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SLIKE MORFO-ELEMENTARNOG SASTAVA POVRŠINE IMPLANATA U ZAVISNOSTI OD METODE ČIŠĆENJA

MORPHO-ELEMENTAL COMPOSITION FEATURES OF IMPLANT SURFACE DEPENDING ON THEIR CLEANING METHODS

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Sažetak

Uvod: *Prisustva mikroskopskih delova različitih elemenata dovodi do kontaminacije površine implanata i razvoja periimplantitisa.*
Cilj rada: *Ispitivanje mikrostrukture, kvalitativnog i kvantitativnog elementarnog sastava implanata, zavisno od efekta čišćenja različitih tipova implanata koji su nađeni kod bolesnika sa periimplantitisom.*
Metode: *Ispitivane su površine 12 implanata: TiU-nite (Nobel BioCare, Švedska), SLA (Xive, Dentsply Implants, Nemačka) i RBM (BioHorizons, SAD), koje su obrađene uz pomoću tri različite metode: Er laserom Cr; YSGG (Waterlase MD, Biolase, SAD), dijamantskim borerom, (Comet, Nemačka) i četkicom (Neobiotech, Koreja).*
Rezultati: *su pokazali da bez obzira na tip površine implanta, najprefinjenija tehnika čišćenja bila je laser tehnika: kada je makrostruktura očišćena, mikroprostori su ostali čisti, a sastavni elementi implanta nisu sadržali spoljašnje opiljke. Dijamantski borer delovao je najtraumatičnije: mikrostruktura i makrostruktura bile su poremećene, prisutnim usecima i zarezima, dijamantske čestice bile su nađene u strukturi implanata, pri čemu je ugljenik dominirao u spektru mikroelemenata.*
Upotreba četkice takođe je dovela do poremećaja u makrostrukturi- i mikrostrukturi površine, pri čemu je detektovan nikl (Ni) u spektru mikroelemenata.
Zaključak: *Rezultati ove pilot studije mogu poslužiti kao osnova za dalje, detaljnije istraživanje i unapređenje načina čišćenja površine implanata.*

Ključne reči: *implant, površina implanata, metoda čišćenja laser, titanijumska četkica, dijamantsko svrdlo, periimplantitis*

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Abstract

Background: *The issue of clinical importance in the development of periimplantitis in the presence of microscopic particles and contaminants on the surface of implants is to be studied.*
Objective: *based on the study of the microstructure and the qualitative and quantitative elemental composition, the cleaning effectiveness for different types of surfaces of implants obtained from patients with periimplantitis was researched.*
Methods: *surfaces of 12 implants were investigated: TiU-nite (Nobel BioCare, Sweden), SLA (XiVE, Dentsply Implants, Germany) and RBM (BioHorizons, USA), which were processed in three ways: with Er laser; Cr; YSGG (Waterlase MD, Biolase, USA), diamond burr, (Comet, Germany); brush (Neobiotech, Korea).*
Results: *regardless of the type of surface, the gentlest cleaning method was laser: when the macrostructure was broken, the microroughness remained, and the composition of elements did not contain extraneous inclusions. Diamond burr was the most traumatic: macro and microstructure breakdowns, the presence of grooves and notches, the introduction of diamond particles into the implant structure have been detected; carbon has dominated in the elemental spectrum. The use of the brush also led to disturbances in the macro- and microstructure of the surface; nickel (Ni) was detected in the microelement spectrum.*
Conclusion: *practical implication: the results of this pilot study are the basis for further more detailed research.*

Key words: *implant, implant surface, the cleaning method, laser, titanium brush, diamond burr, periimplantitis*

Uvod

Dentalni implanti postali su jedna od najpopularnijih metoda za rehabilitaciju pacijenata sa parcijalnom i totalnom bezubošću. Stanje površine implanata značajno određuje inicijalna faza biološke reakcija tokom njihovog ugrađivanja i utiče na proces njihovog koštanog zarastanja[1]. Utvrđeno je da rast i diferencijacija osteoblasta zavise direktno od mikrostrukture implanata: hrapava površina može da ubrza process osteointegracije i poveća procenat preživljavanja implanata[2,3]. Međutim, sa početkom nošenja protetskih nadoknada na dentalnim implantima, javlja se rizik od periimplantitisa –akutne i hronične inflamacije tkiva koje okružuje implant[1,4,5]. Utvrđeno je da, uprkos mehaničkim uzrocima (habanje) implant može podleći procesima korozije koji su uzrokovani formiranjem kiseline od strane bakterija u dentalnom biofilmu i lipopolisaharidne aktivnosti pljuvačke. U isto vreme, otpuštanje nanočestica gvožđa i jona titanijuma ima citotoksični efekat na leukocitno- makrofagni sistem pacijenta[6], što na kraju utiče na kvalitet i vreme oseointegracije, kao i na imunološki status pacijenta, i uspeh lečenja.

Zna se da je glavna stavka sprovođenja efikasne terapije periimplantitisa što raniji početak sveobuhvatnog pristupa oboljenju sa eliminacijom infektivnih agenasa, uz dodatnu korektivnu i regenerativnu bazičnu i hirurška terapiju. Trenutno, mehaničko uklanjanje granulacija i sanacija površina implanata obećavajuće su metode [7-10].

U isto vreme, nisu pronađeni radovi vezani za ovu studiju, koji se bave uticajem tretmana na stanje površine implanata i razvoja periimplantitisa.

Cilj rada bazira se na studiji mikrostrukture od koje su napravljeni implanti i određivanja njihovog kvalitativnog i kvantitativnog elementarnog sastava, kao i uticaja čišćenja površine različitog tipa implanata kod pacijenta sa evidentiranim periimplantitisom.

Introduction

Currently, dental implantation is becoming one of the most popular methods for the rehabilitation of patients with partial and complete adentia. The condition of the implant surface significantly determines the initial phase of biological reactions during its installation and affects the boneimplant healing process[1]. It was found that the growth of osteoblasts and their differentiation on the implant surface directly depends on implant's microstructure: a rough surface can accelerate the process of osteointegration and thereby increase survival rate[2,3]. However, after the patient began using orthopedic constructions based on dental implants, there is a risk of periimplantitis: acute and chronic inflam-mation in the area of the tissues surrounding an implant1[4,5]. It has been established that, in addition to mechanical causes (wear), the implant may undergo corrosion processes caused by both the acid-forming properties of bacteria in the biofilm and the lipopolysaccharide activity of saliva. At the same time, the release of metallic iron nanoparticles and titanium ions has a cytotoxic effect on the patient's leukocyte-macrophage system[6]. This, in turn, affects the quality and timing of osseointegration and the patient's immune status and the treatment success.

It is recognized that the main points of ensuring the effectiveness of periimplantitis therapy are the earliest start and comprehensive approach: elimination of the infectious agent, corrective and regenerative non-surgical and surgical treatment. Currently, mechanical removal of granulations and sanitation of implant surfaces are considered as a promising method[7-10].

At the same time, we did not find any works devoted to the study of the influence of the treatment on the state of the surface of implants and the development of periimplantitis.

Objective based on the study of the microstructure of materials and the determi-nation of their qualitative andquantitative elemental composition, to study the effectiveness of cleaning the surface of different types of implants obtained from patients with periimplantitis evidences.

Materijal i metode

Studijom su ispitivane površine 12 implanata tri različita proizvođača: TiU-nite (Nobel BioCare, Švedska) SLA (XiVE, Dentsply Implants, Nemačka) i RBM (BioHorizonts, SAD), izrađeni od legure titatnijuma TI-6AL-4V, klase V (G5Ti).

Studijsku grupu (n=9) su činile površina implanata kod pacijenata sa dijagnostikovanim periimplantitisom, kod kojih su implanti su ugrađeni 3 do 5 godina pre početka studije. Studijom su analizirane dve zone svakog implanta: zona koja je u bila u direktnom kontaktu sa granulacionim tkivom, i zona koja je čišćena jednom od sledeće tri metode: (1) primenom ErCr lasera; laser YSGG (Waterlase MD, Biolase, SAD) talasne dužine od 2780 nm, snage 1,5 W, frekvencije 15 Hz; (2) primenom fino zrnastog dijamantskog svrdla; (3) primenom četkice za čišćenje površine implanata, napravljene od nikl-titanijumske legure (Neobiotech, Koreja). Kontrolnu grupu (n=3) su činili novi implanti, upakovani u originalno pakovanje proizvođača.

Analiza morfološke strukture površine implanata obavljena je u Centru za kolektivne usluge „Laboratorija za elektronsku mikroskopiju“ Sibirskog Federalnog Univerziteta, na elektronskom mikroskopu JOEL JSM 7001-F (Japan). Parametri uvećanja su bili 1 500x i 5 000x.

Kvalitativna i kvantitativna analiza elemenata površine implanata vršena je energijom disperzivbog X- zračnom spektrofotometrijskom metodom (EDX) na INCA energetskom disperzionom spektrofotometrija Energy Penta FETx3 (Oxford Instruments, Engleska). Metod se zasniva na sledećem: uzorci su bombardovan visokoenergetskim elektronima (1-50 kEV, najčešće 10-15 kEV, što rezultuje emisijom X zraka sa njihove površine. Analizom karakteristika radijacije X zraka, određen je sastav elmenata koji ulazi u strukturu površine implanata, i u kom odnosu.

Mala veličina uzorka (u formi pilot studije) nije dozvolila kompletnu statističku analizu dobijenih rezultata.

Material and methods

This study analyzed surfaces of 12 implants of three different manufacturers: TiU-nite (Nobel BioCare, Sweden), SLA (XiVE, Dentsply Implants, Germany) and RBM (BioHorizons (USA), the main material was titanium alloy of Ti-6Al-4V 5 class (G5Ti).

The study group (n=9)included implants obtained from patients with a diagnosis of periimplantitis and a period of operation of 3-5 years.The surface of each implant was divided into two zones: directly in contact with the granulation tissue and processed using one of the following cleaning methods:ErCr laser; YSGG (Waterlase MD, Biolase, USA) with a radiated wavelength of 2780 nm, a power of 1.5 W, a frequency of 15 Hz, diamond burr (fine grain), (Comet Germany); a brush to clean the implant surfaces made of Ni-Ti alloy (Neobiotech, Korea). The control group (n = 3) was composed of new implants in the manufacturer's package.

The study of the morphological composition of the surface was carried out at the Center for Collective Use “Laboratory of Electron Microscopy” of the Siberian Federal University using scanning electron microscopy on a JEOL JSM 7001-F plant electron microscope (Japan). Magnification parameters used were x1500 and x5000.

Qualitative and quantitative elemental analysis of the surface of the implants was performed by the energy dispersive X-ray spectroscopy (EDX) method on an INCA Energy Penta FETx3 energy dispersive spectrometer (Oxford Instruments, England). The method is based on the following principle: the sample under study is bombarded by high-energy electrons (1–50 keV, usually 10–15 keV), as a result of which X-ray emission from its surface occurs. Based on the characteristic x-ray radiation analysis results, it was determined which elements are included in the implant surface composition, and in which quantitative ratios.

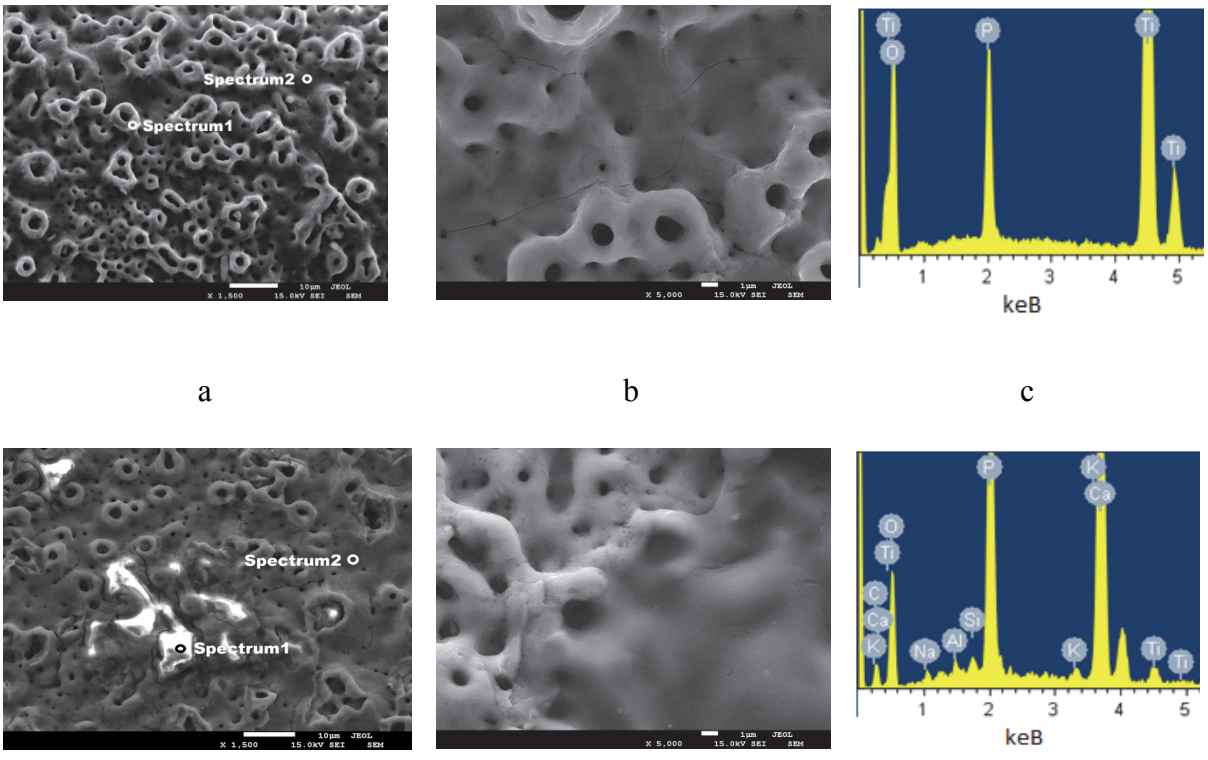
A narrow sample of indicators (pilot survey format) did not allow for complete statistical processing of the data obtained.

Rezultati istraživanja i diskusija

Studija je izvršena na implantima sa TiUn-ite površinom (Nobel BioCare, Švedska) koje se odnose na površinu uzoraka koji su referentni (novi, koji su u pakovanju proizvodjača) i imaju finu strukturu sa porama (Slika 1a), koja je bila gruba na nivou nanoskale, sa produženim mikrokrakovima (Slika 1b). Površina implanata istog proizvođača, dobijena od bolesnika sa periimplantitisom, takođe je imala mikroporoznosti (Slike 1c i, 1d). U isto vreme, kvalitativna i kvantitativna analiza sastavnih elemenata otkrila je tragove impregnacije fosforom (P) na površini referentnog implanta. Takođe su nađeni i ugljenik (C), kalcijum (Ca), fosfor (P), aluminijum (Al) i silicijum (Si). Tipičan spektar koji je uzet sa površine implanta, odnosi se na hemijske elemente detektovane u ovoj regiji (Slike 1 c, 1f).

Research results and discussion

The study of implants with a TiU-nite surface (Nobel BioCare, Sweden) revealed that the surface of reference samples (new ones contained in the manufacturer packaging) had a fine-pore structure (Fig. 1a) which was rough at the nanoscale level, with extended microcracks (Fig. 1b). The surface of the implant from the same manufacturer, obtained from a patient with periimplantitis, also had microporosity (Fig.1c, d). At the same time, the qualitative and quantitative analysis of the composition of elements revealed that traces of phosphorus (P) impregnation were present on the surface of the reference implant, and also carbon (C), calcium (Ca), phosphorus (P), aluminum (Al) and silicon (Si) were detected on the surface of the implants used. Typical spectra taken on implant surfaces reflect chemical elements present in these areas (Fig. 1 c, f).

