implants. Wrong positioning can have functional, technical, biological or esthetic consequences. Using computer-guided implantology provides predictability of the therapeutic results. Although the results of the wrong implant placement can lead to clinically manifested complications only in a few months or years, the first difficulties can arise even in the phase of impression taking when the deviation from the implant angulation prevents correct placing of the transfers. Wide ranges of surgical templates that differ according to the design and their purpose have enabled the clinicians to induce their purpose in the complex cases as well. Yet, the restrictions to the concept of the fully guided implantology are related

to its application only in the case of partially edentulous patients. The implant-prosthetic rehabilitation of the edentulous patients is realized by conventional methods partly or entirely guided by the surgeon.

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Received: 18.8.2020 • Accepted: 2.11.2020

Osnove planiranja navigacione implantat-protetike

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KRATAK SADRŽAJ

Zahvaljujući razvoju digitalnih tehnologija, savremeni koncept protetskom nadoknadom vođene implantologije bazira se na neinvazivnim hirurškim i restaurativnim tehnikama. Kompjutersko planiranje i kompjuterski vođena ugradnja implantata su u velikoj meri obezbedili predvidivost terapijskog ishoda. U prilog tome govore podaci istraživanja vezanih za učestalost implantološke terapije prema kojima je u prvoj polovini 2020. godine ostvaren porast za 9,7%. Međutim, anatomska ograničenja i dalje predstavljaju izazov za implantološki tim. Najčešći problem u vezi sa implantološkom terapijom kod krezubih pacijenata jeste ograničen bezubi prostor u jednoj ili više prostornih ravni. Unapređenjem dizajna hirurških vodiča olakšana je implantacija u prostorno ograničenim i kompleksnim slučajevima. Uvođenjem interaktivne kompjuterizovane tomografije u sferu implantologije, omogućen je trodimenzionalni pristup svakom aspektu planiranja i implantacije.

Ključne reči: protetskom nadoknadom vođena implantologija; kompjutersko planiranje; kompjuterski vođena hirurgija

UVOD

Pozicioniranje implantata prema zahtevima protetike, uz poštovanje kapaciteta koštanih struktura i anatomskih zona rizika, zahteva detaljnu analizu i radiološku vizuelizaciju trodimenzionalne projekcije moguće pozicije implantata [1]. Da bi se osigurala optimalna pozicija implantata, u praksi se koristi procedura „planiranja pozicije implantata unazad" (*eng. backward planning*), odnosno ugradnja implantata prema protetskim potrebama [2]. U okviru predhirurškog tretmana, kliničar uzima anamnezu, vrši klinički pregled, postavlja dijagnozu i planira vrstu zubne nadoknade sa akcentom na način prenošenja okluzalnih sila i dizajn same nadoknade, s obzirom na to da to diktira broj, vrstu i položaj implantata. Prilikom izrade plana terapije terapeut posebnu pažnju posvećuje kvalitetu preostalog tvrdog i mekog tkiva koji usmeravaju hirurško pozicioniranje implantata i naknadnu remodelaciju kosti.

Klinički pregled zahteva detaljnu ekstraoralnu, intraoralnu i radiografsku analizu.

Poznato je da radiološka dijagnostika predstavlja osnovu u planiranju implantološke terapije.

The American academy of oral and maxillofacial radiology preporučuje konvencionalne radiološke metode kao polaznu osnovu planiranja [3]. Ortopantomografski snimak se koristi u okviru inicijalne procene pacijenta, dok intraoralni radiogrami predstavljaju dopunski element radi preciznijeg prikaza određenog segmenta. Kao glavni nedostaci ortopantomografije navode se: deformacija slike, koja po vertikali iznosi 20-30%, a po horizontali čak 60-70%, suprapozicija anatomskih struktura u frontalnoj regiji, nedostatak „treće dimenzije", kao i izostanak informacija o kvalitetu kosti [4, 5].

Navedeno implicira da precizno kreiranje hirurškog plana nije moguće uz dvodimenzionalne radiografske metode i da zahteva primenu računarske tomografije konusnog snopa (*eng. Cone Beam Computer Tomography).* Jedno od najznačajnijih dostignuća u tehnologiji CBCT je interaktivna računarska tomografija (*eng. interactive computed tomography – ICT*) [6].

Većina terapeuta slaze se sa konstatacijom da je pravilna dijagnoza temelj terapijskog uspeha. U implantat-protetici temelji su definisani preciznošću položaja implantata. Idealna pozicija implantata podrazumeva precizno isplaniranu prostornu orijentaciju u odnosu na susedne anatomske strukture i/ili susedni implantat. U literaturi su dostupni podaci o poređenju preciznosti položaja implantata ugrađenih konvencionalnom metodom vođenja rukom hirurga (*eng. free-hand surgery*) i kompjuterski vođenom ugradnjom [7, 8, 9]. Prema rezultatima ovih istraživanja, postoji statistički značajna razlika u preciznosti položaja. Tabela 1 prikazuje rezultate istraživanja Sana i saradnika [7].

Radi ostvarivanja zahteva preciznosti, kliničarima su na raspolaganju različiti sistemi statičke i dinamičke navigacije. Zbog velikih troškova dinamičke navigacije, veću primenu u praksi nalaze hirurški vodiči kao glavni predstavnici statički vođene ugradnje implantata.

Vodiči mogu biti kategorizovani prema različitim parametrima. Na osnovu nosećih tkiva, mogu biti podržani zubima, koštanim ili mekotkivnim strukturama, određeni za krezuba polja ili bezube vilice, zavisno od indikacije [10]. Druga podela, zasnovana na materijalima za izradu hirurških vodiča, odnosi se uglavnom na samovezujuće/svetlosnopolimerizujuće akrilatne smole, iako mogu biti od legure CoCr i titana. Treća podela vodiča odnosi se na dizajn i mogu biti otvoreni ili zatvoreni [11, 12].

Cilj rada je da prikaže hronološki procedurane korake planiranja u implantat-protetici sa osvrtom na predprotetski aspekt planiranja.

CBCT

CBCT daje mogućnost volumetrijskog snimanja kostiju i preoperativnog prikupljanja velikih količina informacija, od kojih su kod krezubih i bezubih vilica najznačajniji: raspoloživi volumen i kvalitet kosti, položaj anatomskih struktura i prisustvo patoloških promena [13]. Imajući u vidu najstariji etički princip antičke medicine *„primum non nocere"*, sa pojavom savremenih metoda radiografisanja, a u vezi sa dozom zračenja, uveden je takozvani ALARA princip (*eng. As Low As Resonable Achievable*), odnosno primena najmanje moguće doze zračenja uzimajući u obzir karakteristike anatomskih struktura koje želimo da prikažemo [13]. Američka akademija za parodontologiju (AAP) konsenzusom je iz 2017. godine dala preporuke za racionalnu primenu CBCT radiografije u oralnoj i maksilofacijalnoj hirurgiji [10].

Kako CBCT slike imaju visok dijagnostički kapacitet, doza radijacije za CBCT snimak po vilici je kao za 2 do 10 ortopana. Postoje različite veličine vidnih polja zavisno od indikacije. U osnovnoj kategorizaciji razlikuju se tri tipa vidnog polja: ograničeno (malo), srednje i veliko. Veliko vidno polje, koje obuhvata širu anatomsku regiju, zahteva veću dozu zračenja, stvarajući sliku manje rezolucije. Ograničeno vidno polje zahvata malu regiju, do 15 cm, primenjujući manju efektivnu dozu zračenja, i pruža sliku veće rezolucije [14]. Smanjenje doze zračenja postiže se izborom manjeg volumena snimanja, tj. manjeg FOV (*eng. Field Of View*) [14]. Autori [14] su dali podatke za efektivne doze zračenja (Tabela 2).

Preuzeto uz modifikacije iz „Cone Beam Computed Tomography in Implant Dentistry: „*A Systematic Review Focusing on Guidelines, Indications, and Radiation Dose Risks*" [14].

ANALOGNO I DIGITALNO PLANIRANJE

Preoperativni segment analognog planiranja započinje izradom dijagnostičkog modela (Slika1). Preliminarna postava zuba na dijagnostčkom modelu može se realizovati kroz upotrebu garniture gotovih PMMA zuba (eng. *set up*) ili modelovanjem zuba u vosku (eng. *wax up*). Odabir je stvar izbora terapeuta. Ipak, postoji preporuka da se fabrički gotovi zubi koriste kod bezubih pacijenata dok se voštano modelovanje jednostavnije realizuje u slučajevima manjih krezubosti [15]. Preliminarna postava zuba na dijagnostičkom modelu je osnova za izradu radiološkog vodiča.

U užem smislu, digitalno planiranje obuhvata domen softverskih alata CBCT aparata i CAD-CAM mašina. Zapis koji nastaje tokom volumetrijskog snimanja anatomskih struktura lica i vilica se obrađuje u softverskom programu aparata u formatu Digital Imaging and Communications in Medicine (DICOM) [16]. Tako dobijeni podaci se objedinjuju sa podacima na izmodelovanom „wax-up"-u. Važan segment planiranja obuhvata i analiza međuviličnih odnosa. Sa uvođenjem tzv. Bari tehnike omogućen je transfer intermaksilarnih i okluzalnih odnosa u sve tri prostorne ravni, i to u digitalnom okruženju. Metoda se zasniva na izradi protetskog stenta koji ima za cilj da prenese okluzalne odnose zabeležene privremenom dijagnostičkom protezom unutar konačne protetske nadoknade na implantatima [17]. Na osnovu navedenih podataka, terapeut ima jasno definisane zahteve protetske komponente i pristupa virtualnom planiranju položaja implantata uključujući dužinu, promer, nagib i dubinu implantata. Nakon toga sledi dizajniranje hirurškog vodiča. Tehnološki postupci izrade hirurških vodiča dele se na aditivne i subtraktivne (stereolitografske) metode [15].

RADIOLOŠKI VODIČ KAO PUTOKAZ ZA USPEŠNO DIZAJNIRAN HIRURŠKI VODIČ

Svrha radiološkog vodiča jeste da omogući prenos informacije o položaju kruničnog dela buduće restauracije na CBCT snimak. Dobra stabilnost vodiča na nosećim tkivima je obavezna. Svako neprecizno naleganje može rezultirati pomeranjem vodiča tokom radiografisanja, što za posledicu ima pomak referentnog objekta. Ukoliko se hirurški vodič izradi na bazi tako dobijenih informacija, kliničar će imati poteškoće da postavi hirurški vodič i celokupna procedura može biti kompromitovana [15]. Da bi se izvršila uspešna radiološka vizuelizacija protetskog dela zubne nadoknade, unutar vodiča se mogu postaviti različiti radioopakni materijali. Mnogobrojni autori [15, 18] poredili su opacitet najčešće korišćenih materijala u te svrhe. Rezultati istraživanja saglasni su da je najveći opacitet zabeležen kod barijum-sulfata ($BaSO_4$), gutaperke i materijala za fiksiranje nadoknada na bazi cink-oksida. Radiološki stent se najčešće izrađuje na bazi dubler modela. Vodiči su od tvrde vakuum folije promera ne većeg od 1 mm. Kod bezubih pacijenata se u svrhu radiološkog vodiča može koristiti i stara proteza pod uslovom da je dobro retinirana na nosećim tkivima. Takođe, savetuje se nanošenje adheziva sa sluzokožne strane proteze pre radiografisanja. Unutar akrilatnih zuba prave se perforacije u koje se postavlja radioopakni materijal [19, 20]. Druga opcija je izlivanje dubler modela na bazi totalne zubne proteze. Dubler model predstavlja radni model na kom se izrađuje radiološki vodič, najčešće od vakuum folije [15].

DINAMIČKA I STATIČKA NAVIGACIJA

Dinamička navigacija je kompjuterski vođena ugradnja implantata. Ova metoda podrazumeva primenu intraoperativnih navigacionih sistema čije se konstrukciono rešenje uglavnom zasniva na optičkim alatima za izračunavanje pozicije implantata. Neki od trenutno prisutnih na tržištu su: Blue Sky Bio Plan Software, Fusion Nobel Biocare, CoDiagnostic software, M-Guide, DentalWings, Simplant Softwere, SMOP Swisseda…

Block i Emery su kao indikacije za primenu dinamičke navigacije naveli uglavnom sve one situacije gde postoje relativna ili apsolutna ograničenja za primenu hirurških vodiča: kod pacijenata sa ograničenim otvaranjem usta, implantacija na teško pristupačnim regijama bočnog segmenta vilica, situacije gde meziodistalna dimenzija krezubog prostora ne dozvoljava postavljanje statičkog vodiča zbog širine cilindra (vođice)… [21]. Terapeut prati kretanje hirurškog instrumenta u toku izvođenja intervencije na monitoru kompjutera [22]. Prednosti dinamičke navigacije su: smanjenje troškova za pacijenta s obzirom na to da se sprovodi bez upotrebe hirurškog vodiča, mogućnost kontinuiranog hlađenja hirurškog polja, veće mogućnosti za kliničara da intraoperativno usmerava hirurški instrument. Kao glavni nedostatak navode se veliki troškovi aparature. Dinamička navigacija se ne preporučuje u terapiji bezubih pacijanata [21]. Statička navigacija bazira se na primeni hirurškog vodiča. Osnovna uloga vodiča je da omogući prevođenje analognog ili digitalnog terapijskog plana u trodimenzionalno intraoralno okruženje. Kao prvi vodiči koristile su se vakuumske folije identične onima koje se primenjuju za radiološke vodiče. Takav vodič daje uvid u položaj buduće krunice, pa hirurg, na osnovu toga, može da mapira mesto implantacije. Dalji tok implantacije je vođen rukom terapeuta i zavisi od njegovog iskustva i spretnosti.

Kada govorimo o savremenim statičkim vodičima, implantacija virtualno isplaniranog postupka ugradnje implantata može se realizovati kroz delimično (*eng. half guided*) ili potpuno vođenu ugradnju (*eng. full guided*) u zavisnosti od dizajna vođica (cilindara) koje su integrisane u vodiču [15, 23, 24]. Potpuno vođena ugradnja podrazumeva primenu hirurškog vodiča čiji dizajn obezbeđuje precizno isplaniranu poziciju, angulaciju, dijametar i dubinu implantata. Vodič je pozicioniran u ustima

pacijenta tokom cele procedure implantacije, ne ostavljajući mogućnost terapeutu da intraoperativno vodi instrument u bilo koji drugi položaj osim onog koji je definisan cilindrima integrisanim unutar vodiča. Zahvaljujući osobinama materijala od kojih su izrađeni vodiči (polimetil-metakrilat ili legure metala) i vođicama, koje mogu biti od legure metala ili cirkonije, osigurana je rigidnost stenta, a samim tim i veća sigurnost za terapeuta [15]. Da bi se dodatno obezbedila sigurnost u radu, vodič bi trebalo da bude dobro retiniran na bezubom grebenu. Ovo je ujedno i razlog zbog kojeg nije opravdano koristiti loše retinirane, stare totalne proteze kao hirurške vodiče.

Termin delimično vođene implantacije odnosi se na vodiče koji koriste terapeutu samo tokom početnih faza implantacije. Ovi vodiči koriste cilindrične vođice koje mogu prihvatiti prvo, i eventualno drugo hirurško svrdlo. Kada ne postoji dovoljno prostora u meziodistalnom pravcu, prednost treba dati vodičima za poluvođenu ugradnju s obzirom na to da cilindi imaju uži promer u odnosu na cilindre za potpuno vođenu hirurgiju [15]. Potpuno vođeni pristup ima prednost u slučajevima sa slabim kvalitetom kosti, s obzirom na to da lagani pokreti ruke tokom plasiranja implantata mogu rezultirati većim odstupanjem za poluvođenu ugradnju [24]. Kako oba sistema imaju svoje prednosti i nedostatke, autori [24] koji su analizirali razliku u preciznosti ugradnje implantata prilikom korišćenja delimično i potpuno vođene hirurgije, zaključili su da je statistički značajna razlika u preciznosti bila evidentna samo u poziciji apikalne trećine implantata. Prednosti potpuno vođene hirurgije su: smanjen rizik od povrede anatomskih struktura, izvođenje hirurškog postupka bez odizanja režnja (*eng. flapless surgery*) i time skraćenje perioda postoperativnog oporavka, mogućnost individualizacije dizajna abatmenta prema poziciji hirurškog vodiča itd. [15].