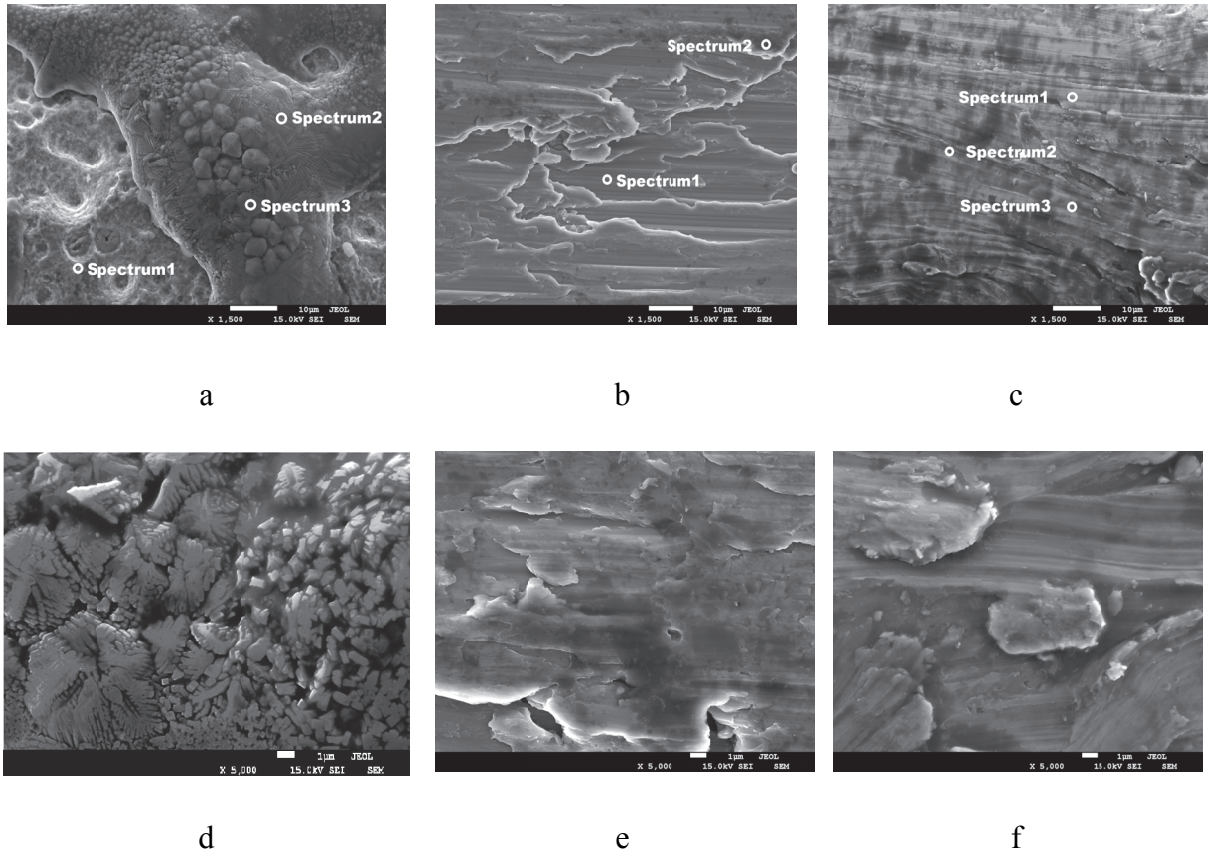


Slika 1. Elektomikroskopska slika tipične površine TiU-nite i tipičan spektar: a, b, c – kontrolni implant; d, e, f – implant sa dijagnozom periimplantitisa : *uvećanje 1,500 x (a, d); uvećanje 5000 x (b, e)*

Figure 1. Electron microscopic image of a typical TiU-nite surface and typical spectrum: a, b, c - control implant; d, e, f - implant with a diagnosis of periimplantitis. *Note: magnification x1500 (a, d), magnification x5000 (b, e)*

Površina TiU-nite implanta imala je tragove niti nakon laserskog tretmana, morfološki se videla restrukturacija, ali se zadržala njegova mikroporozivnost (Slike 2 a i, 2d). Elementarni sastav činili su titanijum (Ti) i kiseonik (O), i mala količina fosfora (P). Nakon tretmana dijamantskim svrdlom, početna tridimenzionalna struktura je izgubljena; površina je postala glatka na makronivou, ali mikroporoznosti nije bilo (Sike 2.b i, 2e); titanijum (Ti) i značajni procenat ugljenika (C) otkriveni su na površini. Nakon četkanja površine implanta, mikrostruktura i makro struktura imale su znake slične onima koji su opisani nakon korišćenja dijamantskog svrdla: originalna 3D mikrostruktura je nestala; hrapavost na niovu nanoskale je bila je očuvana (Slike 2c i, 2f); elementarni sastav uključivao je ugnjenik (C), titanijum (Ti) i nikl (Ni).

The surface of the TiU-nite implant had traces of reflow after laser treatment, and it was morphologically restructured, but retained its microporosity (Fig. 2 a, d).The elemental composition contained titanium (Ti) and oxygen (O), and a small amount of phosphorus (P). After treatment with a diamond burr, the initial three-dimensional structure was lost; the surface became smooth at the macro level, and microporosity was not detected (Fig. 2.b, e); titanium (Ti) and a significant level of carbon (C) were revealed on the surface. After the surface was brushed, the micro and macro structures had signs similar to those described during diamond burr processing: the original 3D microstructure has disappeared; the roughness at the nanoscale level has been preserved (Fig. 2c, f); the elemental composition included carbon (C), titanium (Ti) and nickel (Ni).

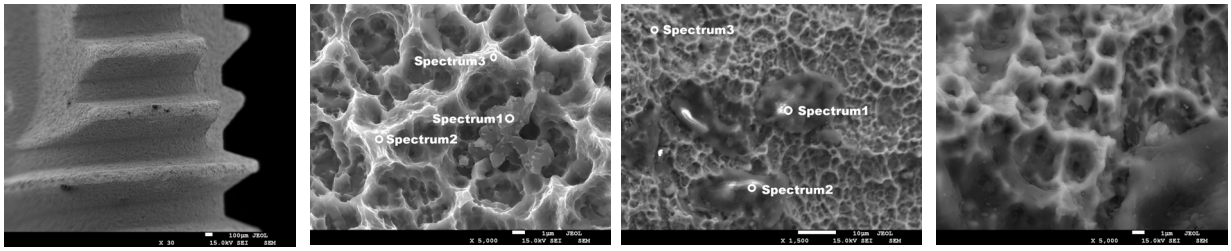


Slika 2. Elektomikroskopska slika površine TiU-nite implanta koja je tretirana: a, d – laserom;
b, e – dijamantskim svrdlom; c, f – specijalnom četkicom. *Poruka: uvećanje 1,500 x (a, b, c); uvećanje 5000 x (d, e, f)*

Figure 2. Electron-microscopic image of the TiU-nite implant treated surface with: a, d – laser; b, e – diamond burr; c, f – a special brush. *Note: magnification x1500 (a, b, c), x500 (d, e, f)*

Ispitivanje površine SLA XiVE implanata (Dentsply Implants, Nemačka) otkriva heterogenu površinu sa mikropukotinama (Slike 3a i, 3b), zbog značajne količine mikroelemenata u detektovanom spektrumu, koji uključuje kiseonik (O), ugljenik (C), titanijum (Ti), minimalne koncentracije kalcijuma (Ca), kalijuma (K), aluminijuma (Al), silicijuma (Si), sumpora (S), cinka (Zn) i hlora (Cl). Na površini implanata, koji su dobijeni od bolesnika sa kliničkim simptomima periimplantitisa (Slike 3c i, 3d), mikrohrapavost je održana kao i kvalitativni sastav elemenata mikrospektruma.

Examination of the SLA XiVE implants (Dentsply Implants, Germany) surface revealed a heterogeneous surface with microroughness (Fig. 3a, b) due to the significant amount of microelements in the spectrum detected, which included oxygen (O), carbon (C), titanium (Ti), minimum concentrations of calcium (Ca), potassium (K), aluminum (Al), silicon (Si), sulfur (S), zinc (Zn) and chlorine (Cl). On the surface of implants, obtained from patients with signs of periimplantitis (Fig. 3c, d), the microroughness was maintained as well as the qualitative composition of the microelement spectrum.



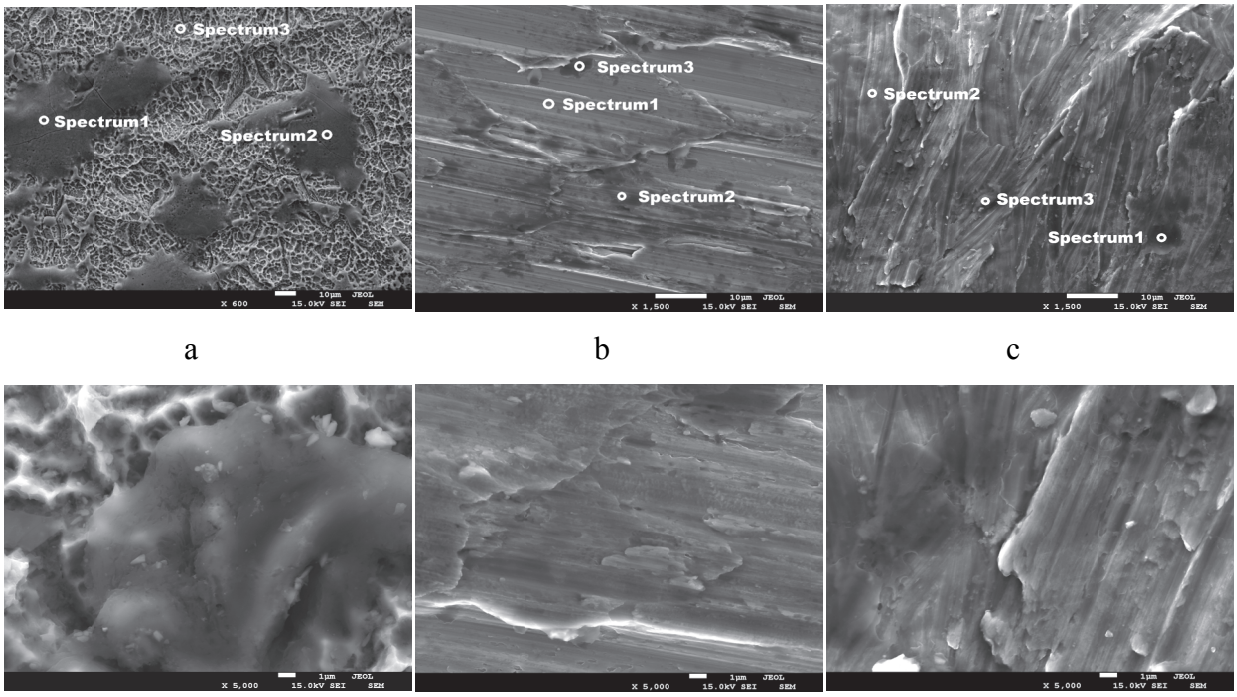
a b c d

Slika 3. Elektomikroskopska slika površine SLA implanta: a – opšti pregled; b – referentni implant; c, d – implant dobijen od bolesnika sa periimplantitisom. *Poruka: uvećanje 1,500 x (a, c); uvećanje 5000 x (b, d)*

Figure 3. Electron-microscopic image of the surface of SLA implants: a – general view; b – reference implant; c, d – implant obtained from a patient with periimplantitis *Note: magnification x1500 (a, c), x5000 (b, d)*

Nakon laserskog tretmana površine SLA implanta, otkriveni su tragovi topljenja i mikropukotine (Slike 4a i, 4d), kao i prisustvo titanijuma (Ti), kiseonika (O) i ugljenika (C). Nakon tretmana dijamantskim svrdlom, površina je izgubila svoju mikrostrukturu i makrostrukturu, a tragovi u vidu ureza i žlebova su otkriveni (Slike 4b, i 4e); titanjium (Ti) i ugljenik (C) preovladavaju u elementarnom sastavu. Nakon četkanja, otkriveno je da je sačuvana makrostrukura sa kompletnim gubitkom hrapavosti na mikro nivou. Brazde koje je napravila četkica (Slike. 4 c i, 4f) vide se na površini; Titanijum (Ti) i ugljenik (C) detektovani su u elementarnom spektru.

After the laser treatment of the SLA implant surface, traces of surface melting and microcracks (Fig.4a, d) and the presence of titanium (Ti), oxygen (O) and carbon (C) were revealed. After treatment with a diamond burr, the surface lost its macro- and microstructure, traces in the form of notches and grooves were detected (Fig. 4b, e); titanium (Ti) and carbon (C) prevailed in the composition of elements. After brushing, it was revealed that macrostructure has been preserved, with complete loss of roughness on the micro level. The furrows left by the brush (Fig. 4 c, f) were visualized on the surface; titanium (Ti) and carbon (C) were detected in the element spectrum.



Slika 4. Elektomikroskopska slika površine SLA implanta koja je tretirana: a, d – laserom; b, e – dijamantskim svrdlom; c, f – četkicom. *Poruka: uvećanje 1,500 x (a, b, c); uvećanje 5000 x (d, e, f)*

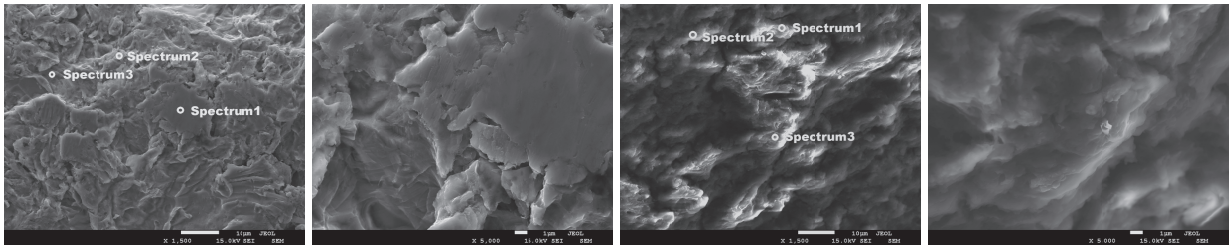
Figure 4. Electron-microscopic image of the SLA implants surface after the treatment: a, d – with a laser; b, e – diamond burr; in, e – brush. *Note: magnification x1500 (a, b, c), x5000 (d, e, f)*

Studija na površini RBM implanata BioHorizons (SAD) otkrila je da referentni uzorci imaju mikrohrapavu strukturu; titanijum (Ti) je dominirao u njihovom elementarnom sastavu, ali nađeni su i: fosfor (P), kalcijum (Ca), aluminijum (Al) i vanadijum (V). Površina implanta dobijenog od pacijenta sa periimplantitisom takođe je imala mikrophrapavost i inkliuzije sa strane (Slika 5c, d), dok se spektar elemenat sastojao od kiseonika (O), ugljenika (C), sumpora (S), i malih količina fosfora (P) i kalcijuma (Ca).

Nakon tretmana laserom, površina RBM je zadržala je svoju mikrostrukturu, ali su prikazani tragovi topljenja (Slike. 6a i, 6d). Ttitanijum (Ti) i kiseonik (O) su dominirali su u elementarnom spektrumu, vanadijum (V) i kalcijum (Ca) su takođe su detektovani. Nakon obrade dijamantskim svrtdlom, površina je kompletno izgubila svoju makrostrukturu i mirostruktutru (Slika 6b). Ttragovi u vidu brazdi zareza, kao i zarezna brazeda načinjena svrdlom videli su se na površini implanta (Slika 6e). Ugljenik (C) i titanijum (Ti) bili su dominatntni u mikroelementarnom spektrumu; kiseonik (O), aluminijum (Al) i vanadijum (V) takođe su bili prisutni.

The RBM study results for BioHorizons implants (USA) surface has revealed that the reference samples had a structure with microroughness; titanium (Ti) prevailed in their elemental composition; phosphorus (P), calcium (Ca), aluminum (Al) and vanadium (V) were present. The surface of the implant obtained from a patient with periimplantitis also had microroughness and foreign inclusions (Fig. 5c, d), the spectrum of elements expanded due to oxygen (O), carbon (C), sulfur (S), minor amounts of phosphorus (P) and calcium (Ca).

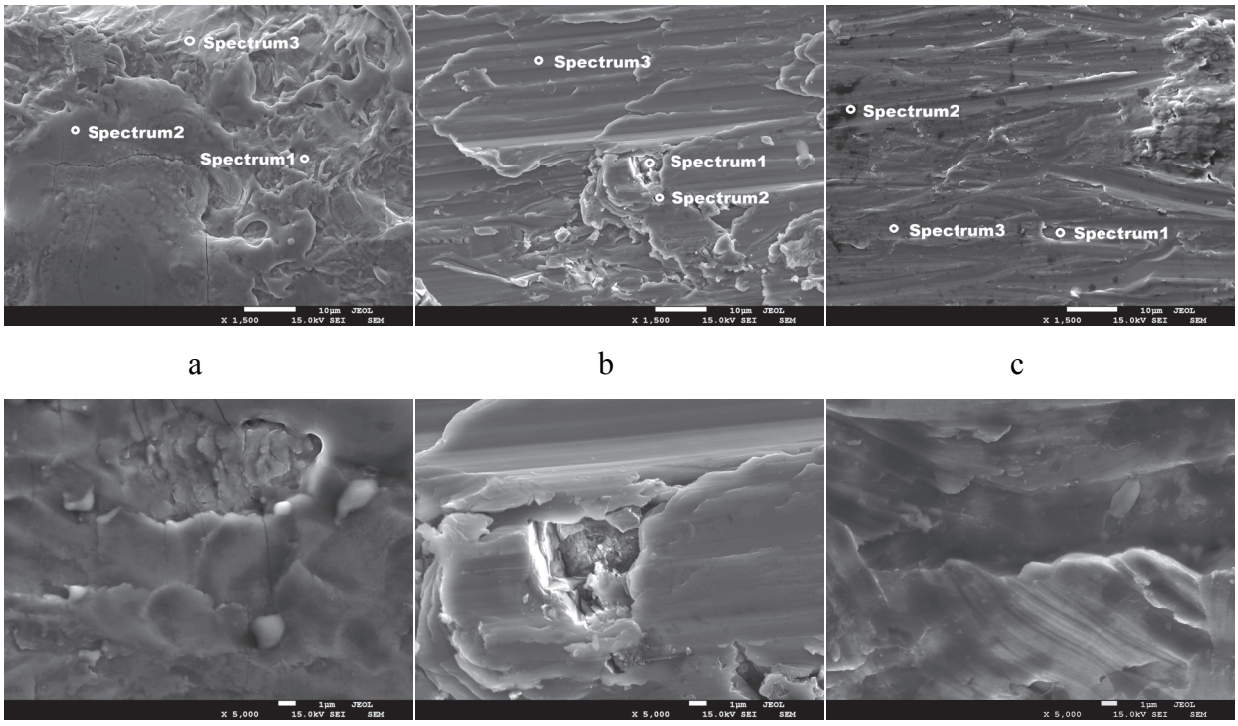
After treatment with an RBM laser, the surface retained its microstructure, traces of melting were shown (Fig. 6a, d), titanium (Ti) and oxygen (O) dominated in the elemental spectrum, and vanadium (V) and calcium (Ca) were also detected. After processing with a diamond burr, the surface completely lost its macro- and microstructure (Fig. 6b); traces of the tool in the form of furrows and notches, as well as the cutting burr fragment embedded in the implant surface (Fig. 6e) were detected; carbon (C) and titanium (Ti) dominated in the microelements spectrum; oxygen (O), aluminum (Al) and vanadium (V) were also present there.



a b c d

Slika 5 . Elekto-mikroskopska slika površine RBM implanata BioHorizons: a, b – referentni implant; b, d – implant dobijen od bolesnika sa periimplantitisom. *Poruka: uvećanje 1,500 x (a, c); 5000 x (b, d)*

Figure 5. Electron-microscopic image of RBM surface of BioHorizons implants: a, b – reference implant; b, d – implant obtained from a patient with periimplantitis. *Note: magnification x1500 (a, c), x5000 (b, d)*



a b c

d e f

Slika 6. Elektomikroskopska slika površine RBM implanta tretiranih: a, d – laserom; b, e – dijamantskim svrdlom; b, f – četkicom. *Poruka: uvećanje 1,500 x(a, b, c); 5000 x (g, d, e)*

Figure 6. Electron-microscopic image of RBM surface of implants treated with: a, d – laser; b, e – diamond burr; b, f – brush. *Note: magnification x1500 (a, b, c), x5000 (g, d, e)*

Nakon četkanja, površina je paraktično izgubila svoju mikrostrukturu, svoje mikroskopske nepravilnosti i žlebovi su zapaženi (Slike 6c i6e), a ugljenik (C), titanijum (Ti), kiseonik (O) i nikl (Ni) preovladavali su u elementarnom sastavu.

After brushing, the surface practically lost its microstructure, microscopic irregularities and grooves were noted (Fig. 6c, e), carbon (C), titanium (Ti), oxygen (O) and nickel (Ni) prevailed in the composition of elements.

Diskusija

Trenutno, pitanje kliničkog značaja prisustva mikroskopskih čestica i kontaminacija površine dentalnih implanata ostaje otvoreno. Utvrđeno je da je prisustvo sledećih elemenata: titanijuma (Ti), aluminijuma (Al) i vanadijuma (V) karakteristično za gradus 5 titanijumsku leguru, koja se koristi u proizvodnji implanata[11,12], što je takođe zapaženo u ovoj studiji, nakon analize podataka sa površine RBM BioHorizons implanata.

U isto vreme, poređenje morfološke slike površine tri tipa novih implanata sa kvalitativnim i kvantitativnim elementarnim sastavom otkrilo je značajnu razliku u mikroelementarom spektrumu: tri, na površini TiU-nite implanta (Nobel BioCare, Švedska), do deset na površini SLA implanta XiVE (Dentsply Implants, Nemačka). Spektar mikroelemenata na površini implanata, koji su u upotrebi, proširen je na osam na površini TiUnite implanata, a ostao isti na površini SLA implanata. Prisustvo kalcijuma (Ca), fosfora (P) i kiseonika (O), koji su smatrani markerima osteosintetičkih procesa[5,13], detektovano je u najvećoj količini na površini TiU-nite implanata, a mnogo manja količina je detektovana je na površini SLA implantaa.

Komparativna analiza stanja implanata nakon tretmana otkrila je sličnu šemu za sve tipove površina: nakon laserskog tretmana primećeno je topljenje i zaglađivanje makrostrukture primećeno, dok je održavanje mikrostrukture (hrapavosti) na nano nivou variralo u stepenu ozbiljnosti, i značajno je smanjen broj mikroelemenata u spektrumu; prevalencije kiseonika (O) i titanijuma (Ti). Otkriven je poremećaj u makrostrukturi i mikrostrukturi nakon tretmana dijamantskim svrdlom, bez obzira na tip implanata, uključujući gubitak njihove strukture, prisustvo žlebova i zareza, ubacivanje dijamantskih čestica u strukuru implanata; ugljenik (C) i titanijum (Ti) dominirali su u elementarnom spektrumu. Proces četkanja vodio je do značajnog, ali ne tako izraženog, kao nakon tretmana dijamantskim svrdlom, poremećaja mikrostukture i makrostrukture površine implanata. Spaktar identifikovanih elementa je uključivao je titanijum (Ti), ugljenik (C), kiseonik (O) i nikl (Ni).

Stoga rezultati ove pilot studije delimično potvrđuju podatke nekoliko izvora iz literature i osnova su za naredna detaljnija istraživanja.

Discussion

Currently, the question on the clinical significance of the presence of microscopic particles and contaminants on the surface of dental implants remains open. It has been established that the presence of elements of titanium (Ti), aluminum (Al) and vanadium (V) is a characteristic of the Grade 5 titanium alloy used in the manufacture of implants[11,12] that was also noted in the present study when analyzing data on RBM surface of BioHorizons implants (USA).

At the same time, a comparison of the morphological picture with the qualitative and quantitative composition of elements of the three types of new implant surface revealed significant differences in the spectrums of microelements: from three on TiU-nite surfaces (Nobel BioCare, Sweden) to ten on SLA surface of XiVE implants (Dentsply Implants, Germany). The spectrum of microelements on the surface of implants that were in use expanded to eight on the TiU-nite surface and remained the same on SLA surfaces of the implants. The presence of calcium (Ca), phosphorus (P) and oxygen (O), which are considered markers of osteosynthetic processes[5,13], is detected in the largest amounts on the TiU-nite surface, and there is much smaller amount of them on the SLA surface.

A comparative analysis of the condition of implants after treatment revealed a similar pattern for all types of surfaces: after laser treatment, the melting and smoothing of the macrostructure were observed while maintaining the microstructure (roughness) at the nanolevel at varying degrees of severity, and significant narrowing of the quantity of microelements in spectrums: the prevalence of oxygen (O) and titanium (Ti). There were revealed macro- and microstructure disturbances after treatment with a diamond burr, irrespective of the type of surface, including loss of their structure, the presence of grooves and notches, the introduction of diamond particles into the implant structure; carbon (C) and titanium (Ti) dominated in the elemental spectrum. Brush processing also led to significant, though not as pronounced as after burr treatment, disruption of the macro- and microstructure of surfaces; the spectrum of identified elements included titanium (Ti), carbon (C), oxygen (O) and nickel (Ni).

Thus, the results of this pilot study partially confirm the data of a few literature sources and are the basis for further more detailed research.

Zaključak

Na osnovu studije mikrostrukture materijala i određivanja kvalitativnog i kvantitativnog elementarnog sastava tri tipa površine implanata, nađeno je da je tretman laserom najnežniji metod čišćenja njihove površine bez obzira na tip implanata. Pod njihovim uticajem, mikrostruktura je delimično promenjena (fenomen topljenja i zaglađivanja), ali je makrostruktura sačuvana, a elementarni sastav ne sadrži spoljne inkluzije koje mogu biti značajne za osteointegraciju implanata.

Najštetniji metod bilo je čišćenja dijamantskim svrdlom, bez obzira na tip površine. Otkriven je poremećaj njihove makrostrukture i mikrostrukture, do potpunog gubitka primarne strukture površine implanta, uz, prisustvo žlebova i zareza, sa upadanjem dijamantskih čestica u strukuru implanata. Ugljenik (C) je dominirao u spektrumu hemijskih elemenata, pa može biti smatran markerom ovih oštećenja.

Korišćenje specijalnih četkica takođe vodi do poremećaja makrostukture- i mikrostrukture površine implanta, mada je manje izraženo, sa prisustvom nikla (Ni) u značajnoj količini u hemijskom spektrumu, pa se nikl (Ni) može smatrati markerom ovog metoda čišćenja.

Rezultati ove pilot studije mogu biti osnova za dalje i detaljnije istraživanje najadekvatnijeg načina čišćenja površine implanta.

Conclusion

Based on the material microstructure study and the determination of the qualitative and quantitative elemental composition of the three types of implant surfaces, it was found that the gentlest method of cleaning the surface, regardless of its type, is laser treatment. Under its influence, the microstructure is partially disturbed (the phenomena of melting, smoothing), but the macrostructure is preserved, and the composition of elements does not contain extraneous inclusions, which may be significant for osseointegration of the implant.

The most damaging was the method of cleaning with diamond burr: after its impact, regardless of the type of surface, there were revealed macro- and microstructure disturbances, up to their loss, the presence of grooves and notches, the introduction of diamond particles into the implant structure, and carbon (C) dominated in the spectrum of chemical elements that can be considered as a marker of these violations.

The use of a special brush also led to macro- and microstructure disruption of the implant surface, although less pronounced; a significant level of nickel (Ni) was detected in the microelement spectrum, which can be considered as a marker of this cleaning method.

The results of this pilot study are the basis for further and more detailed research.

LITERATURA / REFERENCES

1. Renvert S, Polyzois I. Treatment of pathologic peri-implant pockets. Periodontol 2008;76(1):180-190. doi: 10.1111/prd.12149.
2. Piattelli A, Degidi M, Paolantonio M, Mangano C, Scarano A. Residual aluminum oxide on the surface of titanium implants has no effect on osseointegration. Biomaterials 2003; 24(22): 4081-9.
3. Coathup MJ, Blunn GW, Mirhosseini N, Erskine K, Liu Z, Garrod DR., Li L. Controlled laser texturing of titanium results in reliable osteointegration. J Orthop Res 2017; 35: 820-828. doi:10.1002/jor.23340.
4. Renvert S. Polyzoils I. Risk indicators for periimplant mucositis: a systematic literature review. J Clin Periodontol 2015; 42(16): 172–186. doi:10.1111|jcpe.12346.
5. Klinge B, Klinge A, Bertl K, Stavropoulos A. Peri-implant diseases. Eur J Oral Sci 2018; 126(Suppl1):88–94. doi.org/10.1111/eos.12529.
6. Duddeck D, Maghaireh H, Faber FJ, Neugebauer J. Final report of the BDIZ EDI implant study 2014/15.SEM surface analyses of 120 sterile-packed implants. EDI Journal 2015, 2: 64-75.
7. Barão VA, Mathew M, Assunção W, Yuan J, Wimmer M, Sukotjo C.The role of lipopolysaccharide on the electrochemical behavior of titanium J. Dent. Res 2011; 90(5): 613-8. doi: 10.1177/0022034510396880..
8. De Tapia B, Valles C, Amaral T, Mor C, Herrera D, Sanz M, Nart J.The adjunctive effect of a titanium brush in implant surface decontamination at peri-implantitis surgical regenerative interventions: a randomized controlled clinical trial. J Clin Periodontol, 2019;46(5):586-596.doi: 10.1111/jcpe.13095.
9. Schwarz F, Bieling K, Bonsmann M, Latz T, Becker J. Nonsurgical treatment of moderate and advanced periimplantitis lesions: a controlled clinical study. Clin. Oral Investig 2006; 10(4): 279-88. doi: 10.1007/s00784-006-0070-3
10. Renvert S, Polyzois I. Treatment of pathologic peri-implant pockets. Periodontol 2008;76(1):180-190. doi: 10.1111/prd.12149.
11. Amirov MV, Grinin VM. Impact of Er, Cr: YSGG-laser on the tooth root cement in the treatment of chronic periodontal disease (the results of electron microscopic studies) Stomatologiia (Mosk)2012; 1: 20.
12. Jepsen K, Jepsen S, Laine ML, Anssari Moin D, Pilloni A, Zeza B, Sanz M, Ortiz-Vigon A, Roos-Jansaker AM, Renvert S. Reconstruction of Peri-implant Osseous Defects: A Multicenter Randomized Trial. J Dent Res 2016;95:58-66. doi:10.1177/0022034515610056
13. Safioti LM. Kotsakis GA, Pozhitkov AE, Chung WO, Daubert DM. Increased levels of dissolved titanium are associated with periimplantitis – A cross-sectional study J Periodontol 2017;88(5):436-442. doi: 10.1902/jop.2016.160524.
14. Fretwurst T, Buzanich G, Nahles S, Woelber JP, Riesemeier H, Nelson K. Metal elements in tissue with dental peri-implantitis: a pilot study. Clin Oral Implants Res 2016; 27(9):1178-86. doi: 10.1111/clr.12718

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KOMPARACIJA POVRŠINSKE HRAPAVOSTI STOMATOLOŠKIH MATERIJALA KAO FAKTORA ADHEZIJE ORALNOG BIOFILMA

COMPARISON OF SURFACE ROUGHNESS OF DENTAL MATERIALS AS AN ADHESION FACTOR OF ORAL BIOFILM

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Sažetak

Uvod: *Da bi se materijal smatrao biološki prihvatljivim neophodno je da poseduje takav površinski dizajn da što manje reaguje sa tkivom i agensima iz okoline.Nijedna metoda obrade ne može da proizvede molekularno ravnu površinu stomatoloških materijala.*
Cilj: *istraživanja bio je ispitati hrapavost različitih stomatoloških materijala, pomoću mehaničkog profilometra.*
Materijal i metode: *Ispitivani materijal obuhvatio je kompozit, toplo polimerizovani akrilat, hladno polimerizovane akrilate koji se koriste u protetici i ortodonciji, cirkonijum oksidnu keramiku i staklokermiku. Uzorci materijala za istraživanje su napravljeni prema uputstvu proizvođača. Merenje hrapavosti dobijenih uzoraka izvršeno je pomoću Mitutoyo SJ-301 Suftest uređaja, prevlačenjem čitača preko uzoraka, u dva pravca (vertikalno i horizontalno), čime su dobijena dve vrednosti merenja za svaki materijal pojedinačno.*
Rezultati: *Merenjem hrapavosti materijala, utvrđeno je da među ispitivanim uzorcima postoje značajne razlike. Najveća hrapavost izmerena je kod hladno polimerizovanog akrilata koji se koristi u protetici, dok je najmanja hrapavost izmerenakod kompozitnog materijala.*
Zaključak: *Hrapavost je bila značajno veća kod hladno polimerizovanih akrilata u odnosu na ostale ispitivane materijale, te ga, kada je god to moguće, treba zameniti toplo polimerizvanim akrilatom.U cilju smanjenja hrapavosti stomatoloških materijala treba poštovati principe njihove pripreme i posebno površinske obrade (postupak poliranja i glaziranja).*

Ključne reči: *hrapavost; stomatološki materijali*

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Abstract

Introduction: *In order for a material to be considered biologically acceptable, it is necessary to have such a surface design that it reacts as little as possible with tissue and environmental agents. No processing method can produce a molecularly flat surface of dental materials.*
The aim: *of the study was to examine the roughness of various dental materials, using a mechanical profilometer.*
Material and methods: *The test included different materials such as composite, hot polymerized acrylate, cold polymerized acrylates used in prosthetics and orthodontics, zirconium oxide ceramics and glass-ceramics. Samples of the research materials were made according to the manufacturer's instructions. The measurement of the roughness of the obtained samples was performed using a Mitutoyo SJ-301 Suftest device, dragging the reader across the samples, in two directions (vertical and horizontal), thus obtaining two measurement values for each material individually.*
Results: *By measuring the roughness of the material, it was found that there were significant differences between the samples tested. The highest roughness was measured for cold polymerized acrylates used in prosthetics, while the lowest roughness was measured for composite materials.*
Conclusion: *The roughness was significantly higher for cold polymerized acrylates than the other tested materials and should, wherever possible, be replaced by hot polymerized acrylates. In order to reduce the roughness of dental materials, the principles of their preparation and in particular the surface treatment (polishing and glazing process) should be followed.*

Keywords: *roughness; dental materials*

Uvod

Da bi se materijal smatrao biokompatibilnim neophodno je da, između ostalog, poseduje takav površinski dizajn da što manje reaguje sa tkivom i agensima iz okoline[1]. Neravna površina akrilata, keramike i kompozitnih materijala predstavlja predilekciono mesto za akumulaciju plaka, pigmenata i ostataka oralnog tkiva, pa se može smatrati favorizujućim faktorom u nastanku parodontalnih oboljenja i brojnih oralnih infekcija[2-4]. Brojne in vitro i in vivo studije pokazale su da se stomatološki materijali razlikuju po njihovoj podložnosti da adheriraju oralne bakterije[5,6], što se najčešće pripisuje razlikama u hrapavosti podloge i količini slobodne energije[7,8].