Međutim, iako koncept primene hirurških vodiča podrazumeva jednostavan protokol za ugradnju, ovakva rešenja nose sa sobom određene nedostatke. Kao glavni, navode se nedovoljna preglednost operativnog polja, nemogućnost primene hirurškog vodiča u slučaju malog interokluzalnog prostora, opasnost od oštećenja ili kontaminacije svrdla prilikom prolaska kroz cilindar vođice [23]. Da bi se nadomestili pomenuti nedostaci, danas se uveliko razvija metoda ugradnje implantata primenom otvorenog vodiča (TWIN-Guide®, 2Ingis, Brussels, Belgium) [23, 25]. Otvoren dizajn kompenzuje navedene nedostatke zatvorenog sistema vodiča i kompatibilan je sa svim implantološkim sistemima. Takođe, sama implantacija sprovodi se uz kontinuiranu irigaciju operativnog polja. Vodič koristi obrazac otvorenog okvira, dajući kliničaru smernice za implantaciju u vidu dve referentne cilindrične vodilice postavljene sa vestibularne i oralne strane rama hirurškog vodiča.

ZAKLJUČAK

Idealna pozicija implantata podrazumeva prostornu orijentaciju u odnosu na susedne anatomske strukture i/ili susedni implantat. Pogrešno pozicioniranje može imati za posledicu funkcionalne, tehničke, biološke ili estetske posledice. Upotrebom kompjuterski planirane i vođene implantologije može se obezbediti predvidljivost terapijskih rezultata. Iako posledice loše pozicije implantata mogu dovesti do klinički manifestnih komplikacija tek kroz nekoliko meseci, odnosno godina, prve poteškoće mogu nastati već u fazi realizacije otiska za zubnu nadoknadu kada odstupanja u angulaciji implantata sprečavaju pravilno plasiranje prenosnika. Veliki izbor hirurških vodiča, koji se međusobno razlikuju prema dizajnu i svojoj nameni, omogućio je kliničarima da indikuju njihovu primenu i u kompleksnim slučajevima. Ipak, ograničenja koncepta popuno vođene implantologije su u vezi sa njegovom primenom samo kod krezubih pacijenata. Implantatno-protetska rehabilitacija bezubih pacijenata se realizuje konvencionalnim metodama delimično ili potpuno vođenim rukom hirurga.

REVIEW ARTICLE
PREGLED LITERATURE

DOI: https://doi.org/10.2298/SGS2004201A
UDC: 616.31-006.6; 612.313.015:616-074

Biochemical markers in saliva in patients with oral cancer

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SUMMARY

Head and neck cancers account for 3% of all human cancers and are mainly localized in the oral cavity. Early detection of cancer is extremely important for reducing mortality and morbidity from this disease. In addition to clinical trials and histopathological findings, in the last two decades, with technological development, more specific and sensitive methods have been used in the analysis of salivary markers.

The aim of this study was to present a wide range of analyzed markers in saliva: different protein markers (total proteins, albumin, defensins, staterin, cystatins), epithelial and molecular markers (CA125, CA19-9, TPA, CEA, CYFRA 21-1, CD44), enzymes (LDH, ALP, MMP, SOD), cytokines (IL-6, IL-8, IL-1β, TNF-α), oxidative stress markers (8-OHdG, MDA), non-enzymatic antioxidants (glutathione, uric acid, albumin, vitamin C and E) etc. Collecting saliva is simple and painless for the patient, it does not require expensive equipment or specially trained staff, and it is possible to take saliva several times and in unlimited quantities. Extensive research that is increasingly being done with modern techniques indicates that saliva may be useful for early detection of the disease in the near future.

Keywords: saliva; oral cancer; biochemical markers

INTRODUCTION

Head and neck cancers account for 3% of all human cancers and are mainly localized in the oral cavity (48%). The most common (90%) are squamous cell carcinomas, with an incidence of over 300,000 cases per year worldwide. The tongue (over 40%) and floor of the mouth are the most common localizations of this tumor in the oral cavity, and it is less often localized in the area of the gingiva, buccal mucosa, labial mucosa and hard palate. The most important risk factors for the development of oral cancer are smoking, alcohol, tobacco smoke agents, human papilloma virus and others [1, 2, 3].

Early detection of oral cancer is extremely important for reducing mortality and morbidity from this disease. The diagnosis is made on the basis of clinical analyzes and histopathological findings after taking the biopsy. Recently, more work is being done on the potential use of non-invasive methods - "liquid biopsy" - for the detection of diagnostic and prognostic biomarkers in body fluids [4, 5]. Identification and characterization of markers in saliva would help in the diagnosis and monitoring of patients with pre-malignant and malignant lesions of the oral cavity, patients in the postoperative procedure or the application of adequate therapy [6-9]. In the monitoring of oral cancers, the term "salivaomics" has been introduced, for a wide range of technologies that investigate different types of molecules found in saliva [10].

The aim of this study is a detailed presentation of various markers that were analyzed in the saliva of patients with oral cancer.

PROTEIN MARKERS IN SALIVA

Protein markers in the saliva of patients with oral cancer are analyzed individually or in groups, for the purpose of early detection of the disease and timely application of appropriate therapy.

In the saliva of patients with oral cancer, the concentration of total proteins was increased compared to the control group [11, 12]. Other studies have shown that saliva of untreated patients has an increased concentration of total protein compared to treated patients with oral cancer and patients with precancerous lesions [13]. The authors believe that this is a consequence of locally increased protein synthesis. Sanjay et al. came to similar results in cancers with different degrees of differentiation, but the difference in total protein concentration was not statistically significant [14]. The opposite results were obtained, which indicate that the total proteins are reduced in the saliva of patients with oral cancer [15].

In the recent years, with technological developments, more specific and sensitive methods have been used to identify total salivary proteins or peptides, known as salivary proteomes. About a thousand proteins are present in saliva, with different roles in metabolic processes, immune regulation, cell adhesion, communication, etc. [16, 17].

Albumins are plasma proteins that are synthesized in the liver. The roles of albumin are maintaining oncotic pressure, regulation of blood pH, transport of various substances, but also antioxidant protection. Our studies indicate a significant decrease in the concentration of albumin in the saliva of patients with oral cancer compared to the control group [18]. This can be explained by

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the "consumption" of this antioxidant in neutralizing free radicals, which are excessively produced in these pathological conditions. In other studies, the opposite results were obtained [19].

The best known tumor suppressor gene is p53 (16-20 kb DNA) is localized on human chromosome 17. Mutation, inactivation and deletion of the p53 gene are also involved in the pathogenesis of oral tumors. Increased expression of the p53 gene has been found in saliva in oral squamous cell carcinoma. A high percentage (71 %) of tumor-specific mutations in the p53 gene has also been demonstrated in these patients [20].

Defensins are salivary peptides that exhibit antimicrobial activity and are extremely important in maintaining oral health [21]. They are proven in granular leukocytes - neutrophils, so they are called human neutrophil defensins. The concentration of defensin-1 in the saliva of patients with oral squamous cell carcinoma and other oral diseases (lichen planus, leukoplakia, inflammation) is significantly higher compared to saliva of the control group. This is in accordance with the fact that during many diseases in the oral cavity, a large number of neutrophils migrate from the blood through gingival sulcus to the oral environment [22].

Staterin is an acidic salivary protein that prevents the deposition of calcium phosphate in the excretory ducts of the salivary glands and regulates solubility of tooth enamel [21, 23]. In the saliva of patients with oral cancer, the concentration of staterin is reduced, and thus its function in oral cavity is reduced too [24].

Cystatins are proteins by chemical structure and inhibitors of the enzyme cysteine proteases by function. Cystatin SA-I, which has 14 kDa, has been detected in the saliva of patients with oral squamous cell carcinoma. This protein is more pronounced in the saliva of patients before treatment compared to the saliva of treated patients, so it may be a useful biomarker for patients with oral squamous cell carcinoma [25].

Epidermal growth factor (EGF) is a protein that plays a significant role in maintaining the homeostasis of the oral mucosa and mucosa of the upper gastrointestinal tract. It also promotes wound healing in the oral environment. Smoking and alcohol consumption have been shown to reduce the level of salivary EGF, which contributes to the development of oral carcinogenesis. In the saliva of patients with oral cancer, the concentration of EGF is reduced, and thus the possibility of renewal of the epithelium of the oral mucosa in these patients is reduced [26, 27].

SIALIC ACID, EPITHELIAL MARKERS, ENZYMES

Sialic acid is located at the terminal end of glycoproteins and glycolipids and plays a significant role in cell to cell interactions and development of cell adhesion important in malignant transformation [28]. Sialic acid concentration is increased in saliva of well-differentiated squamous cell carcinomas compared to poorly differentiated carcinomas [14]. Other authors have found its increased concentration relative to pre-malignant lesions in healthy individuals [11, 29]. After radiotherapy of patients with oral cancer, the level of sialic acid in the saliva is reduced, so it can be said that sialic acid is a sensitive tumor marker [30].

Epithelial markers (CA125, CA19-9, tissue polypeptide antigen, carcino-embryonic antigen, CYFRA 21-1) have an increased concentration in the saliva of patients with oral squamous cell carcinoma. In particular, the three analyzed markers (CYFRA-21, tissue polypeptide antigen, CA-125) were significantly increased (by 400 %), while for other markers no statistical significance was found [6]. Similar results were obtained by other authors for CYFRA 21-1 [31]. Analysis of these tumor markers in the saliva of patients with oral cancer may be suggested as an aid, rather than as a substitute, for other well-established diagnostic methods.

Molecular marker, the CD44 protein, can be converted to a soluble form by the action of proteases. It is increased in the saliva of patients with oral cancer compared to the control group. A perfect correlation between salivary CD44 molecules and grade and the degree of aggressiveness of the malignant lesion has been demonstrated. There is also a high statistically significant difference between patients with oral cancer and patients with pre-malignant lesions. This is indicated by the fact that the concentration of salivary CD44 between 19.2 and 20.4 ng/mL may indicate malignant transformation of lesions of the oral mucosa [32].

Enzymes, responsible for playing role in metabolic processes in cells, were also analyzed in saliva. The activity of lactate dehydrogenase and alkaline phosphatase is increased in the saliva of patients with oral squamous cell carcinoma [33, 34]. Merza et al. have demonstrated increased activity of these enzymes in the serum of patients with this disease [35]. The authors believe that the release of intracellular enzymes is increased from pathologically altered cells, rather than a consequence of increased biosynthesis. Matrix metalloproteinases (MMPs) are enzymes involved in the pathogenesis of oral cancer. Unregulated MMP activity in tumor tissues is one of the main factors of protein destruction (collagen, elastin, fibronectin). Increased activity of MMP-2 and MMP-9 has been demonstrated in the saliva of patients with oral squamous cell carcinoma (OSCC) [33, 36]. Peisker et al. demonstrated significantly increased MMP-9 activity in patients with OSCC compared to the control group (19.2 %), whether it was the first diagnosis or recurrence. The sensitivity of this marker was 100 % and the specificity 26.7 % [37].

CYTOKINES AND MARKERS OF OXIDATIVE STRESS

Cytokines represent a family of soluble, low molecular weight proteins or glycoproteins, which function as mediators and modulators of the immune response, inflammation, hematopoiesis, and development of malignant tumors. The concentration of interleukin-6 (IL-6), IL-8 and tumor necrosis factor (TNF-α), which

act as promoters in the process of carcinogenesis, was increased in the saliva of patients with oral cancer [38]. The most commonly determined cytokine in the saliva of patients with oral squamous cell carcinoma is IL-6 [39]. Brailo et al. have demonstrated increased concentrations of salivary IL-6 and IL-1β in patients with oral cancer compared to patients with leukoplakia. They leave the possibility to examine whether these cytokines are markers of malignant transformation of leukoplakia before oral cancer becomes clinically evident [40]. Other studies have indicated an increased content of IL-1, IL-6, TNF-α in the saliva of subjects with oral squamous cell carcinoma compared to patients with dysplastic oral lesions and control groups of subjects. Because of the above, salivary cytokines provide useful information on the behavior of epithelium in carcinogenesis and may be potential biochemical markers of oral cancer [41].

In the pathogenesis of oral cancer nowadays free radicals and oxidative stress are given increasing importance. Free radicals of oxygen and nitrogen lead to oxidative modification of proteins, lipids, DNA of oral tissue cells, which can result in their malignant alteration [42]. The most important biomarker of the degree of oxidative DNA damage is 8-hydroxy-deoxyguanosine (8-OHdG), the concentration of which is increased in the saliva of patients with oral squamous cell carcinoma [43]. The end product of lipid peroxidation is malondialdehyde (MDA). By analyzing the concentration of MDA, we showed that in the saliva of patients with periodontal disease there is an increase in its content compared to the group of healthy subjects [44]. Other authors have obtained similar results in the saliva of patients with oral squamous cell carcinoma [45].

In addition, toxic components from tobacco smoke affect the change in the antioxidant capacity of saliva [46]. Decreased antioxidant enzyme activity results in incomplete elimination of H_2O_2 from the oral environment, which reacts with other radicals and molecules to form much more reactive free radicals, which oxidatively damage biomolecules such as DNA, and that can lead to malignant transformation and oral cancer [47, 48]. The concentration of non-enzymatic antioxidants in saliva, such as glutathione, is also reduced. The authors explain this by the interaction of tobacco smoke aldehydes and SH groups of glutathione, when nonfunctional conjugates are formed [11, 46]. It is especially interesting to analyze the concentration of uric acid, as the main non-enzymatic antioxidant, which participates with about 70% in the total antioxidant capacity of saliva. Our and other studies showed that in the saliva of patients with oral cancer, who were smokers, the concentrations of uric acid and albumin were significantly reduced, compared to the group of healthy subjects. These results can be explained by the increased "consumption" of these antioxidants in neutralizing free radicals [18, 49]. Decreased concentrations of vitamins E and C in the saliva of patients with increase of histological grade of oral cancer have also been demonstrated [50]. From the above, it can be concluded that the analysis of the antioxidant capacity of saliva can be useful for improving preventive measures in the development of oral cancer, so, as in the case of periodontitis, the use of various antioxidants is recommended.

CONCLUSION

Based on this review, it was determined that biochemical composition of saliva changes in patients with oral cancer. Saliva analyzes in these patients have advantages and disadvantages. Saliva collection is simple and painless for the patient, it does not require expensive equipment or specially trained staff, which certainly goes in favor of cost-effectiveness. It is also possible to take saliva several times and in unlimited quantities. However, some of the present problems cannot be ignored. Individual biomarkers proven in saliva are not sensitive and specific enough to meet stringent diagnostic criteria. There is also the problem of extremely high saliva viscosity, due to the presence of mucopolysaccharides and mucoproteins, which can interfere with the analytical procedure. Despite these limiting circumstances, extensive research, increasingly done with modern techniques, indicates that saliva may be useful for early detection, diagnosis and monitoring of applied therapy for oral cancer in the near future.

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Received: 1.9.2020 • Accepted: 23.11.2020

Biohemijski markeri u salivi obolelih od oralnog karcinoma

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KRATAK SADRŽAJ

Karcinomi glave i vrata predstavljaju 3% od svih karcinoma čoveka i uglavnom su lokalizovani u usnoj duplji. Rano otkrivanje karcinoma je izuzetno važno za smanjenje mortaliteta i morbiditeta od ove bolesti. Pored kliničkih ispitivanja i histopatološkog nalaza, u poslednje dve decenije, sa tehnološkim razvojem, koriste se specifičnije i osetljivije metode u analizi salivarnih markera.