Tekstura površine je jako važno pitanje u razumevanju prirode materijala i igra važnu ulogu u njegovim funkcionalnim performansama. Čvrste površine, bez obzira na način njihovog formiranja, sadrže nepravilnosti ili odstupanja od propisanih geometrijskih oblika[9-11]. Nijedan metod obrade, koliko god precizan, ne može da proizvede molekularno ravnu površinu materijala. Čak i najglađe površine, kao što su one dobijene dekompozicijom nekih kristala sadrže nepravilnosti. Teorijski, hrapavost površina stomatoloških materijala treba smanjiti ispod 0,2μm, što je praksi nemoće izvesti[12].

Hrapavost se može karakterisati sa nekoliko parametara i funkcija, kao što je visina, parametri talasnih dužina, parametri razmaka i hibridi[13]. Najvažniji parametri u slučaju hrapavosti su parametri visine.

U ostvarivanju zahteva restaurativne stomatologije, kompozitni materijali neprikosnoveni su u stomatološkoj kliničkoj praksi, pre svega zbog estetskih svojstava, zadovoljavajućih bioloških kvaliteta i prihvatljivih fizičkih i hemijskih karakteristika. Niska hrapavost površine za restauraciju prestavlja osnovni zahtev za integritet parodonta zuba, za marginalni integritet restauracije kao i za njenu dugovečnost[14].

Dentalna staklokeramika se može definisati kao kristalna, neorganska smesa koja otvrdnjava sinterovanjem, ili kao bela, transcelularna smesa koja se pečenjem dovodi u čvrsto i glazirano stanje. Osnova staklokeramike je stakleni matriks sa različitom količinom punioca (litijum disilikat,

Introduction

In order for a material to be considered biocompatible, it is necessary, among other things, to have such a surface design that reacts as little as possible with tissue and environmental agents[1]. The rough surface of acrylate, ceramics and composite materials is a predilection site for the accumulation of plaques, pigments and oral tissue residues, and can, therefore, be considered a favored factor in the onset of periodontal diseases and numerous oral infections[2-4]. Numerous in vitro and in vivo studies have shown that dental materials differ in their susceptibility to adhesion to oral bacteria[5,6], which is most often attributed to differences in surface roughness and amount of free energy[7,8].

Surface texture is a very important issue in understanding the nature of a material and plays an important role in its functional performance. Solid surfaces, irrespective of their method of formation, contain irregularities or deviations from the predetermined geometric shapes[9-11]. No processing method, however precise, can produce a molecularly smooth surface of the material. Even the smoothest surfaces, such as those obtained by the decomposition of some crystals, contain irregularities. Theoretically, the surface roughness of dental materials should be reduced below 0.2μm, which is impossible to perform in practice[12].

Roughness can be characterized by several parameters and functions, such as height, wavelength parameters, spacing parameters, and hybrids[13]. The most important parameters in the case of roughness are the parameters regarding the height.

In meeting the demands of restorative dentistry, composite materials are the best choice in dental clinical practice, primarily because of their aesthetic properties, satisfactory biological qualities, and acceptable physical and chemical characteristics. The low roughness of the restoration surface is a basic requirement for the integrity of the periodontium of the tooth, the marginal integrity of the restoration and its longevity[14].

Dental glass-ceramics can be defined as a crystalline, inorganic compound which is sinter-hardened, or as a white, transcellular mixture that is brought into a solid and glazed state in the chemical oven. The basis of glass-ceramics is a glass matrix with different amounts of fillers (lithium disilicate, leucite or fluorapatite) which give transparent mass favorable mechanical and physical properties.

leucit ili fluoroapatit) koji transparentnoj masi daju povoljna mehanička i fizička svojstva.

Prednost ovih keramičkihsistema je da ne deluju štetno na tkiva i organizam čoveka, elektohemijski su postojni, otporni su na slabija mastikatorna opterećenja, estetski su prihvatljivi i mogu se dobro i relativno jednostavno oblikvati i obrađivati[15].

Cirkonijum oksidna keramika se koristi za izradu radikularnih kočića, CAD-CAM jezgra za krunice i punih cirkonijumskih krunica. Polikristalne je strukruture, uz odsustvo staklenog matriksa, te je izuzettna čvrta i povoljna za nadoknadu zubnih struktura u bočnoj regiji. Sem fizičko-mehaničkih svojstva, poseduje i druge druge karakteristike prihvatljive za stomatologiju: bio-kompatibilnost, elektrohemijska neutralnost, niska korozivnost i boja primerena za imitaciju prirodnih zuba[16].

Zbog svojih dobrih fizičko-mehaničkih svojstva i relativno jednostavnog postupka rada toplo polimerizovani akrilati su već dugo najčešće korišćeni preparati za izradu baze proteze. Po hemijskoj strukturi to su etri metakrilne kiseline, transparentne materije različitog viskoziteta i širokog spektra fizičko-mehaničkih katakteristika, koji se lako boje i obrađuju. Na tržištu su najzastupljeniji kao dvokomponentni preparati (prašak i tečnost)[17].

Hladno polimerizovani akrilati su po hemijskom sastavu identični sa toplo polimerizovanim akrilatima, ali se vezuju na sobnoj temperaturi. Jedina ali bitna razlika je u tome što akrilati za hladnu polimerizaciju sadrže i aktivator koji razlaze inicijator polimerizacije na slobodne radikale odgovorne za početak procesa polimerizacije. Kako se proces polimerizacije hladnopolimerizovanih akrilata odvija vrlo brzo i bez pritiska, to su fizička svojstva ovog akrilata nešto lošija od svojstva toplopolimerizovanih akrilata. Najčešće se primenjuju za izradu baze parcijalne skeletirane proteze i nagriznih grebena, mobilnih ortodontskih aparata, individualne kašike, reparature proteze kao i za izradu modela zubne nadoknade[17].

Cilj istraživanja bio je ispitati i uporediti hrapavost najčešće primenjivanih stomato-loških materijala, primenom mehaničkog profilometra.

The advantage of these ceramic systems is that they do not adversely affect tissues and the human body. Instead, they are electrochemically stable, resistant to low masticatory loads, aesthetically acceptable and can be relatively easily designed and processed[15].

Zirconium oxide is used to make root canal post and cores for crowns using CAD-CAM technology and full zirconium crowns. The polycrystalline structure, in the absence of glass matrices, is extremely solid and suitable for the replacement of dental structures in the lateral region. In addition to the physico-mechanical properties, it also contains other characteristics acceptable for dentistry: biocompatibility, electrochemical neutrality, low corrosivity and color suitable for imitation of natural teeth[16].

Due to their good physical-mechanical properties and relatively simple working process, hot polymerized acrylates have long been the most commonly used preparations for the manufacture of denture bases. By their chemical structure, they are methacrylic acid ethers, transparent substances of different viscosities and a wide range of physico-mechanical characteristics, which are easy to color and process. In the market, they can be found as two-component preparations (powder and liquid)[17].

Cold-polymerized acrylates are identical when it comes to chemical composition to hot polymerized acrylates, but they bind at the room temperature. The only but important difference is that cold polymerized acrylates also contain an activator that decomposes the polymerization initiator into the free radicals responsible for initiating the polymerization process. As the process of polymerization of cold polymerized acrylates takes place very quickly and without pressure, the physical properties of this acrylate are slightly worse than the properties of hot polymerized acrylates. They are most commonly used for the production of partial skeletal dentures and alveolar ridge, removable orthodontic appliances, individual spoons, prosthesis reparations, as well as for dental replacement models[17].

The aim of the study was to examine and compare the roughness of commonly used dental materials using a mechanical profilometer.

Tabela 1. Ispitivani materijali
Table 1. Tested materials

Materijal / Material	**Komercijalni naziv proizvoda / Commercial product name**
Toplo polimerizovani akrilat Hot polymerized acrylate	Triplex Hot, Ivoclar Vivadent, Lihtenštajn
Hladno polimerizovani akrilat Cold polymerized acrylate	Triplex Cold, Ivoclar Vivadent, Lihtenštajn
Hladno polimerizovani akrilat Cold polymerized acrylate	Ortopli, GSK, SAD
Staklokeramika Glass-ceramic	IPS Empress, Ivoclar Vivadent, Lihtenštajn
Cirkonijum oksidna keramika Zirconium oxide ceramic	IPS e.maxZirCAD, Ivoclar Vivadent, Lihtenštajn
Kompozit Composite	Evetric, Ivoclar Vivadent, Lihtenštajn

Materijal i metode

Ispitivani materijal prikazan je u tabeli 1.

Uzorci materijala za su pravljeni prema uputstvu proizvođača, a njihova obrada bila je analogna onoj koja se primenjuje u svakodnevnoj praksi. Uzorci su imali izgled pločica pravougaonog oblika, dimenzija 3x1,5cm, debljine 3mm. Merenje hrapavosti dobijenih uzoraka izvršeno je pomoću Mitutoyo SJ-301 Suftest uređaja, prevlačenjem čitača preko uzoraka, u dva aksijalna pravca međusobno postavljena pod pravim uglom,čime su dobijena dve vrednosti merenja za svaki materijal pojedinačno. Od svakog ispitivanog materijala napravljeno je po tri uzorka.

Merene su dve vrednosti: Ry - maksimalna visina profila i Ra - srednja aritmetička vrednost odstupanja profila. Dobijene vrednosti izražene su u μm.

Statistička obrada podataka uključivala je izračunavanje srednje vrednosti Ry i Ra za ispitivane urorke i njihovih standardnih devijacija, u programu SPSS 15,0.

Material and methods

The tested material is shown in Table 1.

Material samples were made according to the manufacturer's instructions, and their processing was analogous to that applied in everyday practice. The samples had the appearance of rectangular tiles, dimension 3 x 1.5cm, and 3mm thick. The measurement of the roughness of the obtained samples was carried out using a Mitutoyo SJ-301 Suftest device by dragging the reader over the samples, in two axial directions arranged at the right angle, thus obtaining two measurement values for each material individually. Three samples were made of each material tested.

Two values were measured: Ry - maximum profile height and Ra - mean arithmetic value of profile deviation. The values obtained are expressed in μm.

Statistical data processing included the calculation of the mean of the Ry and Ra for the samples tested and their standard deviations, in SPSS 15.0.

Rezultati

Merenjem površinske hrapavosti materijala, utvrđeno je da među ispitivanim uzorcima postoje značajne razlike. Najveća hrapavost izmerena je kod hladno polimerizovanog akrilata, dok je najmanja hrapavost bila kod kompozitnog materijala. Dobijene vrednosti prikazane su u tabelama 2-7.

Results

By measuring the surface roughness of the material, it was found that there were significant differences between the tested samples. The highest roughness was measured with cold polymerized acrylate, while the lowest roughness was found in measuring the composite material. The values obtained are shown in Tables 2-7.

Tabela 2. Vrednosti površinske hrapavosti toplo polimerizovanog akrilata (μm)
Table 2. Surface roughness values of hot polymerized acrylates (μm)

Materijal/ Material	**Uzorak/ Sample**	**Ra**	**Ry**	**Ra X**	**Ra SD**	**Ry X**	**Ry SD**
Toplo polimerizovani akrilat/ hot polymerized acrylate *Triplex Hot*	1	0.27	1.54				
	1	0.28	1.75				
	2	0.22	1.10	0.31	0.08	1.67	0.43
	2	0.24	1.23				
	3	0.44	2.09				
	3	0.39	2.28				

Ry X- srednja aritmetička vrednost maksimalne visine profila

Ry X- mean arithmetic value of maximum profile height

Ra X - srednja aritmetička vrednost iodstupanja profila

Ra X - mean arithmetic value of profile deviation

Ra SD- standardna deviaciona mera, koja se koristi za kvantifikaciju količine varijacije skupa vrednsti odstupanja profila

Ra SD-standard deviation measure used to quantify the amount of variation of a set of profile deviation values

Ry SD – standardna devociona mera, koja se koristi za kvantifikovanje količine varijacije maksimalne visine profila

Ry SD - standard deviation measure used to quantify the amount of variation of the maximum profile height

Tabela 3. Vrednosti površinske hrapavosti hladno polimerizovanog akrilata koji se upotrebljava u stomatološkoj protetici (μm)
Table 3. Surface roughness values of cold polymerized acrylates used in dental prosthetics (μm)

Materijal/ Material	**Uzorak/ Sample**	**Ra**	**Ry**	**Ra X**	**Ra SD**	**Ry X**	**Ry SD**
Hladno polimerizovani akrilat/ Cold polymerized acrylate *Triplex Cold*	1	1.76	8.52				
	1	1.85	8.69				
	2	2.03	9.17	1.91	0.09	8.83	0.42
	2	1.99	8.17				
	3	1.87	8.94				
	3	1.94	9.46				

Tabela 4. Vrednosti hrapavosti hladno polimerizovanog akrilata koji se upotrebljava u ortodonciji

Table 4. Roughness values of cold-cured acrylates used in orthodontics

Materijal/ Material	**Uzorak/ Sample**	**Ra**	**Ry**	**Ra X**	**Ra SD**	**Ry X**	**Ry SD**
Hladno polimerizovani akrilat/ Cold polymerized acrylate *Ortopoli*	1	0.51	2.78				
	1	0.22	2.18				
	2	0.51	3.06	0.43	0.10	2.74	0.45
	2	0.41	2.08				
	3	0.43	3.17				
	3	0.50	3.15				

Tabela 5. Vrednosti površinske hrapavosti staklokeramike (μm)
Table 5. Surface roughness values of glass-ceramics (μm)

Materijal/ Material	**Uzorak/ Sample**	**Ra**	**Ry**	**Ra X**	**Ra SD**	**Ry X**	**Ry SD**
Staklo keramika/ Glass-ceramic IPS Empress	1	0.27	1.23				
	1	0.36	1.96				
	2	0.37	1.76	0.40	0.10	1.87	0.45
	2	0.6	2.46				
	3	0.41	2.35				
	3	0.36	1.43				

Tabela 6. Vrednosti površinske hrapavosti cirkonijum oksidne keramike (μm)
Table 6. Surface roughness values of zirconium oxide (μm)

Materijal/ Material	**Uzorak/ Sample**	**Ra**	**Ry**	**Ra X**	**Ra SD**	**Ry X**	**Ry SD**
Cirkonijum oksidna keramika/Zirconium oxide ceramic IPS e.maxZirCAD	1	0.36	2.98				
	1	0.33	2.91				
	2	0.6	4.11	0.50	0.11	3.45	0.43
	2	0.59	3.85				
	3	0.61	3.5				
	3	0.49	3.33				

Tabela 7. Vrednosti površinske hrapavosti kompozitnog materijala (μm)
Table 7. Surface roughness values of the composite materials

Materijal/ Material	Uzorak/ Sample	Ra	Ry	Ra X	Ra SD	Ry X	Ry SD
Kompozit/ Composie	1	0.18	1.08				
	1	0.24	1.47				
Evetric	2	0.22	1.31	0.21	0.06	1.28	0.41
	2	0.13	0.8				
	3	0.31	2.05				
	3	0.17	0.97				

Diskusija

Neravna površina stomatoloških materijala predstavlja predilekciono mesto za akumulaciju plaka, pigmenata i ostataka oralnog tkiva. Iz tih razloga, obavezna je besprekorna higijena zuba na kojima postoje plombe, veštačke krunice i mostovi, kao i mobilnoh proteza. Obzirom na njihovu višedecenijsku ulogu morfološkog i funkcionalnog supstituenta u usnoj duplji, većina od ovih materijala zadovoljava uslove koje je pred njih postavila struka. Ipak, postoji puno prostora za njihovo unapređenje, kako im uloga u usnoj duplji ne bi bila prevashodno mehanička, ili drugim rečima terapijska, već preventivna u svom pravom značenju.

Problem protetskog stomatita (stomatitis protetica) javlja se kod 60 do 65% nosioca akrilatnih zubnih proteza[5,6]. U velikom broju slučajeva njegova etiologija vezuje se za akumulaciju gljiva roda Candida na površini akrilata i tada je praćen suvoćom, pečenjem i žarenjem u ustima[7]. Lyon i Chick su kliničkom studijom dokazali da kandide ima više na akrilatnoj protezi nego na oralnoj sluzokoži pacijenta obolelog od protetskog stomatita[7]. To se, sa sigurnošću može pripisati i površinskoj strukturi ovog materijala, koja je reda veličine medijane hrapavosti: Ry=1,17 za toplopolimerizovani akrilat odnosno Ry=8,83

Discussion

The rough surface of dental materials is a predilection site for the accumulation of plaque, pigments, and oral tissue residues. For these reasons, appropriate dental hygiene of the teeth with fillings, artificial crowns, and bridges, as well as mobile dentures is mandatory. Due to their decades-long role as a morphological and functional substitute in the oral cavity, most of these materials satisfy the rules set by the profession. However, there is a lot of room for improvement, so that their role in the oral cavity is not primarily mechanical, or in other words therapeutic, but preventive in its true meaning.

The problem of prosthetic stomatitis occurs in 60 to 65% of acrylic denture wearers[5,6]. In many cases, its etiology is related to the accumulation of Candida yeasts on the acrylic surface followed by a sense of dryness and burning in the mouth[7]. Lyon and Chick have proven that Candida is located on most of the acrylic prosthesis than on the oral mucosa of a patient with prosthetic stomatitis[7]. This can certainly be attributed to the surface structure of this material, which is of the order of magnitude

(hladno polimerizovani akrilat). Pravilnom pripremom materijala, kao i adekvatnim poliranjem, znatno se smanjuje njegova ukupna površina, pa i mogućnost da se kandida i drugi mikroorganizmi za nju zalepe. Hladno polimerizovani akrilati su pokazali izrazito veće vrednosti hrapavosti u odnosu na akrilat koji se polimerizuje u ključaloj vodi, te njihovu upotrebu treba izbegavati kada su u pitanju podlaganja i reparature zubnih proteza. Obzirom da se hladno polimeruzovani akrilati koriste i za izradu mobilnih ortodontskih aparata, njih pre upotrebe treba ispolirati po protokolu i besprekorno održavati, kako bi se poboljšala njihova biološka svojstva (Ry=2,27).

Srednja vrednost površinske hrapavosti ispitivanog kompozitnog materijala bila je Ry=1,28, što je najmanja izmerena vrednost u odnosu na druge ispitivane materijale. Literaturni podaci su pokazali da kompozitne restauracije akumuliraju više plaka u odnosu na druge vrste stomatoloških materijala[18-21]. Nepotpuna obrada i konsekutivna hrapavost kompozitnih materijala značajno doprinose nakupljanju biofilma na površini kompozita [22,23]. U uslovima usne duplje kompozitni materijali se vremenom degradiraju, što uslovljava srazmerno povećanje njihove hrapavosti i adherencije biofilma. Kolonizacija prostora između zuba i kompozitne restauracije smatra se glavnim uzrokom nastanka sekundarnog karijesa[24].

Nakupljanje biofilma na keramičkim krunicama i inlejima može rezultovati oštećenjima potpornog aparata zuba i razvojem karijesa, te je održavanje oralne higijene kod pacijenata sa ovim vrstama nadoknada imperativ. Rashid i Kawai i sar. su zaključili da glazirana keramika usled postojanja mikrohrapavosti nakuplja više plaka u odnosu na keramiku poliranu dijamantskom pastom [25-27]. Ispitivani uzorci staklokeramike bili su ispolirani, a srednja vrednost hrapavosti iznosila je Ry=1,87μm, što je neznatno više u odnosu na ispolirani kompozit i toplopolimerizovani akrilat. Sa druge strane, hrapavost cirkonijum oksidne keramike bila je viša od očekivane sa medijanom od Ry=3,45μm. Obzirom na mali broj istraživanja u vezi sa biokompatibilnošću ove vrste materijala na ovom nivou nismo u mogućnosti da komentarišemo značajno veću hrapavost

of the median roughness: Ry = 1.17 for hot polymerized acrylate and Ry = 8.83 (cold polymerized acrylate). Proper preparation of he material, as well as adequate polishing, significantly reduces its total surface area, as well as the possibility of adhesion of Candida and other microorganisms to it. Cold polymerized acrylates have shown markedly higher roughness values than acrylate polymerized in boiling water, and their use should be avoided when it comes to relining and reparations. Since cold polymerized acrylates are also used in the manufacture of removable orthodontic appliances, they must be polished prior to use and maintained in order to improve their biological properties (Ry = 2.27).

The mean of the surface roughness of the tested composite material was Ry = 1.28, which is the lowest measured value compared to the other tested materials. Literature data have shown that composite restorations accumulate more plaque than other types of dental materials[18-21]. Incomplete processing and consecutive roughness of composite materials significantly contribute to the biofilm accumulation on the composite surface[22,23]. In the oral cavity, composite materials degrade over time, which causes a proportional increase in their roughness and adhesion of the biofilm. Colonization of the space between the tooth and the composite restoration is considered to be a major cause of secondary caries[24].

The accumulation of a biofilm on ceramic crowns and inlays can result in damage of the supporting apparatus of the teeth and the development of caries, so the maintenance of oral hygiene in patients with these types of restoration is imperative. Rashid and Kawai et al. have concluded that due to the presence of micro-roughness, glazed ceramics accumulate more plaque than ceramics polished by diamond paste [25-27]. The tested samples of glass-ceramics were polished, with a mean roughness of Ry = 1.87 μm, which was slightly higher than the polished composite and the hot polymerized acrylate. On the other hand, the roughness of zirconium oxide was higher than expected with a median Ry = 3.45 μm. Due to the small number of research regarding the biocompatibility of this type of material, we

cirkonije u odnosu na konvencionalno pripremljenu staklokeramiku. Uporedna analiza kvaliteta površinske strukture različitih keramika biće predmet budućih istraživanja, a i sama praksa će pokazati kako će se ove restauracije novije generacije vremenom ponašati prema okolnim tkivima.

Pljuvačka svojim protokom, puferskim kapacitetom i promenom sastava omogućava dinamičnu interakciju materijalima implementiranim u usnu duplju, čime utiče na njihove karakteristike, uključujući i adherentnost[28-29]. Sve nadoknade su u ustima pacijenta obložene salivarnom pelikulom, omotačem koji nastaje međusobnom interakcijom materijala i sastojaka pljuvačke. Ključnu ulogu u njenom formiranju igra precipitacija mucina i glikoproteina pljuvačke [30]. Sam sloj pljuvačke smanjuje adherentnost dentalnog plaka i ostataka hrane za površinu materijala, te im ovaj prirodni omotač poboljšava biokompatibilnost.

Zaključak

Predložena metoda za merenje hrapavosti stomatoloških materijala je jednostavna i ne zahteva skupo istraživanje. Dobijeni rezultati, upoređeni su sa merenjima koja su rađena u dva pravca, jednostavnom analizom otkrivena je statistički značajna razlika stepena hrapavosti. Uzimajući u obzir ograničenja prilikom istraživanja, na osnovu merenja, možemo izvesti sledeće zaključke: najveća hrapavost je kod hladno-polimerizovanog akrilata, dok je najmanja kod kompozitnih materijala. Preliminarni rezultati predstavljaju osnovu za istraživanja ponašanja različitih materijala u kliničkim uslovima.

are not able to comment on the significantly higher zirconium roughness compared to conventionally prepared glass-ceramics. A comparative analysis of the quality of the surface structure of different ceramics will be the subject of future research, and the practice itself will show how these new-generation restorations will behave to the surrounding tissues.

Saliva, through its flow, buffering capacity, and composition change allows dynamic interaction with materials implemented in the oral cavity, thereby affecting their characteristics, including the adherence[28-29]. All restorations are coated with a salivary pellicle, a cover formed by the interaction of saliva material and constituents. A key role in its formation is played by the precipitation of saliva mucin and glycoproteins[30]. The saliva layer itself reduces the adherence of dental plaque and food residues to the surface of the material, and this natural cover enhances their biocompatibility.

Conclusion

The proposed method for measuring the roughness of dental materials is simple and does not require expensive research. The results obtained were compared with measurements that were made in two directions, and a simple analysis revealed a statistically significant difference in the degree of the roughness. Considering the limitations of the research, based on measurements, we can draw the following conclusions: the highest roughness is found in cold polymerized acrylate, while the lowest in the case of composite materials. The preliminary results form the basis for investigating the behavior of different materials under clinical conditions.

LITERATURA / REFERENCES

1. Hanks CT, Watacha JC, Sun Z. In vitro models of biocompatibility: A review. Dent Mater 1996; 12: 186-193.
2. Zissis AJ, Polyzois GL, Yannikakis SA, Harrison A. Roughness of denture materials: a comparative study. Int J Prosthodont 2000; 13(2): 136-140.
3. Bollen CM, Lambrechts P, Quirynen M. Comparison of surface roughness of oral hard materials to the threshold surface roughness for bacterial plaque retention: a review of the literature. Dent Mater 1997; 13: 258-269.
4. Yamauchi M, Yamamoto K, Wakabayashi M, Kawano J. In vitro adherence of microorganisms to denture base resin with different surface texture. Dent Mater J. 1990; 9: 19-24.
5. Gendreau L, Loewy ZG. Epidemiology and Etiology of Denture Stomatitis. J Prosthodont 2011; 20: 251–260.
6. Salerno C et al. Candida-associated denture stomatitis. Med Oral Patol Oral Cir Bucal. 2011; 16: e139-43.
7. Alves, PV et al. Surface roughness of acrylic resins after different curing and polishing techniques. Angle Orthodontist 2007; 77: 528-531.
8. Lloyd CH, Scrimgeour N. Dental materials: 1995 literature review. J Dent 1997; 25: 173-208.
9. Shulev A, Roussev I, Karpuzov S, Stoilov G, Ignatova D. Roughness measurement of dental materials. Journal of Theoretical and Applied Mechanics, Sofia, 2016; 46: pp. 27–36.
10. Bhushan B. Surface Roughness Analysis and Measurement Techniques. home.ufam.edu.br/berti/nanomateriais/8403_PDF_CH02.pdf
11. Kawai K, Urano M. Adherence of plaque components to different restorative materials. Oper Dent 2001;26:396-400
12. Nevzatoglu EU, Ozcan M, Kulak-Ozkan Y, Kadir T. Adherence of Candida albicans to denture base acrylics and silicone-based resilient liner materials with different surface finishes. Int J Prosthodont 1997; 10(5): 473-477.
13. Bollen CM, Lambrechts P, Quirynen M. Comparison of surface roughness of oral hard materials to the threshold surface roughness for bacterial plaque retention: a review of the literature. Dent Mater 1997;13:258-269.
14. Ferracane JL. Resin composite--state of the art. Dent Mater. 2011;27:29-38.
15. Kirmali O. Dental ceramics used in dentistry. Cumhuriyet Dental Journal 2012; 17:316-324.
16. Della Bona A, Pecho OE, Alessandretti R. Zirconia as a Dental Biomaterial. Materials 2015, 8, 4978-4991.
17. Frazer RQ, Byron RT, Osborne PB, West KP. PMMA: an essential material in medicine and dentistry. J Long Term Eff Med Implants 2005; 15: 629-639.
18. Konoshi N, Torii Y, Kurosaki A, Takatsuka T, Itota T, Yoshiyama M. Confocal laser scanning microscopic analysis of early plaque formed on resin composite and human enamel. J Oral Rehabil 2003;30:790–795.
19. Persson A, Claesson R, Van Dijken JW. Levels of mutans streptococci and lactobacilli in plaque on aged restorations of an ion-releasing and a universal hybrid composite resin. Acta Odontol Scand 2005;63:21–25.
20. Beyth N, Bahir R, Matalon S, Domb AJ, Weiss EI. Streptococcus mutans biofilm changes surfacetopography of resin composites. Dent Mater 2008; 24: 732-736.
21. Mei L, Busscher HJ, van der Mei HC, Ren Y. Influence of surface roughness on streptococcal adhesion forces to composite resins. Dent Mater 2011; 27: 770-778.
22. Rashid H. The effect of surface roughness on ceramics used in dentistry: A review of literature. European Journal of Dentistry 2014; 8(4):571-579.
23. Sousa RP, Zanin IC, Lima JP, Vasconcelos SM, Melo MA, Beltrão, HC. In situ effects of restorative materials on dental biofilm and enamel demineralisation. J Dent 2009; 37:44-51.
24. Bremer F, Grade S, Kohorst P, Stiesch M. In vivo biofilm formation on different dental ceramics. Quintessence Int 2011;42:565‐574.
25. Rashid H. Comparing glazed and polished ceramic surfaces using confocal laser scanning microscopy. J Adv Microscop Res 2012;7:208‐213
26. Kawai K, Urano M, Ebisu S. Effect of surface roughness of porcelain on adhesion of bacteria and their synthesizing glucans. J Prosthet Dent 2000;83:664‐667.

27. Zamperini CA, Machado AL, Vergani CE, Pavarina AC, Giampaolo ET, da Cruz NC. Adherence in vitro of Candida albicans to plasma treated acrylic resin. Effect of plasma parameters, surface roughness and salivary pellicle. Arch Oral Biol 2010; 55(10): 763-770.

28. Radford DR, Sweet SP, Challacombe SJ, Walter JD. Adherence of Candida albicans to denture-base materials with different surface finishes. J Dent 1998; 26(7): 577-583.

29. Park MS, Chung JW, Kim YK, Chung SC, Kho HS. Viscosity and wettalilty of animal mucin solutions and human saliva. Oral Dis 2007; 13(2): 181-186.

30. Lindh L. On the adsorption behaviour of saliva and purified salivary proteins at solid/liquid interfaces. Swed Dent J Suppl 2002; (152):1-57.

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PRIKAZ SLUČAJA
CASE REPORT
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RANA PRIMENA PARCIJALNE AKRILATNE OPTURATOR PROTEZE U POSTOPERATIVNOM TRETMANU KOŠTANIH DEFEKATA NAKON MARSUPIJALIZACIJE VELIKIH VILIČNIH CISTI

EARLY USE OF PARTIAL ACRYLIC DENTURE OBTURATOR IN THE POSTOPERATIVE TREATMENT OF BONE DEFECTS AFTER MARSUPIALISATION OF LARGE JAW CYSTS

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Sažetak

Uvod:*Posle marsupijalizacije velikih viličnih cisti nastaju koštani defekti koji ne garantuju stabilnost krvnog koaguluma i zbog toga se ispunjavaju jodoform gazom. Svaka zamena jodoform gaze, radi toalete rane, prouzrokuje manje ili veće krvarenje, što usporava epitelizaciju i organizaciju rane. Zbog toga se, nekoliko nedelja od operativnog zahvata, preporučuje izrada parcijalne akrilatne opturator proteze.*
Prikaz slučaja: *U ovom radu prikazan je slučaj dva pacijenta kod kojih je izrađena parcijalna akrilatna opturator proteza desetog dana nakon operativnog zahvata. To je omogućilo značajno lakšu toaletu rane, bržu epitelizaciju i organizaciju rane, a samim tim i brže koštano zarastanje.*
Zaključak: *Obnovljene funkcije žvakanja, gutanja i govora, kao i estetski izgled ukazuju na značaj rane izrade akrilatne opturator proteze.*

Ključne reči: *ciste, marsupijalizacija, opturator proteza, zarastanje rane*

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Abstract

Introduction: *After marsupialisation of large jaw cysts, there comes to the formation of bone defects which do not guarantee the stability of the blood clot and therefore are filled with iodine gauze. Any replacement of iodine gauze, toilet of the wound, causes minor or major bleeding, which slows wound epithelialisation and organization. Therefore, making the partial acrylic denture obturator is recommended to be done a few weeks after the surgery.*
Case report: *This work presents two patients who had partial acrylic denture obturator made on the tenth day after the surgery. This allowed significantly easier toilet of the wounds, faster epithelialization and organization, and thus faster bone healing.*
Conclusion: *Restored function of chewing, swallowing and speech, as well as the aesthetic appearance suggest that early use of acrylic obturator prosthesis is very significant.*

Keywords: *cysts, marsupialisation, opturator prosthesis, wound healing*

Uvod

Hirurška terapija velikih viličnih cisti često podrazumeva delimično uklanjanje cističnog sakusa i dekompresiju ciste ili marsupijalizaciju (cistostomiju). Operaciju je opisao Partsch još 1892. godine. Intervencija se sprovodi u situacijama kada veličina koštanog defekta ne garantuje stabilnost krvnog koaguluma, ugrožava susedne strukture, preti frakturi donje vilice, kod pacijenata starije životne dobi, koji su rizični za rad u opštoj anesteziji, i naročito kod dece, kada su u pitanju neagresivne cistične lezije[1].