Cilj rada bio je da se prikaže široka paleta analiziranih markera: različiti proteinski markeri (ukupni proteini, albumin, defenzini, staterin, cistatini), epitelni i molekularni markeri (CA125, CA19-9, TPA, CEA, CYFRA 21-1, CD44), enzimi (LDH, ALP, MMP, SOD), citokini (IL-6, IL-8, IL-1β, TNF-α), markeri oksidativnog stresa (8-OHdG, MDA), neenzimski antioksidansi (glutation, mokraćna kiselina, albumin, vitamin C i E) itd. Prednosti prikupljanja salive su jednostavnost i bezbolnost za pacijenta, to što ne zahteva skupu opremu ni posebno obučeno osoblje, a salivu je moguće uzeti više puta i u neograničenim količinama. Obimna istraživanja koja se sve više rade savremenim tehnikama ukazuju na to da saliva može biti od koristi za rano otkrivanje bolesti u bliskoj budućnosti.

Ključne reči: saliva; oralni karcinomi; biohemijski markeri

UVOD

Karcinomi glave i vrata predstavljaju 3% od svih karcinoma čoveka i uglavnom su lokalizovani u usnoj duplji (48%). Najčešće su to (90%) planocelularni karcinomi, čija je incidenca preko 300 000 slučajeva godišnje u svetu. Jezik (preko 40%) i pod usta su najučestalije lokalizacije ovog tumora u usnoj duplji, a ređe je lokalizovan u predelu gingive, bukalne mukoze, labijalne mukoze i tvrdog nepca. Najvažniji faktori rizika za nastanak karcinoma usne duplje su pušenje, alkohol, agensi duvanskog dima, humani papiloma virus i dr. [1, 2, 3].

Rano otkrivanje karcinoma usne duplje je izuzetno važno za smanjenje mortaliteta i morbiditeta od ove bolesti. Dijagnoza se vrši na osnovu kliničkih analiza i histopatoloških nalaza nakon uzimanja biopsije. U poslednje vreme sve se više radi na potencijalnoj upotrebi neinvazivnih metoda – „tečnoj biopsiji" – za detekciju dijagnostičkih i prognostičkih biomarkera u telesnim tečnostima [4, 5]. Identifikacija i karakterizacija markera u salivi bi pomogla u dijagnozi i praćenju pacijenata sa premalignim i malignim lezijama usne duplje, pacijenata u postoperativnom postupku, primeni adekvatne terapije [6–9]. U praćenju oralnih karcinoma uveden je termin "salivomi", za široku paletu tehnologija kojima se istražuju različite vrste molekula koji se nalaze u salivi [10].

Cilj rada je detaljan prikaz različitih markera koji su analizirani u salivi pacijenata sa oralnim karcinomima.

PROTEINSKI MARKERI U SALIVI

Proteinski markeri u pljuvački obolelih od oralnog karcinoma analiziraju se pojedinačno ili grupno, radi ranog otkrivanja oboljenja i pravovremene primene odgovarajuće terapije.

U pljuvački pacijenata obolelih od oralnog karcinoma povećana je koncentracija ukupnih proteina u odnosu na kontrolnu grupu [11, 12]. Druga istraživanja su pokazala da je u pljuvački netretiranih pacijenata povećana koncentracija ukupnih proteina u odnosu na tretirane pacijente sa oralnim karcinomom i pacijente sa prekanceroznom lezijom [13]. Autori smatraju da je to posledica lokalno povećane sinteze proteina. Sanjay i sar. su došli do sličnih rezultata kod karcinoma sa različitim stepenom diferentovanosti, ali razlika u koncentraciji ukupnih proteina nije bila statistički značajna [14]. Dobijeni su i suprotni rezultati, koji ukazuju da su ukupni proteini smanjeni u salivi obolelih od oralnog karcinoma [15].

U poslednjih nekoliko godina, sa tehnološkim razvojem, koriste se specifičnije i osetljivije metode u identifikaciji ukupnih proteina ili peptida salive, poznatih kao salivarni proteomi. U salivi je prisutno oko hiljadu proteina, sa različitim ulogama u metaboličkim procesima, imunoj regulaciji, ćelijskoj adheziji, komunikaciji itd. [16, 17].

Albumini su plazma proteini koji se sintetišu u jetri. Uloga albumina je u održavanju onkotskog pritiska, regulaciji pH krvi, transportu različitih supstancija, ali i u antioksidativnoj zaštiti. Naša istraživanja ukazuju na značajno smanjenje koncentracije albumina u pljuvački bolesnika sa oralnim karcinomom u odnosu na kontrolnu grupu [18]. To se može objasniti „potrošnjom" ovog antioksidansa u neutralisanju slobodnih radikala, koji se prekomerno stvaraju u ovim patološkim stanjima. U drugim istraživanjima su dobijeni suprotni rezultati [19].

Najpoznatiji tumor supresorski gen je p53 (16-20 kb DNA), koji je lokalizovan na humanom hromozomu 17. Mutacija, inaktivacija i delecija gena p53 uključena je i u patogenezu tumora oralne sredine. Povećana ekspresija p53 gena je ustanovljena u pljuvački kod oralnog skvamoznog karcinoma. Takođe je kod ovih pacijenata dokazan visok procent (71%) tumor-specifičnih mutacija na genu p53 [20].

Defenzini su peptidi pljuvačke koji ispoljavaju antimikrobno dejstvo i imaju izuzetan značaj u održavanju oralnog zdravlja [21]. Dokazani su u granuliranim leukocitima – neutrofilima, pa se nazivaju humani neutrofilni defenzini. Koncentracija defenzina-1 u pljuvački pacijenata sa oralnim skvamoznim celularnim karcinomom i drugim oralnim oboljenjima (lichen planus, leukoplakija, inflamacije) značajno je veća u odnosu na pljuvačku kontrolne grupe. To je u saglasnosti sa činjenicom da u toku mnogih oboljenja u usnoj duplji dolazi do migracije velikog broja neutrofila iz krvi kroz gingivalni sulkus u oralnu sredinu [22].

Staterin je kiseli protein pljuvačke koji sprečava taloženje kalcijum-fosfata u izvodnim kanalima pljuvačnih žlezda i reguliše rastvorljivost zubne gleđi [21, 23]. U pljuvački pacijenata obolelih od oralnog karcinoma smanjena je koncentracija staterina, a time je umanjenja i njegova funkcija u usnoj duplji [24].

Cistatini su po hemijskoj strukturi proteini, a po funkciji inhibitori enzima cistein proteaza. U pljuvački pacijenata sa

oralnim skvamoznim karcinomom dokazan je cistatin SA-I koji ima 14 kDa. Ovaj protein je više izražen u pljuvački pacijenata pre tretmana u odnosu na pljuvačku tretiranih pacijenata, tako da može biti koristan biomarker obolelih od oralnog skvamoznog karcinoma [25].

Epidermalni faktor rasta (EGF) jeste protein koji ima značajnu ulogu u održavanju homeostaze oralne mukoze i mukoze gornjih delova gastrointestinalnog trakta. Takođe, pospešuje zarastanje rana u oralnoj sredini. Dokazano je da pušenje i konzumiranje alkohola smanjuju nivo salivarnog EGF, što doprinosi razvoju oralne kancerogeneze. U pljuvački pacijenata obolelih od oralnog karcinoma smanjena je koncentracija EGF, a time je smanjena i mogućnost obnavljanja epitela oralne sluzokože kod ovih pacijenata [26, 27].

SIJALINSKA KISELINA, EPITELNI MARKERI, ENZIMI

Sijalinska kiselina se nalazi na terminalnom kraju glikoproteina i glikolipida i ima značajnu ulogu u ćeliji, ćelijskim interakcijama i u razvoju ćelijske adhezije značajne u malignoj transformaciji [28]. Koncentracija sijalinske kiseline je povećana u pljuvački dobro izdiferentovanih skvamoznih karcinoma u odnosu na slabo diferentovane karcinome [14]. Drugi autori su utvrdili njenu povećanu koncentraciju u odnosu na premaligne lezije i zdrave jedinke [11, 29]. Nakon radioterapije pacijenata sa oralnim karcinomom smanjen je nivo sijalinske kiseline u salivi, pa se može reći da je sijalinska kiselina senzitivni tumorski marker [30].

Epitelni markeri (CA125, CA19-9, tkivni polipeptidni antigen, karcino-embrionalni antigen, CYFRA 21-1) imaju povećanu koncentraciju u pljuvački obolelih od oralnog skvamoznog karcinoma. Posebno su tri analizirana markera (CYFRA-21, tkivni polipeptidni antigen, CA-125) značajno povećana (za 400%), dok za ostale markere nije utvrđena statistička značajnost [6]. Slične rezultate su dobili drugi autori za CYFRA 21-1 [31]. Analiza ovih tumorskih markera u pljuvački pacijenata sa oralnim karcinomom može se predložiti kao pomoć, a ne kao zamena, za druge afirmisane dijagnostičke metode.

Molekularni marker, protein CD44, može dejstvom proteaza da pređe u rastvorljivu formu. On je povećan u pljuvački pacijenata sa oralnim kancerom u odnosu na kontrolnu grupu. Dokazana je savršena korelacija između salivarnog CD44 molekula i gradusa i stepena agresivnosti maligne lezije. Takođe, postoji visoka statistički značajna razlika između pacijenata sa oralnim karcinomom i pacijenata sa premalignim lezijama. Na to ukazuje i podatak da koncentracija salivarnog CD44 između 19,2 i 20,4 ng/mL može ukazati na malignu transformaciju lezija oralne sluzokože [32].

U pljuvački su analizirani i enzimi, odgovorni za odigravanje metaboličkih procesa u ćelijama. U pljuvački pacijenata sa oralnim skvamoznim karcinomom povećana je aktivnost laktat-dehidrogenaze i alkalne fosfataze [33, 34]. Merza i sar. su dokazali povećanu aktivnost ovih enzima i u serumu pacijenata sa ovim oboljenjem [35]. Autori smatraju da je oslobađanje intraćelijskih enzima povećano iz patološki izmenjenih ćelija, pre nego što je posledica povećanja njihove biosinteze. Matriksne metaloproteinaze (MMP) jesu enzimi koji participiraju u patogenezi karcinoma oralne sredine. Neregulisana aktivnost MMP u tkivima tumora jedan je od glavnih faktora destrukcije proteina (kolagena, elastina, fibronektina). U pljuvački pacijenata sa oralnim skvamoznim karcinomom (OSCC) dokazana je povećana aktivnost MMP-2 i MMP-9 [33, 36]. Peisker i sar. dokazali su značajno povišenu aktivnost MMP-9 kod pacijenata sa OSCC u odnosu na kontrolnu grupu (19,2%), bilo da je u pitanju prvo dijagnostikovanje ili recidiv. Osetljivost ovog markera bila je 100%, a specifičnost 26,7% [37].

CITOKINI I MARKERI OKSIDATIVNOG STRESA

Citokini predstavljaju familiju solubilnih, niskomolekularnih proteina ili glikoproteina, koji funkcionišu kao medijatori i modulatori imunog odgovora, inflamacije, hematopoeze, razvoja malignih tumora. U salivi obolelih od oralnog karcinoma povećana je koncentracija interleukina-6 (IL-6), IL-8 i faktora nekroze tumora (TNF-α), koji deluju kao promotori u procesu kancerogeneze [38]. Najčešće određivani citokin u salivi pacijenata sa oralnim skvamoznim karcinomom je IL-6 [39]. Brailo i sar. su dokazali povećanu koncentraciju salivarnog IL-6 i IL-1β kod pacijenata sa oralnim karcinomom u odnosu na pacijente sa leukoplakijom. Oni ostavljaju mogućnost da se ispita da li su ovi citokini markeri maligne transformacije leukoplakija pre nego što oralni karcinom postane klinički evidentan [40]. Druge studije su ukazale na povećan sadržaj IL-1, IL-6, TNF-α u pljuvački ispitanika sa oralnim skvamoznim karcinomom u odnosu na pacijente sa displastičnim oralnim lezijama i kontrolnim grupama ispitanika. Zbog navedenog, citokini salive pružaju korisne informacije o ponašanju epitela u karcinogenezi i mogu biti potencijalni biohemijski markeri karcinoma oralne sredine [41].

U patogenezi oralnog karcinoma danas se sve veći značaj poklanja slobodnim radikalima i oksidativnom stresu. Slobodni radikali, kiseonički i azotni, dovode do oksidativne modifikacije proteina, lipida, DNK ćelija oralnih tkiva, što može imati za posledicu njihovu malignu alteraciju [42]. Najznačajniji biomarker stepena oksidativnog oštećenja DNK jeste 8-hidroksidezoksiguanozin (8-OHdG), čija je koncentracija povećana u salivi pacijenata obolelih od oralnog skvamoznog karcinoma [43]. Krajnji produkt lipidne peroksidacije jeste malondialdehid (MDA). Analizom koncentracije MDA, mi smo pokazali da u pljuvački obolelih od periodontalnih bolesti dolazi do porasta njegovog sadržaja u odnosu na grupu zdravih ispitanika [44]. Drugi autori su dobili slične rezultate u salivi pacijenata sa oralnim skvamoznim karcinomom [45].

Pored toga, toksične komponente iz duvanskog dima utiču na promenu antioksidativnog kapaciteta salive [46]. Smanjenje aktivnosti antioksidativnih enzima ima za posledicu nepotpunu eliminaciju H_2O_2 iz oralne sredine, čijom se reakcijom sa ostalim radikalima i molekulima stvaraju mnogo reaktivniji slobodni radikali, koji vrše oksidativno oštećenje biomolekula kao što je DNK, a što može dovesti do maligne transformacije i nastanka oralnog karcinoma [47, 48]. Takođe je smanjena i koncentracija neenzimskih antioksidanata u salivi, kao što je slučaj sa glutationom. Autori ovo objašnjavaju interakcijom aldehida duvanskog dima i SH grupa glutationa, kada se formiraju nefunkcionalni konjugati [11, 46]. Posebno je interesantno analiziranje koncentracije mokraćne kiseline, kao glavnog neenzimskog antioksidanta, koji učestvuje sa oko 70% u ukupnom antioksidativnom kapacitetu salive. Naša i druga istraživanja pokazuju da je u salivi pacijenata sa oralnim karcinomom, koji su bili pušači, značajno smanjena koncentracija mokraćne kiseline i albumina, u odnosu

na grupu zdravih ispitanika. Ovi rezultati mogu se objasniti pojačanom „potrošnjom“ ovih antioksidanata u neutralisanju slobodnih radikala [18, 49]. Takođe je dokazana smanjena koncentracija vitamina E i C u salivi pacijenata sa rastom histološkog gradusa oralnog karcinoma [50]. Iz navedenog, može se zaključiti da analiza anitoksidativne sposobnosti pljuvačke može biti od koristi za unapređenje preventivnih mera u nastanku oralnog karcinoma, pa se, kao i u slučaju parodontopatije, preporučuje upotreba raznih antioksidanasa.

ZAKLJUČAK

Na osnovu ovog preglednog rada utvrđeno je da se kod pacijenata sa oralnim karcinomom menja biohemijski sastav salive. Analize salive kod ovih pacijenata imaju prednosti i nedostatke. Prikupljanje salive je jednostavno i bezbolno za pacijenta, ne zahteva skupu opremu ni posebno obučeno osoblje, što svakako ide u prilog ekonomičnosti rada. Takođe je moguće salivu uzeti više puta i u neograničenim količinama. Međutim, neki prisutni problemi se ne mogu ignorisati. Dokazani pojedinačni biomarkeri u pljuvački nisu osetljivi i dovoljno specifični da zadovolje stroge dijagnostičke kriterijume. Postoji i problem izuzetno velike viskoznosti salive, zbog prisutnih mukopolisaharida i mukoproteina, što može ometati analitičku proceduru. Uprkos ovim ograničavajućim okolnostima, obimna istraživanja, koja se sve više rade savremenim tehnikama, ukazuju da saliva može biti od koristi za rano otkrivanje, dijagnozu i praćenje primenjene terapije kod oralnih karcinoma u bliskoj budućnosti.