Rez se vrši ivicom budućeg koštanog defekta, uklanja se površinski deo cističnog sakusa i prazni se (aspirira) sadržaj ciste. Mukoperiostalni režanj ubacuje se u nastali koštani defekt ili se obodno ekscidira i ušiva za ivicu koštanog defekta. Kavitet se ispunjava jodoform gazom, koja se menja na sedam dana uz prethodno ispiranje i dezinfekciju rane. Kasnije, posle nekoliko nedelja, preporučuje se izrada parcijalne akrilatne opturator proteze (PAOP). Najjednostvanije proteze mogu se napraviti bez zuba, mada su estetski i funkcionalno daleko bolje one proteze koje uključuju zube, alveole i okolna tkiva[2].

Smanjenje inflamacije cističnog zida, redukcija zapremine i sekundarna dekompresija iniciraju okolnu osteoblastičnu aktivnost. Vremenom dolazi do perifernog stvaranja novog koštanog tkiva i postepenog smanjenja zapremine koštanog defekta. Proces stvaranja nove kosti traje, u zavisnosti od veličine i oblika defekta, nekoliko meseci, pa čak i više od godinu dana. Epilog marsupijalizacije je metaplazija cističnog epitela u pločastoslojevit epitel usne duplje ili perzistencija delova ili celog cističnog sakusa[3]. Naknadna enukleacija vezana je za agresivne kliničke lezije kakve su odontogene keratociste[4]. Odluka se donosi na osnovu histopatološkog nalaza.

Jodoform gaza u koštanom defektu, u vremenskom periodu od nekoliko nedelja, može stvarati znatne neugodnosti pacijentu, od kojih se najčešće apostrofirju: bol prilikom njene zamene, jak miris i neprijatan zadah. Osim toga, svaka zamena jodoform gaze posle operacije uzrokuje uklanjanje površinskih slojeva krvnog koaguluma i krvarenje, što usporava epitelizaciju defekta.

Cilj rada je prikazati uspešnu ranu primenu parcijalne akrilatne opturator proteze (PAOP) u gornjoj i donjoj vilici kod dva pacijenta nakon marsupijalizacije velikih viličnih cisti.

Introduction

Surgical therapy of large jaw cysts often involves partially removing the sac of cysts and cysts decompression or marsupialisation (cystostomy). The operation was described by Partsch in 1892. The intervention is implemented when the size of the bone defect does not guarantee the stability of the blood clot, threatens neighbouring structures, and threatens to fracture of the lower jaw in older patients who are at risk for operation under general anesthesia, and especially in children when it comes to aggressive cystic lesions[1].

The cut goes along the edge of the future bone defect, removing the surface of the cystic sac and emptying (aspirating) the contents of the cyst. Width flap is inserted into the resulting bone defect or circumferentially excised and sutured to the edge of the bone defect. The cavity is filled with iodoform gauze that is changed in seven days with the previous washing and disinfecting the wound. Later, after a few weeks, making partial acrylic dentures obturator (PADO) is recommended. The simplest prosthesis can be made without teeth, although aesthetically and functionally far better are the ones that include teeth alveoli and the surrounding tissue[2].

Decrease of cystic wall inflammation, volume reduction and secondary decompression initiate the surrounding of osteoblast activity. Over time, there is a peripheral formation of new bone and gradual reduction in volume of the bone defect. The process of creating a new bone takes a few months or even more than a year depending on the size and shape of the defect. Epilogue of marsupialisation is metaplasia of cystic epithelia into layered epithelium of the oral cavity or the afterglow of the whole or parts of cystic sac[3]. Subsequent enucleation is associated with aggressive clinical lesions such as odontogenic keratocysts[4]. A decision is made based on histopathological findings.

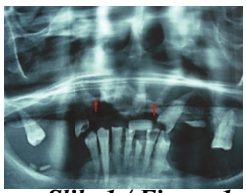
Iodine gauze in the bone defect within a period of several weeks can cause considerable inconvenience to the patient, one of which is usually pain during its replacement, a strong odour and bad breath. In addition, each substitute iodoform gauze after surgery causes removal of the surface layers of a blood clot and bleeding, which slows epithelialization of the defect.

The aim is to show the successful implementation of early partial acrylic dentures obturator (PADO) in the upper and lower jaw in two patients after marsupialisation large jaw cysts.

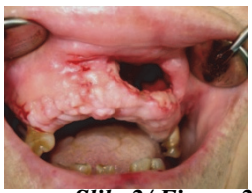
Prikaz slučaja

Pacijenti su operisani u Službi za oralnu hirurgiju Klinike za stomatologiju Medicinskog fakulteta u Nišu na osnovu histopatoloških rezultata preoperativnih biopsija, koji su ukazali na prisustvo radikularnih cisti. Pre hirurške intervencije izvršena je detaljna parodontološka sanacija usne duplje u Službi za parodontologiju i oralnu medicinu Klinike za stomatologiju Medicinskog fakulteta u Nišu. Neposredno posle intervencije pacijenti su upućeni na Odeljenje za stomatološku protetiku Klinike za stomatologiju Medicinskog fakulteta u Nišu, gde im je izrađena PAOP. U oba slučaja histopatološki rezultati intraoperativnih biopsija potvrdili su dijagnozu radikularnih cisti.

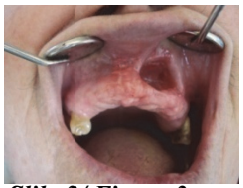
Prvi pacijent P. S. ženskog je pola, starosti 85 godina, sa subtotalnom krezubošću i cističnom lezijom koja se pružala od centralnog sekutića do drugog premolara gornje vilice sa leve strane (slika 1). S obzirom na godine života i veličinu lezije urađena je marsupijalizacija ciste (slika 2,3). U postoperativnom periodu stvoreni defekt čvrsto je ispunjen jodoform gazom. Sedmog dana izvršena je toaleta rane, uzet je otisak alginatnom masom, ponovo je izvršena toaleta rane i zamenjeno je pakovanje jodoform gaze znatno mekšim (predlog: zamenjena je upotrebna jodoform gaza znatno mekšom). Uzimanje otiska neposredno posle operativnog zahvata nije predstavljalo veći problem. Alginatna masa pripremana je nešto ređe, kako bi njeno plasiranje bilo meko, što nije bilo praćeno bolom kod pacijenta, već strahom i neugodnošću. Radi preciznijeg otiska, prvo je otisna masa prstom nanošena u defekt, a zatim je preko nje uziman otisak standardnom kašikom napunjenom alginatom. Desetog dana izrađena je PAOP od toplo polimerizujućeg akrilata i predata pacijentu (slika 4).



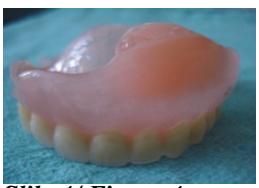
Slika1 / Figure 1



Slika2/ Figure 2



Slika3/ Figure 3

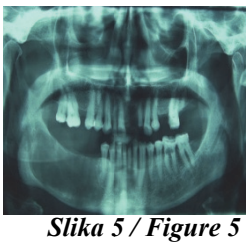


Slika4/ Figure 4

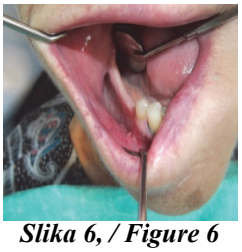
Case report

Patients were operated in the Department of Oral Surgery at Dental Clinic of the Faculty of Medicine based on histopathological results of preoperative biopsy, which indicated the presence of radicular cysts. Before surgery they performed a thorough periodontal rehabilitation of the oral cavity in the Department of Parodontology and Oral Medicine, Clinic of Dentistry Faculty of Medicine. Immediately after the procedure, patients were referred to the Department of Prosthetic Dentistry, Faculty of Medicine, where PADO was made. In both cases, the histopathological results of intraoperative biopsy confirmed the diagnosis of radicular cyst.

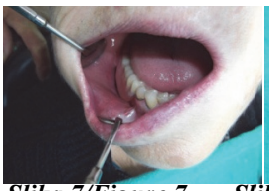
The first patient was P. S., female, 85 years of age, with subtotal toothlessness and cystic lesion extended from the central incisors to the second premolar of the upper jaw on the left side (Figure 1). Due to the age and size of the lesion, marsupialisation of cysts was performed (Figure 2,3). In the postoperative period created defect was firmly filled with iodoform gauze. On the seventh day the toilet of the wound was made, the print was taken with alginate mass, then toilet of the wound was re-made and iodine gauze packing was replaced with considerably softer one. Taking impression immediately after surgery was not a problem. Alginate mass was prepared less thick, so that its placement was soft, not accompanied by pain, fear and discomfort of the patient. For a more precise fingerprint, the first mass fingerprint inflicted the defect, and then the fingerprint was taken over it with standard bucket filled with alginate. On the tenth day a hot-dip polymer acrylate PADO was made and delivered to the patient (Figure 4).



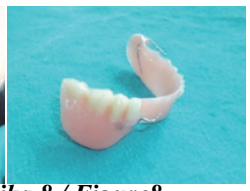
Slika 5 / Figure 5



Slika 6, / Figure 6



Slika 7/Figure 7



Slika 8 / Figure8

Prilikom svakog narednog kontrolnog pregleda, koji je zakazivan na sedam dana, PAOP je obrađivana i delimično skraćivana uz istovremnenu toaletu i dezinfekciju rane. Epitelizacija rane nastala je 25. dana posle operacije, što je pacijentu omogućilo komforniji život u smislu higijene, ishrane i estetike. Potpuno ispunjenje defekta novostvorenim koštanim tkivom nastupilo je 5 meseci nakon operacije, a pacijentkinja je nastavila da nosi PAOP kao definitivni protetski rad.

Drugi pacijent D. R, takođe je osoba ženskog pola, starosti 86 godina, sa jednostranom bezubošću i cističnom lezijom koja se pružala od prvog premolara do trigonuma retromolare donje vilice sa desne strane (slika 5). I u ovom slučaju urađena je marsupijalizacija ciste(slika 6.), plasirana je jodoform gaza , sedmog dana uzet je otisak alginatom i desetog dana postavljena je PAOP (slike 7. i 8.), koja je obrađivana na isti način kao u prethodnom slučaju. Epitelizacija rane nastala je 23. dana. Potpuno ispunjenje defekta novostvorenim koštanim tkivom nastupilo je 8 meseci nakon operacije. I u ovom slučaju PAOP je tako prilagođena da je nošena kao definitivna proteza.

U narednom periodu kod oba pacijenta nisu uočene nikakve smetnje i nepravilnosti, u smislu pojave komplikacija ili cističnih recidiva.

Diskusija

Velike koštane ciste u maksili i mandibuli tretiraju se otvorenom metodom, jer formiranje nestabilnog krvnog koaguluma predstavlja locus minoris resistentiae za nastanak akutne infekcije. Nastali koštani defekti velikog su morbiditeta. Ispunjavaju se jodoform gazom, čiji su zadataci prevencija sekundarnog krvarenja, antiseptički efekat, sprečavanje zapadanja hrane i stranih tela u ranu, kao i eliminisanje negativnog uticaja pljuvačke.

Međutim, jodoform gaza u dužem vremenskom periodu stvara brojne neugodnosti pacijentu, koje se ogledaju u njenom preterano jakom mirisu, bubrenju pod dejstvom pljuvačke i prominiranju iz defekta, što delimično onemogućava i otežava mastikaciju, kao i nakupljanju ostataka hrane, na površini gaze, koja se raspada i neprijatno miriše. Svaka nova zamena gaze prilično je bolna za pacijenta, jer se gaza lepi za periferiju i ivice defekta uklanjajući krvni koagulum, zbog čega rana dodatno krvari. Impregnacija gaze sterilnom

During each follow-up examination scheduled at seven day intervals, PADO was processed and partially shortened simultaneously with toilet and disinfection of wounds. Epithelization of the wound occurred 25 days after the operation which allowed the patient more comfortable life in terms of hygiene, nutrition and aesthetics . Complete filling of the defect with newly created bone tissue occurred 5 months after surgery, and patient continued to carry PADO as the definitive prosthesis.

The second patient, D. R. was also female, 86 years of age, with unilateral edentulous and cystic lesions that stretched from the first premolar to trigonum retromolar lower jaw on the right side (Figure 5). In this case, cysts marsupialisation was performed as well (figure 6.), iodine gas was placed , on the seventh day the alginate print was taken and on the tenth day PADO was set (Figures 7 and 8), which was treated in the same manner as in the previous case. Epithelization occurred on the 23rd day. Complete defect filling with the newly created bone tissue occurred 8 months after surgery. In this case, PADO was adjusted so that it is worn as a definitive prosthesis.

In the forthcoming period, both patients showed no disturbances and irregularities in terms of complications or recurrence of cyst.

Discussion

Large bone cysts in the maxilla and mandible are treated by the open method, because the formation of unstable blood coagulum represents the locus minoris resistentiae for the occurrence of acute infection. The resulting bone defects are major morbidity. They are filled with the iodoform gauze whose task is to prevent secondary bleeding, provide antiseptic effect, prevention of food falling and foreign bodies in the wound, as well as the elimination of the negative impact of the saliva.

However, the iodine gas in a longer time period creates a number of inconveniences to the patient which are reflected in its excessively strong smell, swelling under the action of saliva and prominiranju from the defect which partly prevents and hinders mastication, as well as the build-up of food residue on the surface of the gauze which decomposes and smells. Each new gauze replacement is quite painful for the patient, because the gauze sticks to the periphery and the edges of the defect

parafinskom pastom to delimično, ali nepotpuno onemogućava. Iz tih razloga, epitelizacija rane znatno je sporija i često traje duže od mesec dana.

Osnovni cilj protetske terapije, nakon većih operativnih zahvata u gornjoj i donjoj vilici, je rehabilitacija izgubljenih struktura uz što bržu obnovu funkcija žvakanja, gutanja i govora, kao i poboljšanje izgleda pacijenta[5]. PAOP čini mehaničku barijeru između operisanog dela i usne duplje. Svojom glatkom površinom onemogućava lepljenje koaguluma i sekundarno krvarenje prilikom toalete i dezinfekcije rane. Sprečava nakupljanje tečnosti i hrane, kontaminaciju rane i prouzrokuje bržu epitelizaciju i organizaciju, a samim tim i (predlog: pospešuje) izlečenje rane povezane sa defektom kosti[6]. Shodno tome, brže je i koštano zarastanje, tj. ispunjenje defekta novonastalom kosti.

Rana izrada PAOP ima vrlo značajnu ulogu (predlog: u postoperativnoj nezi) i utiče na poboljšanje kvaliteta života operisanih pacijenata[7,8]. Pri tom, pokazuje sledeće prednosti u odnosu na jodoform gazu: 1) manja trauma tkiva prilikom zamene; 2) odsustvo bola i krvarenja; 3) brža epitelizacija rane; 4) normalna mastikacija; 5) odsustvo mirisa jodoforma; 6) prihvatljiva estetika; 7) lako skidanje i postavljanje; 8) redukcija zadržavanja ostataka hrane i njenog raspadanja; 9) lako održavanje oralne higijene i 10) odsustvo neprijatnog zadaha. Postavljanje PAOP neposredno posle operacije čini pacijenta nesvesnim hirurške deformacije, što je vrlo bitno sa psihičke strane[2]. (Predlog: PAOP skraćuje vreme) Skraćuje se vreme oporavka i omogućava pacijentu da se vrati u zajednicu kao funkcionalan član[2].

U toku procesa zarastanja rane potrebne su česte kontrole i obrade PAOP. Kako se defekt popunjava novostvorenim koštanim i mekim tkivom tako se redukuje površina PAOP koja ispunjava kavitet cističnog defekta. Osim idealnog uklapanja i prilagođavanja rani, ponekad se mogu uraditi i druge modifikacije, u smislu dodavanja zuba radi poboljšanja estetike, mastikacije i govora[9].

Kao što je već istaknuto, obe naše pacijentkinje nastavile su da nose PAOP kao definitivne proteze. Prethodnim korekcijama, tokom koštanog i mekotkivnog zarastanja, PAOP su dovedene u idealnu poziciju prema okolnim tkivima. Uz odsustvo dekubita, bolova i drugih smetnji, kao i uz naviku (predlog: naviknutost) pacijenta na njihovo nošenje, nije bilo potrebe za izradom novih definitivnih proteza. I drugi autori navode da u

The main goal of prosthetic treatment after major surgery in the upper and lower jaw is the rehabilitation of lost structures with advancing the restoration of function of chewing, swallowing and speaking, as well as the improvement in the patient`s appearance[5]. PADO makes a mechanical barrier between the operated and part of the oral cavity. Its smooth surface prevents sticking of the clot and secondary bleeding when doing the toilets and disinfection of the wounds. It prevents the accumulation of fluids and food, contamination of wounds, and causes rapid epithelialization and organization, and consequently wound healing associated with a defect in the bone[6]. Eventually, there is a faster bone healing, i.e., filling of the newly created bone defect.

Early PADO production has a very important role and improves the quality of life of treated patients[7,8]. At the same time, with respect to iodine gauze it shows the following advantages: 1) less trauma in tissue replacement, 2) absence of pain and bleeding, 3) faster wound epithelialization, 4) normal mastication, 5) a lack of odor iodophor 5) acceptable aesthetic, 6) easy to remove and install, 7) reduction of food residue and its decomposition, 8) ease of maintenance of oral hygiene and 9) absence of bad breath. Setting PADO immediately after surgery makes the patient unconscious of surgical deformities, which is very important regarding the psychological side[2]. Recovery time is shorter and allows the patient to return to the community as a functional member[2].

During the healing process, frequent monitoring and processing of PADO is required. As the defect fills the newly created bone with soft tissue, the PADO surface that fills the cavity cystic defect reduces. In addition to an ideal fit and adjustments early, sometimes you can do other modifications in terms of adding teeth to improve aesthetics, mastication and speech[9].

As it has already been pointed out, both our patients continued to wear PADO as definitive prosthesis. With corrections during the healing of bone and soft tissue, PADO is brought in the ideal position in relation to the surrounding tissues. With the absence of decubitus, pain and other disorders, as well as with the habit of the patient to their carrying, there was no need to create a new prosthesis. Other authors state that in certain situations PADO can serve as a definitive prosthesis[10].

Regeneration of bone defects depends on their size. Defects of 3 teeth regenerate for up to 12 months and the damage to more than 3 teeth up to 20 months or more. Defects in the During the healing process, frequent

monitoring and processing of Paope is required. As the defect fills the newly created bone with soft tissue, the Paope surface that fills the cavity cystic defect određenim situacijama PAOP mogu poslužiti kao definitivne proteze[10].

Regeneracija koštanih defekata zavisi od njihove veličine. Defekti (predlog: koji obuhvataju do 3) do 3 zuba regenerišu se za najviše 12 meseci, a defekti (predlog: koje čini) preko 3 zuba regenerišu se, nekada, za 20 i više meseci. Defekti u gornjoj vilici brže regenerišu nego oni u donjoj vilici, zbog bolje prokrvljenosti i obilne spongioze, što se pokazalo i u ovom slučaju[11]. Pri tom, izduženi defekti brže regenerišu u odnosu na okrugle, gde je retrakcija koaguluma izraženija. Kod naših pacijentkinja koštana regeneracija trajala je pet meseci u maksili, odnosno osam meseci u mandibuli, što je s obzirom na njihove godine i veličinu defekta bilo prilično brzo. (predlog: „što je bio prilično kratak period oporavka“ ili „prilično brz oporavak“.)

Zaključak

Rana izrada PAOP pokazala se vrlo efikasnom, u smislu poboljšanja epitelizacije koštanih defekata posle marsupijalizacije velikih viličnih cisti. Komfornost koju pruža i odsustvo negativnih uticaja nekada dozvoljavaju njenu primenu kao definitivne proteze i posle ispunjenja defekta novim koštanim tkivom.

upper jaw regenerate faster than in the lower, due to a better blood circulation and abundant cancellous, as proven in this case[11]. In addition, elongated defects quickly regenerate compared to round, where the clot retraction is pronounced. Bone regeneration lasted five months in the maxilla and eight months in the mandible, which was pretty fast due to their age and size of the defect.

Conclusion

Early PADO development proved to be very effective in terms of improving epithelialization of bone defects after marsupialisation of large jaw cysts. The comfort provided by the absence of the negative impacts sometimes allows its use as a definitive prosthesis, even after the defect is filled with the new bone tissue.

LITERATURA / REFERENCES

1. Pejović M, Stepić J, Marković A, Dragović M, Miličić B, Colić S. Retrospetkivna studija spontane regeneracije kosti posle dekompresije velikih odontogenih cističnih lezija kod dece. Vojnosanitetski pregl; 2016; (73) 2: 129-134.
2. Pravinkumar GP. Surgical obturator duplicating original tissue-form restores esthetics and function in oral cancer. World J Stomatol. 2013; 2(4): 97-102.
3. Gao L, Wang X, Li S, Liu C, Chen C, Li J, Zhi K. Decompression as a treatment for odontogenic cystic lesions of the jaw. J Oral Maxillofac Surg. 2014; 72(2): 327−33.
4. Marin S, Kirnbauer B, Rugani P, Mellacher A, Payer M, Jakse N. The effectiveness of decompression as initial treatment for jaw cysts: A 10-year retrospective study. Med Oral Patol Oral Cir Bucal. 2019; 24 (1): 47-52.
5. Singh M, Bhushan A, Kumar N, Chand S. Obturator prosthesis for hemimaxillectomy patients. Natl J Maxillofac Surg. 2013; 4(1): 117–120.
6. Ray S, Ray PK. Islam R, Chaudhari GR. Prosthetic Rehabilitation of Maxillo-mandibular defects: Case Series. International Journal of Oral Health Dent. 2016; 2(3): 200-205.
7. Brandão TB, Vechiato Filho AJ, Batista VE, de Oliveira MC, Santos-Silva AR. Obturator prostheses versus free tissue transfers: A systematic review of the optimal approach to improving the quality of life for patients with maxillary defects. J Prosthet Dent. 2016; 115(2): 247-253.
8. Loster JE, Ryniewicz W, Gala A, Wieczorek A. Prosthetic obturators used in the treatment of cystic jaw bones. J Stomat. 2015; 68 (5): 531-538.
9. Kamarudin KH, Hattori M, Sumita YI, Taniguchi H. A chairside technique to add customized anterior acrylic resin teeth to a surgical obturator. The Journal of Prosthetic Dent. 2018; 119 (5): 852-854.
10. 10. Husein M, Hassan SI, Khan MY, Khan M, Tanveer W. Retention in Mandibular Obturator. Professional Med J. 2014; 21(4): 755-759.
11. Narwa A. Chugh A, Swami R. Immediate Prosthetic Rehabilitation of Surgically Enucleated Pinborg Tumour: A Case Report. Annals of International Medical and Dental Research 2016; 2 (6): 28-31.

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UTICAJ RADIOTERAPIJE I HEMOTERAPIJE NA ORALNA TKIVA
THE EFFECTS OF RADIOTHERAPY AND CHEMOTHERAPY ON ORAL TISSUES

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Sažetak

Uvod:*Tretman bolesnika koji boluju od raka, u smislu hemoterapije i radioterapije, značajno je evoluirao od svog začetka. Obe terapije, naročito ako se koriste u kombinaciji, imaju veoma ozbiljan potencijal da dovedu do neželjenih efekata, koji narušavaju kvalitet života i potencijalno povećavaju mortalitet bolesnika obolelih od raka.*
Cilj rada:*U ovom radu opisan je uticaj radioterapije i hemoterapije na oralna tkiva. Oralne komplikacije koje se posledično javljaju mogu se svrstati u sledeće kategorije: mukozsitis, kserostomija, gljivične, virusne i bakterijske infekcije, disgeuzija, disfagija, profuzno krvarenje, osteonekroza i mišićni trizmus.*
Zaključak:*Budući da je potreban širok spektar preventivnih i kurativnih mera, pojavljuje se potreba za sastavljanjem posebnih timova za brigu o bolesnicima pre, tokom i nakon radioterapije i hemoterapije. Takav onkološki tim trebalo bi imati doktora stomatologije, specijalistu oralne medicine kao aktivnog člana.*

Ključne reči: *mukozitis, radioterapija, hemoterapija*

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Abstract

Introduction: *Cancer treatment, in terms of chemotherapy and radiotherapy has evolved significantly from its beginning. Both therapies, especially used in combination, had the potential to cause side effects, that potentially decrease in quality of life and lead to increased mortality rate in patients with cancer.*
The aim:*of the study: The effects of radiotherapy and chemotherapy were described. The oral complications which consequently occurred could be classified into following categories: mucositis, oral dryness, fungal, viral and bacterial infections, disgeusia, disfagio, profuse bleeding, osteonecrosis and muscle trismus.*
Conclusion: *Because of the wide range of preventive and curative measures, it is necessary to create a special team for caring of patients before, during and after radiotherapy and chemotherapy. In such case, dentist, oral medicine specialists should be an active member of oncology team.*

Key words: *mucositis, radiotherapy, chemotherapy*

Uvod

Tretman bolesnika koji su oboleli od raka značajano je evoluirao u pogledu povećane efikasnosti i podnošljivosti od 1940. godine, kada su korišćeni antagonisti folne kiseline i azotni iperiti (citostatici) za lečenje leukemije i limfoma. Takođe, radioterapija je u upotrebi za lečenje bolesnika obolelih od raka više od 100 godina i napredovala je u smislu sofisticiranosti, efikasnosti i smanjenja neželjenih propratnih efekata. Međutim, oba tretmana, posebno ukoliko se koriste u kombinaciji jedan sa drugim, imaju veliki potencijal koji se ogleda u bolnim i iznurujućim neželjenim efektima koji jasno narušavaju kvalitet života bolesnika i potencijalno povećavaju mortalitet. Oralne komplikacije koje nastaju u toku tretmana ovakvih bolesnika su: mukozitis, kserostomija, gljivične, bakterijske i virusne infekcije, disgeuzija, disfagija, profuzno krvarenje, osteonekroza i mišićni trizmus. Mukozitis je inflamacija oralne mukoze koju uzrokuju jonizujuće zračenje i hemoterapija[1].

Epidemiološki podaci pokazuju da su uzroci smrtnosti u svetu: kardiovaskularna oboljenja (29%), infektivne bolesti (19%) i maligna oboljenja (13%)[2]. Prevalencija malignih neoplazmi glave i vrata kod muškaraca je tri puta veća nego kod žena[2-4]. U poslednjih nekoliko decenija prevalencija preživljavanja bolesnika sa neoplazmama glave i vrata (usana, usne duplje, faringsa i laringsa) povećala se za 10%[5]. Terapeutske metode za lečenje malignih bolesti obuhvataju: hiruršku terapiju, radioterapiju, hemoterapiju, hormonsku terapiju, imuno-terapiju, kao i njihovu kombinaciju[6].

Radioterapija

Radioaktivno zračenje koristi se u eksperimentalne, dijagnostičke i terapeutske svrhe. Jonizujući zraci deluju na najosetljivije delove ćelija – gene i enzimski sistem, pa nastaju funkcionalni i morfološki poremećaji koji indirektno izazivaju biohemijska oštećenja, stvarajući slobodne radikale i toksične produkte, koji povećavaju obim oštećenja. Najpre strada hemopoetični sistem, koji je najosetljiviji. Oralne promene mogu nastati nakon sekundarnog zračenja kod osoba koje u ustima imaju metalne protetske radove. Zbog toga je potrebno pre zračenja ukloniti metal i destruirane ili kariozne zube, koji su pripremani za ekstrakciju[7].

Introduction

The treatment of cancer patients has evolved significantly in case of increased efficiency and tolerability from the year 1940, when the folic acid antagonist and nitrous iperites were used in treatmentof leukemia and lymphoma. Also, the radiotherapy was used in the cancer treatment for more than 100 years and it progressed in terms of being sophisticated, efficient and the side effects were reduced. Both therapies, especially used in combination, have the potential to cause side effects, which potentially decrease the quality of life and lead to a potential increase in mortality rate in patients with cancer. The oral complications which consequently occurred could be classified into following categories: mucositis, oral dryness (xerostomia), fungal, viral and bacterial infections, dysgeusia, dysphagia, profuse bleeding, osteonecrosis and muscle trismus. Mucositis is inflammation of the oral mucosa which was caused by ionizing radiation and chemotherapy[1].

Epidemiological data showed that causes of death worldwide were cardiovascular diseases (29%), infectious diseases (19%), and malignant diseases (13%)[2]. Men are about three times more likely than women to be diagnosed with the malignant head and neck cancer[2-4]. Survival from head and neck cancers (lip, oral cavity, pharynx, and larynx) has increased by 10% over the past few decades[5]. Therapeutic strategies for the treatment of malignant diseases include: surgical therapy, radiotherapy, chemotherapy, hormonal therapy, immunotherapy and combination of these therapies[6].

Radiotherapy

Radioactive radiation is used for the experimental, diagnostic and therapeutic purposes. Ionizing radiation affects the most sensitive parts of cells – genes and enzymatic system, as well as the functional and morphologic disorders indirectly cause impairs of biochemical parameters by making free radicals and toxic products which increase the damage. Primarily, the most sensitive hematopoietic system has been destroyed. The oral changes may be found after secondary radiation of patients with metal prosthetic devices. Because of that, before radiation, it is necessary to remove the metal and badly decayed or damaged teeth[7].

Radioterapija je primarna u terapiji karcinoma glave i vrata. Efekati terapije se, pored bolesnog tkiva, vide i na zdravom tkivu. Promene u usnoj duplji mogu biti rane i pozne. Rane promene javljaju se obično u toku prve nedelje i manifestuju se enantemom i edemom. U toku druge nedelje javljaju se erozije i ulceracije pokrivene sivožutim fibrinoznim eksudatom. Subjektivno se javljaju malaksalost, oralna suvoća i bolovi u toku govora i ishrane, kao i gubitak osećaja ukusa. Kada se zrače pljuvačne žlezde, osnovni problem je oralna suvoća. Spontano oporavljanje, nastaje nakon završene terapije. Pozne promene javljaju se nekoliko meseci nakon prestanka zračne terapije i eventualnog zarastanja oralnih lezija. Manifestuju se suvom i atrofičnom sluzokožom i floridnim cervikalnim karijesom, kao i pogoršanjem parodontopatije[8].

Potencijalne oralne komplikacije uzrokovane radioterapijom mogu biti akutne i hronične. Akutne komplikacije uključuju mukozitis, kserostomiju, infekcije, disgeuziju, disfagiju i malnutriciju, dok su hronične komplikacije kserostomija, cervikalni karijes, teleangiektazije, miofibritis, trizmus, oštećenje vaskularizacije, nekroza mekih tkiva, osteoradionekroza, dentofacijalne malformacije (ukoliko je bolesnik izložen radioterapiji pre perioda adolescencije) i malnutricija[9].

Hemoterapija

Hemoterapija je često korišćena kao pomoćni terapeutski metod, zajedno sa radioterapijom ili kao metoda izbora kod transplantacije koštane srži. Hemoterapija, koja se daje za maligne lezije glave i vrata, može takođe uzrokovati promene na oralnoj mukozi. Lokalna sekundarna oralna infekcija, kao posledica mijelosupresije najčešća je komplikacija hemoterapije i može dovesti do sepse i smrtnog ishoda[10]. Druge komplikacije vezane za hemoterapiju su: disbalans elektrolita, hemoragija, akutna intoksikacija lekovima (uključujući povraćanje i mučninu), fotosenzitivnost, disfunkcija centralnog nervnog sistema, alopecija i malnutricija. Sonis i sar.[11] opisali su oralne komplikacije (mukozitis, ulceracije i kserostomiju) kod 40% bolesnika koji su lečeni standardnom hemoterapijom, a nisu imali malignitete vezane za region glave i vrata.

Radiotherapy is a primary treatment for head and neck cancer. The effects of the therapy, beside healthy tissue have been seen in damaged tissue. The changes in the oral cavity could be named as early and late. The early changes usually appear during the first weak and manifested with enanthema and edema. During the second week, the erosions and ulcerations covered with grey-yellow fibrinous exudate may be present. Subjective fatigue, xerostomia and pain during talking and eating, as well as dysgeusia were found in these patients. When the salivary glands were under radiation, the main problem has been xerostomia. Recovering starts after the finished therapy. Late changes will appear several months after the finished radiotherapy and complete healing of oral lesions. These changes are manifested in dry and atrophic mucosa and florid caries, as well as in exacerbation of periodontal disease[8].

The potential oral complication of radiotherapy could be an acute and chronic. Acute complications include: mucositis, infections, dysgeusia, dysphagia, and malnutrition, while the chronic complications are: xerostomia, cervical caries, telangiectasia, myofibritis, trismus, impaired vascularisation, necrosis of soft tissues, osteoradionecrosis, dentofacial malformation (the patient was exposed to radiotherapy as an adolescent) and malnutrition[9].