REVIEW ARTICLE
PREGLED LITERATURE
DOI: https://doi.org/10.2298/SGS2004208S
UDC: 614.253

The role of tag questions in medical encounters

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SUMMARY
The discourse of medical encounters is deemed to be an excellent example of both institutional talk and discourse of power. Asking questions is probably the most prominent characteristic of doctor- patient interaction and this paper deals with tag questions as one of the question types that can be found in almost every medical encounter. We will explore tag questions by reviewing current research results in the field of medical discourse and by comparing and discussing examples from transcribed medical encounters in English and Serbian. It will be discussed how often tag questions are used in both corpora, whether doctors and patients use them in the same way and what role these questions have in a medical encounter. Finally, having in mind that getting to ask any question in institutional talk requires a certain amount of power, we will also try to determine if using tag questions affects doctor and patient's positions in a medical encounter.
Keywords: contrastive analysis; discourse of power; institutional talk; medical encounter; tag questions

INTRODUCTION

Institutional communication has been explored from various aspects and in a multidisciplinary manner by scholars from different fields (i.e. linguistics, sociology, anthropology, psychology, etc.). This type of communication usually involves interactions such as teacher-student, doctor-patient, police officer-witness or journalist-interviewee, where one participant in communication is an official representative of an institution and the other one is the client. While everyday communication usually implies a symmetrical interaction between the two parties that have equal rights, institutional communication is commonly characterized by a conspicuous asymmetry and an unequal distribution of power [1]. For this reason, Fairclough believes such interactions should be called *unequal encounters* [2].

Doctor-patient communication is believed to be an excellent example of a specific distribution of power in the field of institutional communication. It may be explored from various aspects, but the use of questions is probably the best way to illustrate some significant differences between the roles of an institution representative and of its client.

This paper will first briefly present the classification of questions and general reasons for asking questions in this type of institutional communication. In next section, the category of tag questions will be defined and explored in more detail. Examples from two corpora (i.e. English corpus and Serbian corpus) will be used to illustrate the results that have been provided by comparing and contrasting recordings of doctor-patient communication in two languages. This paper aims at exploring how often tag questions are used, how doctors and patients use this type of questions and what role these questions have in a medical encounter in two different languages and two different cultures. Finally, we will try to determine to what extent the use of tag questions affects doctors and patients' roles in a medical encounter.

QUESTIONS IN MEDICAL ENCOUNTERS

Different authors offer different definitions of questions asked in medical encounters and the same is true for the types of questions and the role they have in doctor-patient interaction. However, multiple authors have reported that most of the questions are asked during the phase of history taking and that they are mostly asked by doctors, not patients [3, 4].

Mischler was one of the first authors who dealt with this aspect of medical encounter and in his study he identified several types of questions – yes/no questions,[1] polar/disjunctive questions,[2] restrictive WH-questions,[3] moderately open How-questions[4] and open How-questions[5] [4]. He also came to a conclusion that most of the questions asked by a doctor restricted patients' answers because of

1 E.g. *Do you have temperature?* The only two possible answers to such questions are *yes* or *no.*
2 Two alternative answers are provided in this type of question, e.g. *[...] this cough, are you producing anything or is it a dry cough?* [4].
3 E.g. *When did you first notice that symptom?* The patient is expected to provide a specific answer.
4 Questions beginning with *How about*, e.g. *How about your legs?* They provide an interlocutor with an opportunity to tell their story about a particular thing (i.e. their legs), without being limited to a specific answer.
5 E.g. *How are you feeling?*

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the way these questions were formed, which consequently allowed the doctor to control both the interview and the patient's contribution to it to a great extent [4].

Ainsworth-Vaughn opted for a slightly different classification where she identified the following types of questions: WH-questions,[6] inverted auxiliary,[7] "search" WH-questions,[8] elliptical questions,[9] tag questions and rising intonation pattern.[10] She also explored the so-called rhetorical questions that are more like requests or statements than real questions as there is no need for an actual answer [5].

Boyd & Heritage and Hayano explored doctors' questions and they emphasized the triple function doctors' questions had in a medical encounter – (1) to limit the patient's answer by imposing a specific agenda,[11] (2) to assume various aspects of the patient's health and their medical knowledge,[12] and (3) to favour one type of an answer over another[13] [3, 6]. Boyd & Heritage also insisted on *the optimization principle* – the fact that doctors' questions during the phase of history taking are formulated in such a way that they always predict the best-case scenario [3][14].

Interestingly enough, most of the studies deal only with doctors' questions and do not take patients' questions into consideration [3, 4, 6]. Some authors, like Mischler, do not even believe a patient can ask a question during a medical encounter, as they consider this to be an exclusive privilege of a doctor [4]. Having analysed over 2500 recordings, Byrne & Long came to a conclusion that it was asking questions that gave doctors such a great power over patients whose contribution was entirely insignificant and limited to the very end of the encounter [7]. Fairclough claims that the entire encounter is based on doctors' questions and that a doctor has a complete control over the turn-taking system in this type of communication [8]. He also believes that the patients' contribution is absolutely negligible and that patients actually speak only when they are encouraged or prompted to do so by the doctor's questions. However, some other authors have proved that patients do ask questions during a medical encounter and that they even do so regularly, but certainly less frequently than doctors [5, 10].[15]

Why do doctors and patients ask questions in a medical encounter? Klikovac states several reasons for doctors to ask questions – (1) they want to find out about everything they might consider important prior to giving a diagnosis or deciding on a treatment, (2) they wish to direct the patient towards a particular response or to encourage them to continue talking and say more about a particular topic or (3) they do this in order to make a conclusion [11].

Cordella studied both doctors' and patients' questions and she identified several different *voices* both groups used according to a situation or a personality type [12]. Concerning the patients, Cordella determined only one group of patients (i.e. *the voice of initiator*) who actually asked questions and they did so in order to find out more about their health, to understand their situation better and take a better care of their health [12]. McKenzie conducted a study that involved pregnant women carrying twins and most of them admitted they believed they should make a list of questions they wanted to ask their doctors in advance, before going to their surgery, as well as that they were unsatisfied with the fact their doctors did not share information with them [13]. Adler et al. even stated that some patients[16] thought it was inappropriate to ask any question whatsoever as it would indulge the doctor-patient relationship [14].

TAG QUESTIONS

Tag questions are commonly used to check if something is true or to ask for an agreement [16]. In English, tags are usually composed of an auxiliary verb or the verb *do,* depending on the form of the entire sentence, and they are positioned at the very end of the question, behind a comma. A negative question tag is normally used after a positive sentence, whereas a positive question tag is used after a negative sentence [17].[17]

In Serbian, tag questions have not been explored much, but there are two terms that could be used as equivalents to the English term question tags – *dopunska pitanja* [18] and *finitivne rečenične upitne forme* [9]. Just like in English, an interrogative word is located at the end of the sentence and such position is considered to change the communicative status of the sentence turning a statement into a question [9]. It is important to say that only an

6 The questions that Mischler [4] classified as restrictive WH-questions.

7 Yes/no questions in Mischler's classification [4].

8 In this type of questions, a question word never occupies the initial position, but it is usually located at the very end of the question, in the position that matches its syntactic role. E.g. *You have an appointment when?*

9 These are not real questions, but they have a communicative value of a question. [9] In these questions, the topic from a previous context is emphasised, so that both interlocutors know what the question is about, e.g. *Everything else remains unchanged?* (here both the doctor and the patient know exactly what *everything else* is referred to).

10 At first sight, these are not questions at all, as they have the structure of a statement. However, owing to its rising intonation, they have an interrogative communicative value [9], e.g. *You've got the previous report?*

11 Imposing a specific topic or offering an agenda concerning a specific activity expected from the patient (i.e. to give an affirmative or a negative answer, to give an explanation, etc.)

12 This is more often the case in WH-questions than in yes/no questions. In the example *What medications do you take?* the patient is not expected to say whether they take medications or not, but they are just supposed to give an answer to a restrictive question.

13 This actually means that a question is formulated in such a way that an affirmative or a negative answer are naturally expected (e.g. *You don't suffer from heartburn?*).

14 For example, doctors would always rather ask *Is your father alive?* than *Is your father dead?*

15 In Frankel's study patients asked only 1% of the total number of questions [10], West's study reported a total of 9% of patients' questions [15] and in Ainsworth-Vaughn's research the number of patients' questions rose to 39% [5].

16 Those were oncological female patients aged 65 to 85.

17 E.g. You haven't got the results yet, *have you*?; She doesn't look well, *does she*?

Table 1. Tag question distribution in English and Serbian corpora
Tabela 1. Raspodela dopunskih pitanja u korpusima na engleskom i srpskom jeziku

	Total number of questions Ukupan broj pitanja	Number of tag questions Ukupan broj dopunskih pitanja	Number of tag questions asked by doctors Ukupan broj dopunskih pitanja koja je doktor pitao	Number of tag questions asked by patients Ukupan broj dopunskih pitanja koja su pacijenti pitali
ENGLISH CORPUS KORPUS NA ENGLESKOM	334	8 (2.4%)	4	4
SERBIAN CORPUS KORPUS NA SRPSKOM	497	40 (8%)	30	10

affirmative answer is expected to these questions and they are related to something that was previously stated [18]. Most frequently used interrogative markers in Serbian tag questions are the following: *je l'?, je l' da?, zar ne?, je li?, a?* and unlike English tag questions they never change their form depending on a tense or a structure of the sentence[18]. These tags are called *(dopunski) upitni operatori* [9] or *privesci* [19]. Interestingly, Hudeček & Vukojević state that tag questions are found exclusively in everyday communication, which could be important in determining the genre of a medical encounter [20].[19]

Tag questions are interesting to explore, as they are quite different from most of the other types of questions. As it is always an affirmative answer we expect to such questions, they are often not even seen as questions; this could be an explanation for the reason why only Ainsworth-Vaughn counted them as questions [5]. We thought it would also be useful to see how often doctors and patients asked tag questions and if they used them to the same purpose. Since tag questions are commonly used to check a particular piece of information or ask for an agreement, they could be seen as a power-claiming tool (i.e. expecting someone to agree with you, never to oppose you or state their own opinion) or simply as a way to encourage another person to say more about something.

RESEARCH RESULTS

In order to check how often doctors and patients use tag questions and what role these questions have in a medical encounter, we compared recordings of medical encounters in English and Serbian.

The English corpus consists of 19 recordings, whereas the Serbian corpus contains 80 recordings, but both corpora were approximately 5 hours long and could be considered equal in length. The recordings from the English corpus are a curtesy of Prof. Richard Frankel, they have been made in a tertiary referral hospital in the USA and they belong to the fields of orthopaedic surgery (14 recordings) and internal medicine (5 recordings). The recordings from the Serbian corpus have been made in a tertiary referral hospital in Belgrade, Serbia, and they belong to the fields of pulmonology (37 recordings) and paediatrics (43 recordings).

Out of the total of 334 questions asked in the English corpus, there were only 8 tag questions (2.4%); doctors asked 4 tag questions and patients asked 4. In the Serbian corpus there were 40 tag questions out of the total number of 497 questions (8%); 30 tag questions were asked by doctors (75%) and 10 (25%) were asked by patients. So, we can conclude that tag questions are rather rare in English corpus, whereas in Serbian corpus they are more frequently used, but more by doctors than by patients. The results are presented in Table 1.

Doctors in English corpus always asked tag questions simply to check a particular piece of information (Example 1).

Example 1:
D: [...] **The Doxicycline is a one hundred, is it?**
P: Oh: my gosh I don't know.
D: It comes in a fifty and a one/hundred.
P: Yeah.

In this example the doctor used a tag question to check a piece of information – the dosage of the medication the patient is currently taking. By opting for this particular type of the question, the doctor also directs the patient to a particular answer he considers adequate. So, by asking this question the doctor does not seek a new piece of information, but he just wants to confirm his assumption of the information he already possesses.

Unlike their American colleagues, the doctors from the Serbian corpus used tag questions in several different ways. They most often chose these questions to check a particular piece of information (Example 2), but they also opted for them when they wanted to check if the patients understood what they had previously told them (Example 3), to make the atmosphere more relaxed (Example 4), to get more time or make the patient change their mind (Example 5). Paediatricians also used tag questions to direct their patients towards a particular answer (Example 6).

Example 2:
L: [...] **You still have that Seratide 250, don't you?**
P: Yeah. That's what doctor prescribed las' time. Everything was ok, he said, and then he listened to my lungs and realized [...]

18 E.g. *To je sve, je l' da?*

19 While some authors firmly believe that a medical encounter is a typical interview with strictly defined roles of an interviewer and an interviewee [4, 10], some other authors claim it is actually a combination of two genres – an interview and everyday communication [5, 21, 22, 23].

The doctor obviously asked this tag question either to make a statement or to check something he already knew, so he did not really expect the patient to answer. By asking this question, he hopes for a confirmation, not for a negative answer. The tag *don't you* (Serb. *je l'*) which is used here is the most frequent tag in the entire Serbian corpus. As expected, the patient confirms the doctor's statement by using a minimal response *yeah* (Serb. *a-ha*).

Example 3:
D: Now, when you start using the new dosage 80, you should follow what's going on. If you see it's stable, that nothing changes, then go on with it. If you see something's going on, come before the end of 3 months (..) Or maybe better 2 months. As we've got a low dosage, so we should follow your reaction (.). **We've understood each other, haven't we?**
P: Yes.

In this citation, the doctor is giving instructions to the patient, concerning a new dosage of the medication he has already been using. For the most part of his turn, the doctor is determining the patient's behaviour by telling him what to do and by revealing the two possible scenarios. Interestingly, the doctor suddenly starts using the 1st person plural - *we've got a low dosage* (Serb. *imamo malu dozu), we should follow your reaction* (Serb. *da vas ispratimo*). He uses the 1st person plural either to denote both himself and the patient in an activity that only seems to be mutual but actually depends only on the doctor or to denote himself and other doctors, as professionals [11]. Finally, the tag question *We've understood each other, haven't we?* (Serb. *Razumeli smo se, je l' tako?*) is used only to check if the patient has heard and understood everything, but it is also a good example of the discourse of power in institutional communication – the doctor only expects a confirmation (so, the patient is supposed to understand well everything he's been told) and by using the 1st person plural he may put himself in the position of an authority.

Example 4:
D: It's salty, the sea. **It's too salty, isn't it?**
P: Yeah.

Here the paediatrician uses a tag question only to make her little patient laugh and help him feel more relaxed. She makes a joke about the sea being salty and she obviously does not expect to get a real answer to her question, she only expects her patient to agree with her and get the joke.

Example 5:
D: OK, have you solved your:
P: //No
D: **You haven't, have you?**
P: I don't have it during the day, but at night [...]

In this example, the tag question is asked in order to make the patient re-think what he has just said or simply to provide the doctor with some more time to think about what he has just heard. It is also possible that the doctor expected to get a positive answer and was thus a bit confused, so he took some more time to think about the problem.

Example 6:
D: So, tell me, how often do you have these headaches?
P: Well, twice a week.
D: When you're on holiday and when you go to school? When you have obligations and when you don't? Or are they more frequent when you have obligations. Now during the summer holiday **it happens less frequently, doesn't it?**
P: Yes.

This is a typical example of directing the patient towards a particular answer or helping them to answer properly. Paediatricians used tag questions to this purpose rather frequently, whereas there was not a single example of this usage in encounters with a pulmonologist. This might be connected with differences between paediatrics and almost all the other branches of medicine – paediatricians talk to children (and their parents) and they need to find a way to learn everything they would like to know, without intimidating the patient.

The patients in English corpus usually used tag questions only to check a particular piece of information (Example 7).

Example 7:
P: [...] **There isn't any other (...) treatment for it either, is there**?
D: Prednisone it/I've never/I've never heard of anything else that works [...]
P: Mmm (.) It works, I think it does help (...) **make you retain water though don't it/doesn't it?**
D: A little [...]

In this quote the patient asked two tag questions. The first question was negatively formulated and even though the patient asked it hoping that there is an alternative treatment, he still expected to get a negative answer. The doctor hesitated, as if he did not want to disappoint the patient, but he finally admitted the medication the patient was currently using is the only option. The patient then asked another tag question, asking for a confirmation of what even he himself had noticed.

The patients in Serbian corpus used tag questions in the same way – to check information (Example 8), but also to check if they have understood their doctor correctly (Example 9).

Example 8:
P: [...] **I'll have to get a referral once again, won't I?**
D: //No, you won't.

In this example the patient simply checked whether a piece of information he had was correct so that he would not make a mistake. Instead of asking a yes/no question (e.g. *Will I have to get a referral once again?*), he turned it into a tag question, as he believed it would be necessary

for him to get a referral before seeing his doctor again. Surprisingly enough, the doctor gave him a negative answer.

Example 9:
D: No, don't do it now, change it if you need to.
P: **If I need to, right?**
D: Yes

This is the final phase of the medical encounter and the doctor is discussing the therapy and giving instructions. So, the patient's tag question *If I need to, right?* (Serb. *Po potrebi, je l'?* has a role of finding out if he has understood the doctor correctly, to make sure he will do everything properly. This is not a typical tag question, as it is a bit elliptical, but we can certainly consider it a tag question, as an affirmative answer is expected.

CONCLUSION

Doctor-patient communication, as one of the most researched types of institutional communication, is explored from various aspects. Asking questions in a medical encounter is believed to be one of the most important features of this type of communication. According to some authors, the right to ask questions is an exclusive privilege of doctors, whereas some other authors claim patients can ask questions as well, but less frequently and to different purposes.

It is thought that having a privilege to ask questions provides doctors with a powerful tool for controlling the entire encounter – they use questions to direct patients towards a particular response, to encourage them to say more about a topic or to determine their behaviour during the encounter. Patients do ask questions as well, but they obviously do it in a significantly different way, usually with the purpose of finding out more about their health.

Tag questions have not been researched as much as some other types of questions and they were counted as questions in only one larger study [5]. These questions might not even look like questions, as only an affirmative answer is expected. So, posing a tag question basically means asking for a confirmation or checking information.

In our research, medical encounters from two different corpora, English and Serbian, have been compared in order to check how often tag questions are used, how doctors and patients use them and what role they have in a medical encounter. According to the research results, tag questions are almost four times more frequent in Serbian than in English corpus. In English corpus doctors and patients asked the equal number of tag questions and both groups posed these questions only in order to check a particular piece of information. In Serbian corpus, doctors asked tag questions much more frequently than patients. Apart from checking information, they used tag questions in several other ways – to help the patient relax, to get more time or make the patient re-think what they had said, to check if the patient had understood something or to direct the patient towards a particular answer. Patients in the Serbian corpus used tag questions to check particular information or to check if they had understood their doctor and instructions correctly.

When it comes to the discourse of power and the actual positions of doctors and patients in a medical encounter, we cannot agree that patients are completely deprived of the possibility to ask any kind of questions, including tag questions. In the English corpus there are almost no differences whatsoever between doctors and patients. However, in the Serbian corpus doctors ask these questions much more than patients and certain characteristics of the discourse of power can be recognized – doctors sometimes use tag questions to direct their patients to a particular answer they find most appropriate. On the other hand, patients never ask tag questions to this purpose, but exclusively in order to check a particular piece of information or if they have understood doctor's instructions correctly, which again proves the existence of asymmetry in doctor-patient interaction.

Transcription symbols used in the paper [24, 25, 26]:

//	the beginning of overlap/interruption
=	tightly connected elements, no pause
(..)	1 to 3 seconds long pause
(...)	pause longer than 3 seconds
/	repair
↑	rising intonation
:	prolonged syllable
[...]	a part of conversation that has not been included in the excerpt
?	interrogative intonation

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Received: 8.9.2020 • Accepted: 1.12.2020

Uloga dopunskih pitanja u medicinskom susretu

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KRATAK SADRŽAJ

Diskurs medicinskih susreta smatra se odličnim primerom kako institucionalne komunikacije tako i diskursa moći. Postavljanje pitanja predstavlja verovatno najupadljiviju odliku interakcije lekara i pacijenta, a ovaj rad se bavi dopunskim pitanjima kao jednim od nekoliko tipova pitanja koja se sreću u gotovo svakom medicinskom susretu. Bavićemo se dopunskim pitanjima kroz predstavljanje rezultata nekih dosadašnjih istraživanja u oblasti medicinskog susreta, te poređenjem i komentarisanjem transkribovanih snimaka medicinskih susreta na engleskom i srpskom. Utvrdićemo koliko često se ovaj tip pitanja sreće u datim korpusima, kako se ovim pitanjima služe lekari a kako pacijenti, kao i kakvu ulogu ona imaju u medicinskom susretu. Najzad, imajući u vidu činjenicu da postavljanje bilo kakvog pitanja u okviru institucionalne komunikacije zahteva izvesnu količinu moći, takođe ćemo pokušati da utvrdimo da li upotreba dopunskih pitanja utiče na položaj lekara i pacijenta u medicinskom susretu.

Ključne reči: kontrastivna analiza; diskurs moći; institucionalna komunikacija; medicinski susret; dopunska pitanja

UVOD

Institucionalna komunikacija se istražuje sa različitih aspekata i na multidisciplinaran način u okviru brojnih naučnih oblasti (lingvistike, sociologije, antropologije, psihologije itd.). Ovaj tip komunikacije uglavnom podrazumeva interakciju poput one koja se sreće između nastavnika i učenika, lekara i pacijenta, policajca i svedoka/uhapšenika ili novinara i osobe koju intervjuiše, gde jedan učesnik u komunikaciji ima ulogu zvaničnog predstavnika određene institucije, a drugi ulogu klijenta te institucije. Dok tzv. svakodnevna komunikacija uglavnom podrazumeva simetričnu interakciju između sagovornika koji imaju potpuno jednaka prava, institucionalna komunikacija se uglavnom odlikuje upadljivom asimetrijom i nejednakom raspodelom moći [1]. Iz ovog razloga, Ferklaf smatra da takvu interakciju treba nazvati *nejednakim susretom* [2].

Komunikacija između lekara i pacijenta smatra se odličnim primerom specifične raspodele moći u oblasti institucionalne komunikacije. Može se istraživati sa različitih aspekata, ali upotreba pitanja je verovatno najbolji način da se predstave neke važne razlike koje postoje među ulogama predstavnika institucije i korisnika usluga koje ta institucija pruža.

Ovaj rad će se najpre ukratko pozabaviti klasifikacijom pitanja i opštim razlozima za postavljanje pitanja u ovom tipu institucionalne komunikacije. U narednom odeljku, detaljnije ćemo se baviti definisanjem i odlikama dopunskih pitanja. Služićemo se primerima iz dva korpusa (korpusa na engleskom jeziku i korpusa na srpskom jeziku) kako bismo predstavili rezultate koje smo dobili poređenjem snimaka razgovora između lekara i pacijenta na engleskom i srpskom jeziku.

Ovaj rad ima za cilj da istraži koliko često se koriste dopunska pitanja u datim korpusima, kako se njima služe lekari a kako pacijenti i kakvu ulogu ova pitanja imaju u medicinskim susretima koji se odvijaju na dva različita jezika i samim tim u dve različite kulture. Najzad, pokušaćemo da utvrdimo i da li i u kojoj meri upotreba ovog tipa pitanja utiče na položaj lekara i pacijenta u medicinskom susretu.

PITANJA U MEDICINSKOM SUSRETU

Različiti autori nude različite definicije pitanja koja se postavljaju u medicinskim susretima, kao i kada je reč o vrstama pitanja i ulozi koju imaju u interakciji lekara i pacijenta. Međutim, mnogi autori tvrde da se većina pitanja postavlja tokom faze uzimanja anamneze i da ih uglavnom postavljaju lekari, ne pacijenti [3, 4].

Mišler je bio jedan od prvih autora koji su se bavili ovim aspektom medicinskog susreta, a u svom istraživanju izdvojio je nekoliko vrsta pitanja – da/ne pitanja,[1] alternativna/disjunktivna pitanja,[2] posebna (pronominalna) pitanja,[3] umereno otvorena pitanja[4] i otvorena pitanja[5] [4]. Pored toga, on je došao do zaključka da je većina pitanja koja su postavili lekari bila tako koncipirana da je ograničavala odgovore koje su davali pacijenti i samim tim omogućavala lekarima da upravljaju kako razgovorom tako u velikoj meri i pacijentovim doprinosom razgovoru [4].

Ejnsvort-Von se opredelila za nešto drugačiju klasifikaciju, u kojoj je izdvojila sledeće vrste pitanja: posebna (pronominalna) pitanja,[6] pitanja sa da/ne odgovorom,[7] eho-pitanja,[8] eliptična pitanja,[9] dopunska pitanja i intonacioni upitni iskazi.[10] Takođe se bavila takozvanim retoričkim pitanjima, koja više podsećaju na naredbu ili iskaz nego na prava pitanja jer se ne očekuje davanje pravog odgovora [5].

1 Npr. *Da li imate temperaturu?* Jedina dva moguća odgovora na ovo pitanje jesu *da* ili *ne.*

2 Ovakva pitanja nude dva alternativna odgovora, npr. *[...]ovaj vaš kašalj, iskašljavate li nešto ili je kašalj suv?* [4].

3 Npr. *Kada ste prvi put primetili taj simptom?* Od pacijenta se očekuje da da konkretan odgovor.

4 Pitanja koja počinju sa *A šta je sa …* ili *A …*, npr. *A šta je sa vašim nogama?* Ovakva pitanja sagovorniku pružaju mogućnost da ispriča svoju priču o konkretnom događaju ili problemu (u ovom slučaju o nogama), bez ograničavanja na konkretan odgovor.

5 Npr. *Kako se osećate?*

6 Pitanja koja je Mišler klasifikovao kao posebna (pronominalna) pitanja [4].

7 Da/ne pitanja u Mišlerovoj klasifikaciji [4].

8 U ovom tipu pitanja upitna reč nikada ne zauzima inicijalnu poziciju, već se uglavnom nalazi na samom kraju pitanja, na poziciji koja odgovara njenoj sintaksičkoj ulozi, npr. *Imate zakazano kada?*

9 Ovo nisu prava pitanja, ali imaju komunikativnu vrednost pitanja [9]. U ovakvim pitanjima naglašava se tema iz prethodnog konteksta, tako da oba sagovornika znaju na šta se pitanje odnosi, npr. *Sve ostalo nepromenjeno*? (ovde i lekar i pacijent znaju tačno na šta se sve ostalo odnosi).

10 Na prvi pogled, ovo uopšte nisu pitanja, jer su formulisana kao izjavne rečenice. Međutim, zahvaljujući uzlaznoj intonaciji, ona imaju upitnu komunikativnu vrednost [9], npr. *Imate prethodni izveštaj*?

Bojd & Heritidž i Hajano istraživali su pitanja koja postavljaju lekari, pri čemu su posebno naglasili trojaku funkciju koju ovakva pitanja imaju u medicinskom susretu – (1) ograničavaju pacijentov odgovor nametanjem odgovarajuće agende,[11] (2) sadrže pretpostavke o različitim aspektima pacijentovog zdravlja i njegovog poznavanja medicine[12] i (3) favorizuju jednu vrstu odgovora u odnosu na drugu[13] [3, 6]. Bojd & Heritidž takođe insistiraju na tzv. *principu optimizacije* – činjenici da su lekarova pitanja tokom faze uzimanja anamneze najčešće formulisana tako da predviđaju najbolji mogući scenario[14] [3].

Zanimljivo je to što se većina istraživanja bavi samo pitanjima koja postavljaju lekari, a što se pitanja koja postavljaju pacijenti uopšte ne uzimaju u obzir [3, 4, 6]. Neki autori, poput Mišlera, uopšte ne veruju da pacijent može da postavi pitanje tokom medicinskog susreta, jer to smatraju isključivo privilegijom lekara [4]. Nakon što su analizirali preko 2500 snimaka, Birn i Long su došli do zaključka da upravo postavljanje pitanja lekara daje veliku moć nad pacijentima, čiji je doprinos sasvim beznačajan i ograničen na sam kraj razgovora [7]. Ferklaf tvrdi da se čitav medicinski susret zasniva na lekarovom postavljanju pitanja i da lekar ima potpunu kontrolu nad sistemom preuzimanja reči u ovom vidu komunikacije [8]. On takođe smatra da je pacijentov doprinos u potpunosti zanemarljiv, te da pacijenti zapravo govore tek onda kada ih lekar na to podstakne svojim pitanjima. Međutim, neki autori su dokazali da pacijenti ipak postavljaju pitanja tokom medicinskog susreta, pa čak i da to čine redovno, ali svakako znatno ređe nego lekari [5, 10].[15]

Zašto lekari i pacijenti postavljaju pitanja tokom medicinskog susreta? Klikovac navodi nekoliko razloga za to što lekar postavlja pitanja – (1) želi da sazna sve što se može smatrati važnim pre nego što postavi dijagnozu ili predloži način lečenja, (2) želi da usmeri pacijenta ka određenom odgovoru ili da ga ohrabri da nastavi da govori i kaže više o konkretnoj temi razgovora ili (3) želi da izvede zaključak [11].

Kordela se bavila i pitanjima koja postavljaju lekari i onima koje postavljaju pacijenti i izdvojila je nekoliko različitih *glasova* kojima se i jedni i drugi služe prema situaciji ili tipu ličnosti [12]. Kada je reč o pacijentima, Kordela je utvrdila da je samo jedna grupa pacijenata (tzv. *glas inicijatora*) zapravo postavljala pitanja i da su to činili kako bi saznali više o svom zdravlju, da bi bolje razumeli svoje stanje i da bi se bolje brinuli o svom zdravlju [12]. MekKenzi je sprovela istraživanje u kojem su učestvovale žene sa blizanačkim trudnoćama, od kojih je većina priznala da veruje kako je potrebno da unapred napravi spisak pitanja koja želi da postavi svom lekaru, pre nego što uđe u ordinaciju, kao i da su bile nezadovoljne činjenicom da im njihovi lekari nisu saopštavali informacije [13]. Adler i dr. su čak izneli tvrdnju da su neki pacijenti[16] smatrali da je neprimereno postavljati lekaru pitanja jer se time može pokvariti odnos lekara i pacijenta [14].

DOPUNSKA PITANJA

Dopunska pitanja se uglavnom koriste kako bi se proverilo da li je nešto tačno ili kako bi se zatražilo da se sagovornik složi sa izgovorenim [16]. U engleskom jeziku, dopunska pitanja se grade upotrebom pomoćnog glagola ili glagola *do*, koji se smeštaju na sam kraj pitanja, iza zareza. Negativno dopunsko pitanje koristi se uz afirmativnu rečenicu, dok se pozitivno dopunsko pitanje uvek sreće u kombinaciji sa negativnom rečenicom [17].[17]

U srpskom jeziku dopunska pitanja nisu često istraživana, ali nailazi se na dva termina koja bi mogla biti ekvivalenti terminu na engleskom jeziku – *dopunska pitanja* [18] i *finitivne rečenične upitne forme* [9]. Baš kao u engleskom jeziku, upitna reč se smešta na kraj rečenice, a smatra se da takva pozicija menja komunikativni status rečenice pretvarajući je iz izjave u pitanje [9]. Važno je naglasiti da se kao odgovor na ovakva pitanja očekuju isključivo potvrdni odgovori, kao i da se odnose na nešto o čemu je prethodno bilo reči [18]. Najčešći upitni markeri u dopunskim pitanjima na srpskom jeziku su: *je l'?, je l' da?, zar ne?, je li?, a?*, a za razliku od dopunskih pitanja na engleskom jeziku oni nikada ne menjaju svoj oblik u zavisnosti od upotrebljenog vremena ili gramatičke strukture.[18] Ovakvi markeri nazivaju se *(dopunskim) upitnim operatorima* [9] ili *privescima* [19]. Zanimljivo je pomenuti da su Hudeček i Vukojević došli do zaključka da se dopunska pitanja sreću isključivo u svakodnevnoj komunikaciji, što može biti važno prilikom utvrđivanja žanra medicinskih susreta [20].[19]

Zanimljivo je proučavati dopunska pitanja jer se znatno razlikuju od većine drugih vrsta pitanja. Pošto iza takvog pitanja uvek očekujemo potvrdni odgovor, često se i ne smatraju pitanjima; to bi moglo da bude objašnjenje za činjenicu da ih je jedino Ejnsvort-Von brojala kao pitanja u svom istraživanju [5]. Smatrali smo da bi bilo korisno proveriti koliko često lekari i pacijenti koriste ovu vrstu pitanja, kao i da li ih koriste u iste svrhe. Pošto se dopunska pitanja uglavnom postavljaju kako bi se proverila određena informacija ili kako bi se od sagovornika zatražilo da se složi sa izrečenim, mogu se posmatrati i kao demonstracija moći (od sagovornika se očekuje da se složi sa izrečenim, da se ne suprotstavlja, da ne iznosi svoje mišljenje) ili jednostavno kao način da se druga osoba ohrabri da kaže nešto više o određenoj temi.

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11 Nametanjem određene teme ili nametanjem agende koja se odnosi na posebnu aktivnost koja se očekuje od pacijenta (da dâ potvrdan ili odričan odgovor, da objasni nešto itd.)

12 Ovo je mnogo češće slučaj sa posebnim (pronominalnim) pitanjima nego sa da/ne pitanjima. U primeru *Koje lekove uzimate?* od pacijenta se ne očekuje da kaže da li uzima lekove ili ne, već se samo očekuje da dâ odgovor na pronominalno pitanje.

13 Ovo zapravo znači da je pitanje tako formulisano da se prirodno očekuje potvrdan ili odričan odgovor (npr. Ne patite od gorušice?).

14 Na primer, lekar bi uvek radije pitao *Da li vam je otac živ?* nego *Da li vam je otac mrtav?*

15 U Frenklovom istraživanju pacijenti su postavili samo 1% od ukupnog broja pitanja [10], u istraživanju koje je sprovela Vest prijavljeno je 9% pitanja koja su postavili pacijenti [15], dok je kod Ejnsvort-Von taj procenat porastao na čak 39% [5].

16 Reč je o onkološkim pacijentima ženskog roda starosti između 65 i 85 godina.

17 Npr. You haven't got the results yet, *have you*?; She doesn't look well, *does she*?

18 Npr. *To je sve, je l' da?*

19 Dok neki autori čvrsto veruju u to da je medicinski susret klasičan intervju sa jasno definisanim ulogama onoga ko postavlja pitanja i onoga ko na njih odgovara [4, 10], neki drugi smatraju da se zapravo radi o kombinaciji dva žanra – intervjua i svakodnevne komunikacije [5, 21, 22, 23].

REZULTATI ISTRAŽIVANJA

Kako bismo proverili koliko često lekari i pacijenti koriste dopunska pitanja i kakvu ulogu ova pitanja imaju u medicinskom susretu, uporedili smo snimke medicinskih susreta na engleskom i srpskom.

Korpus na engleskom jeziku sastoji se od 19 snimaka, dok korpus na srpskom jeziku sadrži 80 snimaka, pri čemu i jedan i drugi korpus traju po oko pet sati, što ih čini jednakima po dužini. Snimke iz korpusa na engleskom jeziku dobili smo ljubaznošću profesora Ričarda Frenkla sa Medicinskog fakulteta Univerziteta u Indijani, SAD. Ovi snimci načinjeni su na jednoj univerzitetskoj američkoj klinici, a pripadaju oblastima ortopedske hirurgije (14 snimaka) i interne medicine (pet snimaka). Snimci iz korpusa na srpskom jeziku nastali su u jednoj ustanovi tercijarne zdravstvene zaštite u Beogradu, a pripadaju oblastima pulmologije (37 snimaka) i pedijatrije (43 snimka).

Od ukupno 334 postavljena pitanja u korpusu na engleskom jeziku, bilo je svega osam dopunskih pitanja (2,4%); četiri dopunska pitanja postavili su lekari, a četiri pacijenti. U korpusu na srpskom jeziku bilo je 40 dopunskih pitanja od ukupno 497 postavljenih pitanja (8%); 30 dopunskih pitanja postavili su lekari (75%), a 10 pacijenti (25%). Dakle, može se zaključiti da su dopunska pitanja dosta retka u korpusu na engleskom jeziku, dok se u korpusu na srpskom jeziku javljaju češće, te da ih lekari koriste više nego pacijenti. Rezultati su prikazani u Tabeli 1.

Lekari iz korpusa na engleskom jeziku uvek su postavljali dopunska pitanja jednostavno da bi proverili određeni podatak (Primer 1).

Primer 1:
D: [...] **Doksiciklin od 100, je l' tako?**
P: O bože, ne znam.
D: Proizvodi se od 50 i od 100.
P: Da.

U ovom primeru lekar se služi dopunskim pitanjem kako bi proverio određeni podatak – dozu leka koji pacijent trenutno uzima. Izborom baš ove vrste pitanja, lekar takođe usmerava pacijenta ka određenom odgovoru koji lično smatra adekvatnim. Dakle, postavljanjem ovakvog pitanja lekar ne traži nikakvu informaciju, već samo želi da potvrdi svoju pretpostavku o podatku koji već ima.

Za razliku od svojih američkih kolega, lekari iz korpusa na srpskom jeziku koristili su dopunska pitanja na nekoliko različitih načina. I oni su najčešće posezali za ovom vrstom pitanja kako bi proverili određeni podatak ili informaciju (Primer 2), ali su ih takođe koristili kada su želeli da provere da li je pacijent razumeo nešto što su mu prethodno saopštili (Primer 3), kako bi opustili pacijenta (Primer 4), te da bi dobili na vremenu ili naterali pacijenta da promeni mišljenje (Primer 5). Pedijatri su se takođe služili dopunskim pitanjima kako bi pacijenta naveli na određeni odgovor (Primer 6).

Primer 2:
L: [...] **Vi imate još uvek onaj Seratide od 250, je l' tako?**
P: A-ha. To je zadnji put doktor prepis'o. Kao, sve u redu i onda po/posluša me i vidi [...][20]

U ovom slučaju lekar postavlja dopunsko pitanje iz dva moguća razloga – kako bi nešto izjavio ili da bi proverio nešto što već zna, a u oba slučaja ne očekuje od pacijenta da odgovori na pitanje. Izborom ovog pitanja lekar se nada potvrdnom, nikako negativnom odgovoru. Dopunski operator *je l'* koji je ovde zastupljen ujedno je i najčešći dopunski operator u celom korpusu na srpskom jeziku. Prema očekivanjima, pacijent potvrđuje lekarovu izjavu upotrebom minimalnog responsa *a-ha*.

Primer 3:
L: Sad ćete, kad pređete na ovih 80, pratite. Ako vidite da se/da to ide stabilno, da se ništa ne menja, onda nastavite. Ako vidite da se nešto događa, javite se pre ova tri meseca (..) Ili bolje dva. Pošto imamo malu dozu pa da vas ispratimo (.) **Razumeli smo se, je l' tako**?

U ovom odlomku lekar pacijentu daje uputstva u vezi sa promenjenom dozom leka koji već koristi. U većem delu svog turnusa, lekar određuje pacijentovo ponašanje govoreći mu šta da radi i otkrivajući dva moguća scenarija. Zanimljivo je to što lekar iznenada počinje da se služi prvim licem množine (mi) – *imamo malu dozu, da vas ispratimo*. On se služi prvim licem množine iz jednog od dva razloga – da označi sebe i pacijenta u aktivnosti koja je samo naizgled zajednička ali zapravo zavisi samo od lekara ili da označi sebe i druge lekare kao profesionalce [11]. Najzad, dopunsko pitanje *Razumeli smo se, je l' tako?* upotrebljeno je samo kako bi lekar proverio da li je pacijent čuo i razumeo sve o čemu je bilo reči, ali je ujedno i dobar primer diskursa moći u okviru institucionalne komunikacije – lekar očekuje isključivo potvrdu (dakle, od pacijenta se očekuje da dobro razume sve što mu je rečeno) i izborom prvog lica množine lekar možda sebi dodeljuje ulogu autoriteta.

Primer 4:
L: Slano to more. **Presoljeno, je l' da**?
P: A-ha.

U ovom primeru pedijatar koristi dopunsko pitanje samo kako bi nasmejala svog malog pacijenta i pomogla mu da se opusti. Šali se na račun toga što je more slano i očigledno ne očekuje da dobije odgovor na svoje pitanje, već samo da se pacijent složi sa njom i da shvati šalu.

Primer 5:
L: Dobro, jeste li sad rešili to što:
P: // Ne
L: **Niste je l'**?
P: Preko dana nemam, nego preko noći [...]

Ovde je dopunsko pitanje postavljeno kako bi lekar naterao pacijenta da još jednom razmisli o onome što je upravo odgovorio ili jednostavno kako bi lekaru obezbedilo još malo vremena da razmisli o onome što je upravo čuo. Takođe je moguće da je lekar očekivao potvrdan odgovor, pa se stoga zbunio i bilo mu je potrebno malo dodatnog vremena kako bi razmislio o problemu.

Primer 6:
L: A, kaži mi, koliko često se te glavobolje događaju?
P: Pa, dva puta nedeljno.

20 D: [...] You still have that Seratide 250, don't you?
P: Yeah. That's what doctor prescribed las' time. Everything was ok, he said, and then he listened to my lungs and realized [...]

L: I kad si na raspustu i kad si u školi? = Kad imaš obaveze i kad nemaš obaveze↑ **Sad preko raspusta je ređe, je l' tako?**
P: Da.

Ovo je tipičan primer navođenja pacijenta na određeni odgovor ili pomaganja pacijentu da odgovori na postavljeno pitanje. Pedijatri su često koristili dopunska pitanja u ovu svrhu, dok u razgovorima sa pulmologom nije bilo nijednog primera ovakve upotrebe dopunskih pitanja. Ova činjenica može biti u vezi sa razlikama koje postoje između pedijatrije i gotovo svih drugih grana medicine – pedijatri komuniciraju sa decom (i njihovim roditeljima) i moraju da nađu način da saznaju sve što žele a da pritom ne preplaše pacijenta.

Pacijenti u korpusu na engleskom jeziku uglavnom su koristili dopunska pitanja samo kako bi proverili neku informaciju (Primer 7).

Primer 7:
P: **[...] Ne postoji (...) neki drugi lek za ovo, je l'?**
Li: Prednizon je/nikad nisam/nisam čuo ni za šta drugo što ima efekta [...]
P: Mhm (.) Ima efekta, mislim da pomaže (...) **ali zbog njega čovek zadržava tečnost, zar ne?**
D: Pomalo [...]

U ovom primeru pacijent postavlja dva dopunska pitanja. Prvo pitanje je negativno polarizovano i čak iako ga pacijent postavlja nadajući se da možda ipak postoji neki drugi način lečenja, on ipak očekuje od lekara negativan odgovor. Lekar okleva, kao da ne želi da razočara pacijenta, ali najzad priznaje da je lek koji pacijent trenutno koristi jedina mogućnost. Pacijent potom postavlja još jedno dopunsko pitanje, tražeći potvrdu za nešto što je i sam već primetio.

Pacijenti iz korpusa na srpskom jeziku koristili su dopunska pitanja na isti način – da bi proverili neku informaciju (Primer 8), ali i kako bi proverili da li su dobro razumeli svog lekara (Primer 9).

Primer 8:
P: [...] **Onda ću opet morati da uzmem uput, je l' tako**?
L: // Ne morate.

U ovom primeru pacijent prosto proverava da li je informacija koju poseduje ispravna kako ne bi napravio grešku. Umesto da postavi da/ne pitanje (*Da li ću morati ponovo da uzmem uput?*), on ga pretvara u dopunsko pitanje jer veruje da će biti neophodno da uzme novi uput pre nego što ponovo poseti svog lekara. Na njegovo iznenađenje, lekar mu daje negativan odgovor.

Primer 9:
L: A, nemojte sada, pređite po potrebi.
P: **Po potrebi, je l'**?
L: Jeste.

Ovo je završna faza medicinskog susreta i lekar raspravlja o terapiji i daje pacijentu uputstva. Stoga pacijentovo pitanje *Po potrebi, je l'?* ima za cilj da proveri da li je pravilno razumeo lekara i da se uveri da će sve sprovesti kako treba. Ovo nije klasično dopunsko pitanje, budući da je pomalo eliptično, ali svakako ga možemo smatrati dopunskim pitanjem jer se očekuje potvrdan odgovor.

ZAKLJUČAK

Komunikacija lekara i pacijenta, kao jedan od najčešće istraživanih tipova institucionalne komunikacije, istražuje se sa više aspekata. Postavljanje pitanja unutar medicinskog susreta smatra se jednom od najvažnijih odlika ovog vida komunikacije. Prema nekim autorima, pravo na postavljanje pitanja pripada isključivo lekarima, dok neki drugi autori tvrde da pacijenti ipak mogu postavljati pitanja, ali da to čine ređe od lekara i u potpuno različite svrhe.

Veruje se da privilegija da postavljaju pitanja lekarima omogućava da kontrolišu čitav susret – oni se služe pitanjima da navedu pacijenta na određeni željeni odgovor, da ih ohrabre da kažu više o određenoj temi ili da im uslove ponašanje tokom susreta. Pacijenti takođe postavljaju pitanja, ali to očigledno čine na drugačiji način, uglavnom sa ciljem da se raspitaju o svom zdravlju.

Dopunska pitanja nisu istraživana u jednakoj meri kao neke druge vrste pitanja i ubrojana su u pitanja u samo jednom većem istraživanju [5]. Ova pitanja možda i ne liče na pitanja, jer se iza njih očekuje isključivo potvrdan odgovor. Dakle, postavljanje dopunskog pitanja znači traženje potvrde ili proveravanje nekog podatka.

U našem istraživanju medicinski susreti iz dva različita korpusa, na engleskom i srpskom jeziku, poređeni su kako bismo proverili koliko često se koriste dopunska pitanja, kako ih koriste lekari a kako pacijenti i kakva je njihova uloga u medicinskom susretu. Dobijeni rezultati pokazuju da je upotreba dopunskih pitanja četiri puta češća u korpusu na srpskom jeziku nego u korpusu na engleskom jeziku. U korpusu na engleskom jeziku lekari i pacijenti postavili su podjednak broj dopunskih pitanja, pri čemu su i jedni i drugi tu vrstu pitanja postavljali isključivo da bi proverili određenu informaciju. S druge strane, u korpusu na srpskom jeziku lekari su postavljali dopunska pitanja mnogo češće nego pacijenti. Pored toga što su ovim pitanjima proveravali određenu informaciju, koristili su dopunska pitanja na još nekoliko načina – da pomognu pacijentu da se opusti, da dobiju na vremenu ili da nateraju pacijenta da ponovo razmisli o onome što je rekao, da provere da li je pacijent razumeo nešto što su mu rekli ili da navedu pacijenta na određeni odgovor. Pacijenti u korpusu na srpskom jeziku koristili su dopunska pitanja kako bi proverili informaciju ili da bi proverili da li su dobro razumeli svog lekara i instrukcije koje su od njega dobili.

Kada je reč o diskursu moći i položaju lekara i pacijenta u medicinskom susretu, ne možemo se složiti sa time da su pacijenti potpuno lišeni prava da postave bilo kakvo pitanje, uključujući dopunsko pitanje. U korpusu na engleskom jeziku gotovo da ne postoje razlike između lekara i pacijenta. Međutim, u korpusu na srpskom jeziku lekari su postavljali dopunska pitanja znatno češće od pacijenata, a možemo prepoznati i izvesne karakteristike diskursa moći – lekari povremeno koriste dopunska pitanja kako bi pacijenta usmerili ka odgovoru koji smatraju adekvatnim. Sa druge strane, pacijenti nikada ne postavljaju dopunska pitanja u tu svrhu, već isključivo kako bi proverili tačnost određene informacije ili da li su dobro razumeli šta lekar od njih očekuje, što takođe ukazuje na postojanje asimetrije u komunikaciji između lekara i pacijenta.

Simboli koji su korišćeni prilikom transkripcije razgovora [24, 25, 26]:

//	početak preklapanja/prekidanje sagovornika
=	tesno povezani elementi, bez pauze
(..)	pauza duga od jedne do tri sekunde
(...)	pauza duža od tri sekunde
/	popravka
↑	uzlazna intonacija
:	produženi slog
[...]	deo razgovora koji nije uključen u odlomak
?	upitna intonacija

CASE REPORT
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DOI: https://doi.org/10.2298/SGS2004219P
UDC: 615.28.06:616.314; 616.314-085

Periradicular tissue necrosis caused by accidentally injected sodium hypochlorite through *fausse route* in upper maxillary canine

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SUMMARY

Sodium hypochlorite (NaOCl) is a strong antiseptic agent that is usually used as endodontic irrigant for dissolving organic parts of pulp and dentin and neutralizing toxic products. However, the use of sodium hypochlorite may cause destruction of blood vessels, soft tissues and bone necrosis if extruded into the periapical region. Urgent treatment of the NaOCl accident should be oriented on pain relief, infection control and recovery.

This paper shows a case of periradicular tissue necrosis after accidental extrusion on NaOCl through *fausse route* of right maxillary canine, and complete tissue regeneration after surgical debridement and bone augmentation with addition of platelet rich fibrin (PRF) that occurred in a 53-year old patient at the dental clinic of Faculty of Dentistry in Pancevo.

Keywords: sodium hypochlorite toxicity; periradicular extrusion; bone necrosis; tissue regeneration

INTRODUCTION

Root canal treatment is routinely performed using a combination of mechanical and chemical debridement of pulp remnants and bacteria from the root canal system. Sodium hypochlorite (NaOCl) is most commonly used irrigant in endodontics that dissolves organic component of soft tissue in the root canal [1, 2]. It has high pH value (11-12.5) and great antimicrobial effect [3]. It is useful adjunct to mechanical debridement of the canal, especially in curved, accessory or lateral canals [4]. In some rare cases, NaOCl may cause bone and soft tissue necrosis if extruded trough the apex into the periapical tissue or maxillary sinus [5, 6]. *In vitro* study has shown that even low concentrations of NaOCl were lethal to human fibroblasts [3].

NaOCl is very toxic to intraoral tissues where it causes dissolution of organic parts and destruction of blood vessels [7]. For that reason, it is very important to prevent extrusion of NaOCl from root canal into periradicular and surrounding tissues.

Urgent treatment of the NaOCl accident should be oriented on pain relief, infection control and recovery. Analgesics and local anesthetics may help in pain control. Cold compresses may be useful in reducing oedema and discomfort in patients, such as burning sensations. Surgical debridement of necrotic tissue is very important in infection control and tissue regeneration [8].

The aim of this report was to show periradicular tissue necrosis after accidental extrusion of NaOCl throughout *fausse route* of right maxillary canine, and complete tissue regeneration after surgical debridement and bone augmentation with addition of platelet rich fibrin (PRF).

CASE REPORT

A 53 year-old female patient presented at the dental clinic of the Faculty of Stomatology in Pancevo for endodontic treatment of right maxillary canine. The patient had neither systemic diseases nor allergy, and was classified in ASA I group. She complained of severe, dull, almost constant pain in the region of right maxillary canine. The young dentist who was in the office that day took anamnestic data, did the clinical examination, and analyzed ortopantomogram image of the patient. The tooth #13 was diagnosed with irreversible pulpitis. Vital pulpectomy was performed after injection of local anesthesia (4% articaine with adrenaline 1:100 000). Instrumentation was done with hand and rotary endodontic files. Irrigation of the root canal was achieved by 2% NaOCl. Immediately after irrigation, oedema of the right cheek was evident, and the right nasolabial fold was completely erased (Figure 1). After the local anesthesia ceased, the patient felt strong pain in the right upper vestibule, above the root of the upper canine. Following two days the patient was filling strong pain, resistant to common painkillers and came back to our clinic. Clinical examination revealed necrotic alveolar mucosa, in diameter, in the upper vestibule, above the region of right maxillary canine and first premolar (Figure 2).

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Figure 1. Swelling of the right cheek immediately after irrigation with sodium hypochlorite
Slika 1. Otok desnog obraza neposredno posle irigacije kanala natrijum-hipohloritom

Figure 2. Soft tissue necrosis
Slika 2. Nekroza mekog tkiva

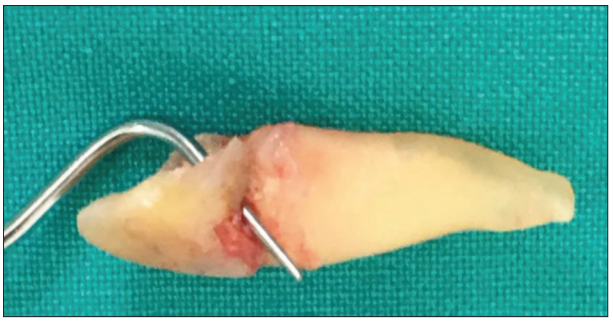

Figure 3. *Fausse route* – extracted right maxillary canine
Slika 3. Perforacija korena na izvađenom gornjem desnom očnjaku

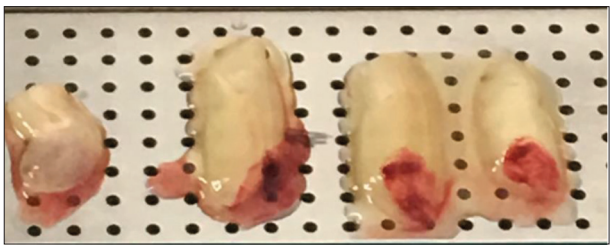

Figure 4. Prepared PRF membranes
Slika 4. Pripremljene PRF membrane

Figure 5. Bone defect filled with cortico-spongious bone granules mixed with PRF
Slika 5. Defekt kosti ispunjen granulama kortikospongiozne kosti pomešane sa PRF

Under local anesthesia, trapezoidal mucoperiosteal flap was raised, involving necrotic mucosa, and necrotic bone was observed. Tooth #13 was examined carefully and *fausse route* was found in the cervical third of the root. After the tooth #13 extraction, *fausse route* in the cervical third of the root was confirmed extraorally with endodontic file (Figure 3). Surgical debridement of the wound was done using Lucas surgical curette. In order to improve soft and bone tissue healing, we decided to make PRF membranes from patient`s blood. PRF was prepared according to the instructions. Briefly, 10 mL of patient`s blood (in dry, 10-mL Monovette tubes without anticoagulant or other additional chemical agents) was obtained from venous blood and centrifuged immediately for 10 min at 3, 000 rpm in a laboratory centrifuge (TDZ5-WS, XIANGYI, Hunan, China). The centrifuged product consisted of three layers, with the PRF clot being located in the middle layer. The PRF clot was harvested with forceps and gently pressed into a membrane between two sterile pieces of gauze using soft compression for 10 seconds to maintain the wetness of the membrane (Figure 4). The alveolar bone defect was filled with granulated bone particles (BioOss®, Geistlich, Switcerland) mixed with patient`s blood and the particles of PRF (Figure 5). Then, double layer of PRF membranes was placed over the bone graft (Figure 6), and mucoperiosteal flap primarily sutured with silk suture 4-0. Postoperative antibiotics (Amoxicilin®, Hemofarm, Serbia) were prescribed three times a day for 7 days. The wound healed uneventfully. Complete soft tissue healing was observed 15 days after the surgery.

Figure 6. PRF membranes placed over the bone graft
Slika 6. PRF membrane postavljene preko koštanog grafta

Figure 7. Complete wound healing two weeks after surgery
Slika 7. Kompletno zarastanje rane dve nedelje posle hirurške intervencije

DISCUSSION

Sodium hypochlorite is the most important irrigant in everyday endodontic practice. In rare cases, NaOCl may cause tissue necrosis if extruded over the root apex [9]. It was shown, in few case reports, that NaOCl can be accidentally injected instead of local anesthetic and cause gingival and bone necrosis [10, 11]. Although rarely, inadvertent extrusion of NaOCl beyond root apex could cause permanent nerve damage [12]. In our patient, there was no permanent nerve damage. Haton et al. reported a case of accidentally injected NaOCl throughout root perforation of the first upper premolar [8]. Their patient experienced oedema and pain of the right cheek that resolved after palliative treatment with intravenous antibiotics, corticosteroids and painkillers. In our patient, NaOCl was injected trough *fausse route* of right upper canine, and caused painful bone and soft tissue necrosis.

Two main symptoms of root perforation (*via falsa*) are intensive bleeding from root canal (periodontal ligament) and intensive pain. Both symptoms were masked in our patient, having in mind that 4 ml of articaine with adrenaline (1:100 000) as a vasoconstrictor was administered. Namely, local anesthetic blocked pain impulses, so the moment of perforation of the root and damage of periodontal ligament were not painful. Likewise, adrenalin from local anesthetic solution caused vasoconstriction and for that reason bleeding from root canal perforation was not obvious as usually in *fausse route* cases. Beside canine root perforation, the possible explanation for massive periradicular tissue necrosis may be the anatomical variation in bone morphology. In our patient, dehiscence of vestibular alveolar bone was probably present and may be the reason for severe and easy extrusion of NaOCl in connective tissue.

Panfacial oedema is the most frequent sign of extrusion of NaOCl into periapical tissues [13]. Oedema of facial soft tissues could be explained by toxic and hyperosmotic properties of NaOCl. In some cases, NaOCl had dissolved blood vessel walls and produced ecchymosis of facial or even neck region [14]. In our patient only facial oedema without ecchymosis of the skin was present. Strong pain that our patient felt could be explained by tissue ischemia and direct neurotoxic effect of NaOCl. Pain completely disappeared after surgical debridement of necrotic tissues.

Platelet rich fibrin (PRF) is a natural biomaterial, with high concentration of thrombocytes, growth factors and leucocytes [15]. Autologous PRF membranes provide enhanced healing of soft and bone tissue [16]. PRF has been used in dentistry for different procedures, such as: alveolar socket preservation, sinus-lift, periodontal flap surgery, augmentation of bone defects and implant therapy [17]. Growth factors in high concentration in PRF provide fast and stimulative effect to new blood vessels formation and faster regeneration of soft and bone tissue, with direct stimulative effect on bone marrow stem cells and osteogenic differentiation [18]. Our case confirmed excellent soft tissue healing after using PRF membranes. Indirectly, we assumed that bone tissue was also regenerated successfully, but without bone biopsy and histological evaluation, we cannot be completely sure.

CONCLUSION

NaOCl accident is very stressful incident for the dentist. Appropriate and fast diagnosing and treatment are necessary, as well as follow up. To date, there are no national guidelines available on the management of this condition, so precaution should be taken by dental practitioner in order to reduce potential damage caused by extrusion of NaOCl into the periradicular tissues.

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Received: 12.8.2020 • Accepted: 29.10.2020

Apikalna ekstruzija materijala za kanalno punjenje tokom uklanjanja gutaperke i resilona

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KRATAK SADRŽAJ

NaOCl predstavlja jako antiseptično sredstvo koje se najčešće koristi kao endodonstki irigans zbog svoje sposobnosti rastvaranja organskog dela dentina, razgradnje vitalnog i nekrotičnog tkiva i neutralizacije toksičnih materija. Međutim, upotreba NaOCl može imati i neželjene efekte u vidu oštećenja krvnih sudova, okolnog mekog tkiva i nekroze kosti ukoliko se rastvor ekstrudira u periapeksno tkivo.

Hitan tretman oštećenja izazvanih dejstvom NaOCl treba da se bazira pre svega na otklanjanju bola, sprečavanju razvoja infekcije i pospešivanju tkivne regeneracije. Na slučaju 53-godišnje pacijentkinje sa klinike Stomatološkog fakulteta u Pančevu prikazano je oštećenje periapeksnog tkiva gornjeg desnog očnjaka izazvanog dejstvom akcidentalno ekstrudiranog rastvora NaOCl kroz *fos rut* pomenutog zuba, kao i primer kompletne tkivne regeneracije primenom koštane augmentacije i trombocitima obogaćenog fibrina (PRF).

Ključne reči: toksičnost natrijum-hipohlorita; ekstrudiranje u periapeks; nekroza kosti; tkivna regeneracija

UVOD

Postupak lečenja kanala korena predstavlja kombinaciju mehaničke instrumentacije i primene hemijskih agenasa u cilju uklanjanja nekrotičnih ostataka pulpe i mikroorganizama iz kanalnog sistema korena [1, 2]. Natrijum-hipohlorit neretko predstavlja irigans izbora u endodontskoj terapiji zbog visoke pH vrednosti (11–12,5) i zadovoljavajućeg organolitičkog i antimikrobnog dejstva [3]. Upotreba NaOCl prilikom intsrumentacije omogućava lakšu evakuaciju debrisa, rastvaranje tkiva i uklanjanje razmaznog sloja, što je naročito značajno kod povijenih korenova odnosno kompleksnijih kanalnih sistema [4]. Međutim, upotreba NaOCl može imati i neželjene efekte u vidu oštećenja okolnog mekog tkiva i nekroze kosti ukoliko se rastvor ekstrudira u periapeksno tkivo [5, 6].

Pojedine *in vitro* studije su dokazale da čak i jako niska koncentracija NaOCl ima toksičan efekat na humane fibroblaste [3].

Imajući u vidu da NaOCl može izazvati ozbiljna oštećenja krvnih sudova i mekih tkiva, od izuzetne je važnosti naglasiti da se samo pažljivim i savesnim rukovanjem može izbeći transportacija rastvora u periapeks [7].

Hitan tretman oštećenja izazvanih dejstvom NaOCl treba da se bazira pre svega na otklanjanju bola, sprečavanju razvoja infekcije i pospešivanju tkivne regeneracije. Primena analgetika i lokalnog anestetika može biti efikasna u otklanjanju bolnih senzacija, dok korišćenje hladnih obloga može smanjiti otok i neprijatan osećaj pečenja koji se javlja kod pacijenata. S druge strane, adekvatan hirurški debridman nekrotičnog tkiva sprečava nastanak infekcije i omogućava lakšu regeneraciju tkiva [8].

Cilj ovog rada bio je prikaz oštećenja periapeksnog tkiva gornjeg desnog očnjaka izazvanog dejstvom akcidentalno ekstrudiranog rastvora NaOCl kroz *fos rut* pomenutog zuba, kao i prikaz kompletne tkivne regeneracije primenom koštane augmentacije i trombocitima obogaćenog fibrina (PRF).

PRIKAZ BOLESNIKA

Pacijent ženskog pola, starosti 53 godine, javlja se na kliniku Stomatološkog fakulteta u Pančevu radi lečenja gornjeg desnog očnjaka. Pacijentkinja negira bilo kakva sistemska oboljenja, prisutvo alergija i svrstava se u prvu ASA grupu.

Dežurni lekar tog dana izvršio je klinički pregled pacijenta, analizu ortopanskog snimka i na osnovu anamneze zabeležio je prisustvo konstantog, jakog i pulsirajućeg bola u predelu gornjeg desnog očnjaka.

Na osnovu prikupljenih podataka postavljenja je dijagnoza ireverzibilnog pulpitisa na zubu 13.

Posle aplikacije lokalnog anestetika (4% artikaina sa adrenalinom 1:100 000) izvršena je vitalna ekstirpacija puple. Prilikom mehaničke obrade kanala korišćeni su ručni i mašinski endodontski proširivači. Irigans izbora bio je 2% NaOCl. Neposredno posle ispiranja kanala rastvorom NaOCl primećen je otok desnog obraza, dok je desna nazolabijalna brazda bila evidentno „izbrisana". Nakon što je prestalo dejstvo anestetika, pacijentkinja je počela da oseća bolove u predelu gornjeg desnog vestibuluma u nivou projekcije korena očnjaka.

Ni posle dva dana bol nije nestao niti se smanjivao na analgetike, što je pacijentkinju navelo da se ponovo obrati za pomoć. Ponovnim kliničkim pregledom otkrivena je nekroza alveolarne mukoze gornjeg desnog vestibuluma, promera 3 cm, koja je zahvatala regiju očnjaka i prvog premolara.

U lokalnoj anesteziji izvršeno je odizanje trapezoidnog mukoperiostalnog režnja nakon čega je dijagnostikovana i nekroza kosti. Detaljnom opservacijom zuba 13, uočen je *fos rut* u cervikalnoj trećini korena. Posle ekstrakcije zuba 13, *fos rut* je potvrđen i ekstraoralno pomoću endodotske iglice. Hirurška sanacija rane obavljena je pomoću Lukasove hirurške kirete. U cilju boljeg zarastanja mekotkivnih i koštanih struktura, odlučili smo se za primenu PRF-a. Naime, uzeli smo 10 ml venske krvi pacijenta (u suvu, Monovet serumsku epruvetu, bez prisustva antikoagulanasa i drugih hemijskih agenasa) koju smo potom

centrifugirali 10 min. na 3000 rpm u laboratorijskoj centrifugi (TDZ5-WS, XIANGYI, HUNAN, China).

Posle procesa centrifugiranja, dobija se troslojna struktura u čijoj sredini se nalazi ugrušak PRF-a. Pomocu klešta, izdvojili smo ugrusak PRF-a i nezno ga prislonili na membranu između dva sloja sterilne gaze i potom nežno pritisnuli 10 s. kako bi se očuvala vlažnost membrane.

Alveolarni koštani defekt popunjen je granuliranim koštanim partikulama (BioOss, Geistlich, Switcerlanda) pomešanim sa krvlju pacijenta i delovima PRF-a. Potom, dvoslojna PRF membrana je postavljena preko koštanog grafta, mukoperiostalni režanj je vraćen na svoje mesto i zašiven svilenim koncem 4-0.

Pacijentu je prepisana antibiotska terapija u trajanju od sedam dana (Amoxicil, Hemofarm, Srbija 3× na dan).

Nakon 15 dana zabeleženo je potpuno zaceljenje mekih tkiva.

DISKUSIJA

Najčešće korišćen irigans u svakodnevnoj endodotskoj praksi je NaOCl, koji zaista u jako retkim slučajevima ispoljava svoja toksična svojstva [9]. Prema literaturnim navodima, to su situacije kada se umesto anestetika greškom aplikuje rastvor NaOCl ili momenti nenamerne transporatcije NaOCl u periapeks [10, 11]. U takvim slučajevima, osim nekroze kosti i okolnih mekih tkiva, može doći do ozbiljnih i trajnih oštećenja nerava [12].

Haton i saradnici [8] navode primer pacijenta kod koga je usled ekstrudiranja rastvora preko perforacije na korenu gornjeg prvog premolara došlo do pojave otoka i bola u predelu desnog obraza. To je uslovilo dalju palijativnu terapiju i primenu intravenski aplikovanih antibiotika, kortikosteroida i analgetika.

U slučaju našeg pacijenta, posledice ubrizgavanja NaOCl kroz *fos rut* na zubu 13 bile su bolna nekroza mekih tkiva i kosti, bez oštećenja nervnih struktura.

Pouzdani znaci koji ukazuju na mogući nastanak perforacije korena (*fos rut*) jesu profuzno krvarenje iz samog kanala i oštar bol.

Oba simptoma u našem slučaju su bila maskirana usled dejstva lokalnog anestetika. Prisustvo adrenalina u anestetičkom rastvoru izazvalo je lokalnu vazokonstrikciju krvnih sudova, što je sprečilo krvarenje, dok je dejstvo lokalne anestezije blokiralo prenos bolnih nadražaja.

Moguće objašnjenje za ovako masivno oštećenje periapikalnog tkiva, osim prisutnog *fos ruta*, može biti dehiscencija bukalne koštane lamele usled koje je rastvor NaOCl lako i brzo difundovao u periapeks.

Panfacijalni edem predstavlja prvi i najčešći znak da je došlo do transportacije NaOCl u okolno tkivo, što se objašnjava izrazito toksičnim i hiperosmotskim osobinama rastvora [13]. U nekim slučajevima, usled oštećenja krvnih sudova može doći do pojave ekhimoza po koži lica, ali i vrata [14]. Kod naše pacijentkinje, osim evidentno prisutnog otoka nisu zabeležene ekhimoze. Bol, koji se naknadno javio, najverovatnije je posledica tkivne ishemije i direktnog toksičnog dejstva natrijum-hipohlorita.

Na sreću, bol je prestao u potpunosti nakon hirurškog uklanjanja nekrotičnog tkiva.

Trombocitima obogaćen fibrin (PRF) predstavlja frakciju krvi bogatu trombocitima, leukocitima i faktorima rasta [15]. Autologna PRF membrana omogućava brže i lakše zarastanje tkiva [16], zbog čega se u savremenoj stomatologiji koristi za različite namene: sinus lift procedure, režanj operacije, augmentacije koštanog grebena ili ugradnju implantata [17].

Prisustvo faktora rasta, koji su u velikom broju sadržani u PRF-u, pozitivno utiče na stvaranje kolagena i novih krvnih sudova, deluje kao modulator rasta i razvoja ćelija, podstičući sintezu matriksa i transformaciju ćelija [18].

U slučaju našeg pacijenta, posle primene PRF-a došlo je do izvrsne i potpune regeneracije mekih tkiva. Mi pretpostavljamo da je takođe došlo i do zaceljenja kosti, ali bez biopsije i histološke procene uzorka ne možemo to i da tvrdimo.

ZAKLJUČAK

Oštećenja izazvana primenom NaOCl, sasvim sigurno predstavljaju neprijatno i stresno iskustvo za svakog stomatologa. Danas, još uvek, ne postoji zvaničan protokol terapije oštećenja izazvanih rastvorom natrijum-hipohlorita, ali ono što je sigurno jeste da takva stanja zahtevaju hitan tretman i redovno praćenje takvih pacijenata.

Pažljivim i savesnim rukovanjem moguće je izbeći komplikacije koje toksičnost ovog rastvora nosi sa sobom.

Da li ste pažljivo čitali radove?

1. Institucionalna komunikacija se istražuje u okviru:
   a) psihologije
   b) biologije
   c) filozofije

2. NaOCI je sredstvo:
   a) za medikaciju kanala
   b) za irigaciju kanala
   c) za opturaciju kanala

3. Karcinomi glave i vrata su uglavnom lokalizovani:
   a) u usnoj duplji
   b) na nosu
   c) na bradi

4. Aktuelni koncept protetskih nadoknada bazira se:
   a) na invazivnim hirurškim mehanizmima
   b) na neinvazivnim hirurškim mehanizmima
   c) na nehirurškim mehanizmima

5. CA 125 je:
   a) epitelni i molekularni marker
   b) neenzimski antioksidans
   c) marker oksidativnog stresa

6. Komunikacija između lekara i pacijenta je primer:
   a) specifične raspodele moći
   b) nespecifične raspodele moći
   c) vaninstitucionalne raspodele moći

7. Karcinomi glave i vrata predstavljaju:
   a) 1% svih karcinoma čoveka
   b) 3% svih karcinoma čoveka
   c) 8% svih karcinoma čoveka
8. Kompjuterom vođena implantacija obezbeđuje:
   a) predvidiv terapijski ishod
   b) nepredvidiv terapijski ishod
   c) teško predvidiv terapijski ishod

9. Mokraćna kiselina pripada grupi:
   a) markera oksidativnog stresa
   b) enzima
   c) neenzimskih antioksidanasa

10. Većina pitanja u komunikaciji lekar–pacijent se postavlja:
    a) tokom prijema
    b) tokom anamneze
    c) tokom kliničkog pregleda

11. NaOCI poseduje sposobnost:
    a) rasi neorganskog dela dentina
    b) rasivi organskog dela dentina
    c) ras neorganskog i organskog dela dentina

12. Analiza salivalnih markera se može koristiti u ranom otkrivanju karcinoma usne duplje?
    a) Da
    b) Ne
    c) Nikad se ne koristi

13. Učestalost implantološke terapije je u 2020:
    a) porasla
    b) smanjila se
    c) ostala na istom nivou

14. ALP je:
    a) enzim
    b) citokin
    c) neenzimski antioksidans

15. Tokom medicinskog susreta mogu se postaviti pitanja da/ne?
    a) Mogu
    b) Ne mogu
    c) Retko se postavljaju

16. NaOCI može uzrokovati:
    a) oštećenje krvnih sudova
    b) oštećenje nervnih elemenata
    c) stimulaciju dentinogeneze

17. Proteinski markeri salive su:
    a) CA 125
    b) IL-6
    c) citokini

18. Učestalost implantološke terapije je u 2020 porasla za:
    a) 5,7%
    b) 9,7%
    c) 12,7%

19. CD 44 je:
    a) molekularni marker
    b) citokin
    c) marker oksidativnog stresa

20. Otvorena pitanja tokom medicinskog susreta su sastavni deo komunikacije?
    a) Da
    b) Ne
    c) Nisu obavezna u komunikaciji

21. NaOCI može dovesti do nekroze kosti?
    a) Da
    b) Ne
    c) Nikad ne dovodi do nekroze kosti

22. Epitelni i molekularni markeri salive su:
    a) CA 19-9
    b) IL-8
    c) defenzini

23. Najčešći problem u implantološkoj terapiji krezubih pacijenata je:
    a) ograničen bezubi prostor
    b) vrsta implantata
    c) stanje preostalih zuba

24. CA 19-9 je:
    a) enzim
    b) neenzimski antioksidans
    c) epitelni marker

25. Većina pitanja koja postavljaju lekari:
    a) ne ograničava odgovore pacijenta
    b) ograničava odgovore pacijenta
    c) ne utiče na odgovore pacijenta

26. Hitin tretman nakon prebacivanja NaOCI u periapeks je:
    a) aplikacija medikamenta u oštećenu regiju
    b) eliminacija bola
    c) stimulacija represije

27. CBCT daje mogućnost:
    a) volumetrijske analize kostiju
    b) određivanja sadržaja kostiju
    c) eliminacije patoloških promena

28. Dinamička navigacija je:
    a) kompjuterski vođena ugradnja implantata
    b) ugradnja implantata na osnovu raspoloživog prostora
    c) ugradnja implantata na osnovu anatomskih detalja

29. Retorika pitanja tokom medicinskog susreta:
    a) više podsećaju na naredbu
    b) su prava pitanja
    c) ne podsećaju na naredbu ili iskaz

30. Akcidentalno oštećenje PA tkiva dejstvom NaOCI je otkriveno:
    a) na Klinici Stomatološkog fakulteta u Pančevu
    b) na Klinici Stomatološkog fakulteta u Beogradu
    c) na Klinici Medicinskog fakulteta u N. Sadu

31. Enzimi kao salivarni markeri su:
    a) staterin
    b) CEA
    c) LDH

32. Prisustvo patoloških promena u kostima je moguće dobiti uz pomoć CBCT-a?
    a) Da
    b) Ne
    c) Samo kod tumorskih promena

33. Pitanja koja postavljaju lekari mogu da:
    a) favorizuju jednu vrstu odgovora
    b) otežaju odgovor pacijenta
    c) isključe ispravan odgovor pacijenta

34. Akcidentalno oštećenje PA tkiva dejstvom NaOCI je zabeleženo na:
    a) gornjem levom očnjaku
    b) donjem levom očnjaku
    c) gornjem desnom očnjaku

35. Najčešći citokini kao markeri salive su:
    a) IL-1B
    b) T PA
    c) CD 44

36. Uz pomoć CBST je moguće videti položaj anatomskih struktura u kosti?
    a) Da
    b) Ne
    c) Zavisi od debljine kosti

37. Tokom medicinskog susreta uglavnom su važna:
    a) pitanja koja postavljaju i pacijenti i lekari
    b) pitanja koja postavljaju pacijenti
    c) pitanja koja postavljaju lekari

38. Oštećenje PA tkiva kod gornjeg očnjaka je nastalo:
    a) preko glavnom kanala
    b) preko lateralne perforacije (fos zut)
    c) preko oštećenog potpornog aparata

39. Markeri oksidativnog stresa salive su:
    a) MDA
    b) CEA
    c) SOD

40. Vitamini C i E pripadaju grupi:
    a) citokina
    b) neenzimskim antioksidansima
    c) markera oksidativnog stresa

41. Postavljanje pitanja lekara u medicinskom susretu:
    a) daje lekaru neznatnu moć
    b) daje lekaru veliku moć
    c) ne daje lekaru nikakvu moć

42. LDH i ACP pripadaju grupi:
    a) enzima
    b) molekularnih markera
    c) neenzimskih antioksidanasa

43. Kompletna tkivna regeneracija oštećenjem PA tkiva je ostvarena primenom:
    a) kom augmentacije
    b) PA medikacije
    c) apikotomije

44. TNF-alfa je salivarni marker:
    a) iz grupe citokina
    b) oksidativnog stresa
    c) enzima

45. Pacijent sa akcidentalnim oštećenjem PA tkiva je bio:
    a) uzrasta 33 godine
    b) uzrasta 43 godine
    c) uzrasta 53 godine

46. Neenzimski antioksidansi kao markeri salive su:
    a) mokraćna kiselina
    b) cis
    c) ACP

47. Citokin IL-8 pripada grupi:
    a) proteinskih markera
    b) markera oksidativnog stresa
    c) citokina

48. Staterin je salivarni marker:
    a) iz grupe molekularnih markera
    b) iz grupe proteinskih markera
    c) iz grupe markera oksidativnog stresa

49. Glutation pripada grupi:
    a) proteinskih markera
    b) molekularnih markera
    c) neenzimskim antioksidansima

50. Cistatini pripadaju grupi:
    a) proteinskih markera
    b) citokina
    c) enzima

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Address:
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11000 Belgrade
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E-mail: stomglas@bvcom.net
Web site: http://www.stomglas.org.rs

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616.31

STOMATOLOŠKI glasnik Srbije = Serbian
Dental Journal / glavni i odgovorni urednik
Slavoljub Živković. - God. 1, br. 1 (1955)-
. - Beograd (Džordža Vašingtona 19) :
Srpsko lekarsko društvo, 1955- (Beograd :
Službeni glasnik). - 29,5 cm

Dostupno i na: http://www.stomglas.org.rs - Tromesečno

ISSN 0039-1743 = Stomatološki glasnik Srbije
(Štampano izd.)
COBISS.SR-ID 8417026