Chemotherapy

Chemotherapy is often used in conjunction with radiotherapy like additional therapeutic method or like a choice method in the bone marrow transplantation. Chemotherapy, for the malignant head and neck lesions, can cause alteration of the oral cavity mucosa. Local secondary oral infection, as a consequence of myelosuppression, is the most frequent complication of chemotherapy, and could lead to the septic shock and death[10]. Other chemotherapy side effects are: electrolyte imbalance, hemorrhage, acute drug intoxication (including vomiting and nausea), photosensitivity, central nervous system dysfunction, alopetion and malnutrition. Sonis et al.[11] described the oral complications (mucositis, ulcerations and xerostomia) in 40% of all patients who received standard chemotherapy, and they had no malignant head and neck lesions.

Oralne komplikacije prijavljene su kod 75% bolesnika, koji su na visokim dozama hemoterapeutika, 70% do 80% bolesnika kojima je presađena koštana srž i 100% bolesnika koji primaju radioterapiju za malignitete glave i vrata[12]. Hemoterapeutici imaju uticaj na koštanu srž i dovode do smanjenja mijeloproliferacije, što ima za posledicu, između ostalog, trombocitopeniju, leukopeniju i neutropeniju. Ovi agensi takođe izazivaju promene na oralnoj mukozi, koje se manifestuju kao smanjenje mitotičke aktivnosti oralnih epitelnih ćelija, što za posledicu ima epitelnu atrofiju, smanjenu otpornost epitela na mehaničke iritacije, mukozitise i oralne ulceracije[12,13]. Ulceracije obezbeđuju slobodan prolaz sekundarnoj infekciji, zbog virulentnih mikroorganizama oralne flore. Prisustvo neutropenije može dovesti do sepse i njenih ozbiljnih komplikacija, pa i do smrtnog ishoda.

Stomatolog u onkološkom timu

Onkološkom timu potreban je doktor stomatologije da bi mogao da ublaži komplikacije koje su posledica teške akutne radioterapije i spreči razvoj hroničnih komplikacija[14-16].

Bolesnici koji su planirani za zračnu terapiju glave i vrata ili oni koji primaju hemoterapiju moraju se podvrgnuti stomatološkom pregledu i tretmanima koji su podeljeni na one koje se izvode pre, u toku i nakon radioterapije i hemoterapije.

Procedure koje se izvode pre radioterapije ili hemoterapije

– oralni klinički pregled zuba i vilica x-zračenjem (ortopantomografija ili retro-alveolarno snimanje zuba);
– edukacija bolesnika, instrukcije i motivacija za održavanje višeg nivoa oralne higijene pre, u toku i nakon terapije; agresivni protokol o održavanju oralne higijene;
– kompletno i temeljno lečenje svih zuba obe vilice;
– radikalni pristup lečenju zuba;
– estrakcija svih zuba koji nemaju prognozu opstanka dužu od 5 godina;
– indikacije za ekstrakciju su: avitalni zubi, zubi sa apikalnim parodontitisom, zubi koji zahtevaju endodontski tretman, zubi sa džepovima dubljim od 6 mm i vidljivim furkacijama, sa destruiranim krunicama i zaostalim korenovima korenima zuba, impaktirani zubi i zubi koji su povezani sa tumorom[6];

Oral complications were reported in 75% of all patients who were receiving high dose of chemotherapy, in 70%-80% of all patients who were undergoing bone marrow transplantation and in 100% of patients who were receiving radiotherapy for malignant head and neck lesions[12]. Chemotherapeutics have an impact on bone marrow and lead to impaired myeloproliferative activity, which consequently lead to the thrombocytopenia, leucopenia and neutropenia. These agents also cause the changes on oral mucosa, which manifest thought impaired mitotic activity within oral epithelial cells, and consequently lead to epithelial atrophy, impaired epithelial activity on the mechanical irritations, mucositis and oral ulcerations[12,13]. The ulcerations provide free entrance for secondary infections, caused by virulent microorganisms of oral flora. The presence of neutropenia may lead to septic shock and their severe complications, as well as lethal outcome.

A dentist on the oncology team

The oncology team needs a dentist who would reduce complication appearing as a consequence of severe acute radiotherapy and stop the development of further chronic complications[14-16].

Patients who were planned for radiotherapy of head and neck or they who received chemotherapy should have dental check up and treatments which are divided before, during and after radiotherapy and chemotherapy.

The procedures performed before undergoing radiotherapy and chemotherapy

– the clinical oral examination of teeth and jaw by dental X-rays (orthopantomography and retroalveolarradiography);
– education of patients, instructions and motivation for improving oral hygiene methods before, during and after therapy; more aggressive protocol for maintaining good oral hygiene;
– complete and thorough dental treatment of both jaws;
– radical dental treatment approaches:
– extraction of the teeth with survival rates no higher than5 years;
– indications for extraction: avital teeth, teeth with apical peridontitis, teeth that

– kod bolesnika kod kojih je zakazana radioterapija i hemoterapija, ekstrakcija zuba izvodi se 14 –20 dana (minimum 10 dana) pre terapijske procedure;
– ekstrakcionu ranu ne bi trebalo ostavljati sa oštrim ivicama alveolarne kosti, tako da bi trebalo izvesti alveoloplastiku nakon ekstrakcije zuba;
– nakon ekstrakcije zuba, ranu treba ušiti kako bi ona zarasla "*per primam*"; svež koagulum je osetljiv na radijaciju;
– režim davanja atibiotske terapije posle ekstrakcije zuba isti je kao kod bolesnika sa infektivnim endokarditisom, sa mogućim produženjem terapije[17];
– potrebno je odraditi cistektomiju, ukoliko su prisutne ciste u vilicama;
– mobilne proteze ne treba nositi tokom zračne terapije i duže vreme posle toga; mobilne proteze mogu se nositi samo tokom jela i prilikom socijalnih kontakata, uz odobrenje i redovne kontrole stomatologa;
– individualni splint za aplikaciju 1% gela fluora mora biti urađen.

Procedure koje se izvode u toku radioterapije i hemoterapije:

– kontrola mukozitisa (ultra meka četkica za zube, zubni konac za higijenu interdentalnih prostora bez provokacije krvarenja, hlorheksidin, lokalna aplikacija 1% sodium-fluoridnog gela korišćenjem specijalno dizajniranog individualnog splinta);
– kontrola bola (lokalni anestetici u obliku gela);
– prevencija sekundarne infekcije (pranje usta nekoliko puta dnevno pomoću miksture sode bikarbone i kuhinjske soli, hlorheksidina, nistatina i mikonazola).

Procedure koje se izvode nakon radioterapije i hemoterapije:

– sav trud treba se usmeriti na oralnu negu zuba, gingive, oralne mukoze i faringsa[18,19];
– zube treba prati mekom četkicom nakon svakog obroka i pre spavanja;
– treba koristiti paste na bazi fluora;
– vratove zuba (cervikalni karijes) i interdentalne prostore treba održavati pomoću interdentalnog konca i interdentalnih stimulatora, međutim ne sme se provocirati gingivalno krvarenje;

require endodontic treatment, teeth with pockets deeperthan 6 mm and visible furcations, teeth with destructed crowns and radices relictae, impacted teeth and teeth associated with the tumor[6];
– in patients undergoing radiotherapy and chemotherapy, appointed tooth extraction was performed 14–20 days (minimum 10 days) before therapeutic procedure;
– an extraction wound should not be left with sharp edges and alveoloplasty of the alveolar bone should be performed after tooth extraction;
– after tooth extraction, the wound should be sutured to heal "*per primam*", the fresh blood coagulum is sensitive to radiation;
– the antibiotic treatment regimes after tooth extraction is the same as well as in patients with infective endocarditic, with potential treatment elongation[17];
– cystectomy is to be performed, if the cysts are found in the jaws;
– the mobile dental prosthesis should not be worn during radiotherapy and for a long time after; mobile dental prosthesis may be worn during eating and social contact, with the approval and regular dental checkups;
– anindividual splintused for application of fluoride 1% dental gel should be done.

The procedures performed during undergoing radiotherapy and chemotherapy:

– control of oral mucositis (ultra soft tooth brush, dental floss for interdental species without bleeding provocation, chlorhexidine, local application of 1% of sodium fluoride gel used with specially designed individual splint);
– the pain control (local anesthetic dental gel); and
– preventing of a secondary infection (several times per day using of mouthwash of baking soda and table salt, nystatin and miconazole).

The procedures performed after undergoing radiotherapy and chemotherapy:

– all efforts should be putinto maintaining a good oral hygiene of teeth, gingiva, oral mucosa and pharynx[18,19];
– the teeth should be brush with a soft brush after every meal and before sleeping;
– the fluoride toothpaste should be used;

– usta treba ispirati nekoliko puta dnevno rastvorom kuhinjske soli sa dodatkom sode bikarbone;
– post-radijaciona kserostomija je česta komplikacija; ovim bolesnicima trebalo bi dati sledeća uputstva: tegobe će biti blaže ukoliko pijuckate neko hladno piće; preporučuje se da se maslinovim uljem sa sokom od limuna ispere usna duplja[20];
– treba koristiti veštački slani rastvor (Glandosane sprej, Oral Balance gel, Xero-Lube);
– mogu se propisati stimulatori pljuvačke (rastvor pilokarpin-hidrohloridSalagen tablete);
– vitaminske kreme (d-pantenol) (konstantno oblagati usne njima);
– kontrolne posete stomatologu, minimum jednom u tri meseca.

Komplikacije na maksili i mandibuli uzrokovane radioterapijom (osteonekroza)

Komplikacije na maksili i mandibuli predstavljaju specifičan problem sa kliničkom slikom osteomijelitisa, i osteonekroze nakon zračne terapije i sekvestracije[21]. Rizik od ovih komplikacija značajno je smanjen ukoliko se koriste odgovarajuće zaštitne mere pre zračne terapije. Međutim, zračna terapija smanjuje regenerativnu sposobnost kostiju, oštećuje interkoštani protok krvi i smanjuje broj osteocita i osteoklasta. Rizik je veći ukoliko se vadi zub u polju koje je bilo ozračeno. Promene su često praćene limfedemom. Mandibula je znatno osetljivija u odnosu na maksilu.

Sledeće mere su predložene ukoliko se jave neke od ovih komplikacija:

–visoke doze atibiotika prema antibiogramu. Oksigenacija u hiperbaričnoj komori da bi se povećala oksigenacija tkiva, što stimuliše angiogenezu, funkciju osteoblasta i fibroblasta[22];

–kritičko razmatranje hirurške terapije ukoliko ne postoji sekvestracija.

– tooth cervices (cervical caries) and interdental spaces need c to be cleanedby interdental floss and interdental stimulators, however gingival bleeding should not be provoked;
– the mouth should be rinsed few times per day by using solution of tablesalt and baking soda;
– radiation-induced xerostomia is a frequent complication:these instructions should be explained to the patient*:* the symptoms may be milder if you drink cold drink; it is recommended to rinse mouth by olive oil with lemon juice[20];
– the artificial saline solution should be used (Glandosan spray, Oral Balance gel, Xero-Lube);
– the salivary stimulants may be prescribed (solution of pilocarpine-hydrochloride, Salagen tablets);
– vitamin creams (d-panthenol) (applying lip productsrepeatedly); and
– regular dental check-ups, minimum one per three months.

Complications in the maxilla and mandible caused by radiotherapy (osteonecrosis)

Complications in the maxilla and mandible represent specific problem of radiotherapy-induced clinical signs of osteomyelitis, osteonecrosis and sequestration[21]. The risk of these complications is significantly reduced if the protective measures are properly used before radiotherapy. However, radiotherapy reduces the ability to regenerate bone, impairs intercostal blood flow through blood vessels and reduces number of osteocites and osteoblasts. The risk is higher if the tooth extraction is in the area of radiation. The changes are frequently associated with lymphedema. The mandible is noticeably more sensitive as compared to the maxilla.

The following measures are suggested if some of these complications occur:

– High doses of antibiotic according to the antibiogram. Oxygenation in hyperbaric chamber to increase tissue oxygenation, which stimulates angiogenesis, osteoblasts and fibroblasts function[22]; and
– A critical consideration of the surgical treatment, if there isno sequestration.

Mukozitis

Oralni mukozitis predstavlja inflamaciju sluzokože usne duplje uzrokovanu radio-terapijom i hemoterapijom. Oralni mukozitis pogoršava kvalitet života bolesnika. Uzimanje hrane i pića je teško, a nekada je čak neizvodljivo, što vodi malnutriciji i dehidrataciji.

Komunikacija je otežana zbog bolnih lezija[23-25]. Kliničko vrednovanje mukozitisa predstavljeno je prema kriterijumima Svetske zdravstvene organizacije modifikovanihod strane Scully i sar.[26] (Tabela 1).

Oralni mukozitis predstavlja promenu epitela usne duplje u vidu eritema, erozija, ulceracija i deskvamacija (Slika 1).

Promene se mogu podeliti, prema WHO klasifikaciji, na sledeći način:

1. Lokalizovani eritem bez bola;
2. Generalizovani eritem bez bola, ili lokalizovani eritem sa ulcerom i slabim bolom < 20%;
3. Generalizovani eritem sa brojnim ulceracijama i umerenim bolom pri uzimanju čvrste hrane;
4. Generalizovani eritem sa brojnim ulceracijama, praćen jakim bolom pri uzimanju tečne hrane.

Mukozitis počinje trećeg dana, a maksimum dostiže dvanaestog do četrnaestog dana zračne terapije i hemoterapije. Tkivne promene rezultat su delovanja terapije na enzimski sistem, DNK, RNK i stvaranje slobodnih radikala koji remete ćelijski genetski materijal, stvarajući ćelije mitotički inkompetentne ili uzrokujući programiranu ćelijsku smrt – apoptozu. To rezultira poremećajem keratinizacije, atrofijom epitela, atrofijom i degeneracijom kolagenih vlakana, vaskularnim promenama, ulceracijama i nekrozom[8].

Mucositis

Oral mucositis represents inflammation of oral mucosa caused by radiotherapy and chemotherapy. Oral mucositis decreases the patients' quality of life. Taking food and drinks is difficult and sometimes even impossible, and can lead to malnutrition and dehydration. Communication is difficult because of painful lesions[23-25]. Clinical assessment of mucositis is represented by criteria of World Health Organization (WHO), modified by Scully et al.[26] (Table 1).

Oral mucositis represents the change of epithelium of oral cavity in form of erosions, ulcerations and desquamations (Figure 1).

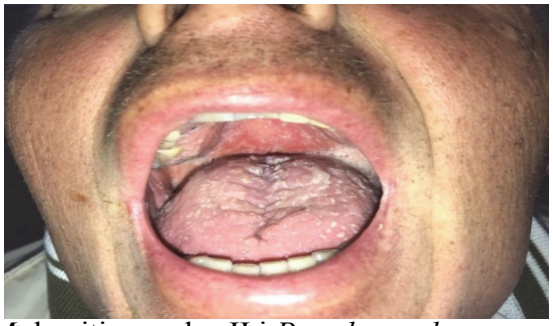
The changes can be divided according to WHO classification into:

1. Local erythema without pain symptoms
2. Generalized erythema without pain symptoms, or local erythema with ulceration and mild pain <20%
3. Generalized erythema with multiple ulcerations and moderate pain during taking a solid foods
4. Generalized erythema with multiple ulcerations associated with severe pain during taking liquid foods.

Radiotherapy and chemotherapy induce oral mucositis which starts on the third day, but reaches its maximum on the twelfth to fourteenth day. Tissue changes are a result of the therapy impact on DNA, RNA and free radicals which disturbed genetic material, by making mitotic incompetent cells, or cause process of programmed cell death-apoptosis. That results in disturbed keratinization, atrophy and degeneration of collagenous fibers, vascular changes, ulcerations and necrosis[8].

Tabela 1. Kliničko vrednovanje mukozitisa
Table 1. Clinical assessment of mucositis

Gradus **Grade**	**Klinički izgled** **Clinical signs**
0	Nisu prisutne lezije mukoze Oral mucosa lesions were absent.
1	Osetljivost mukoze – blag eritem Oral *mucosal sensitivity*–mild erythema
2	Eritem/-ulceracije, moguće uzimanje čvrste hrane Erythema-ulcerationes, possible eating solid foods
3	Teške ulceracije i eritem – dijeta koja podrazumeva unošenje isključivo tečne hrane Big ulcerations and erythema – diet with liquid food
4	Nekroza i krvarenje–hranjenje preko usne duplje Necrosis and bleeding – taking food *through* the *mouth* is impossible



Slika 1. Mukozitis, gradus II i *Pseudomembranous candidiasis*
Figure 1. Mucositis, Gradus II and *Pseudomembranous candidiasis*

Terapija oralnog mukozitisa

Terapija oralnog mukozitisa obuhvata široki spektar lekova i procedura: lokalni anestetici, kortikosteroidi, sistemski analgetici, sistemski ili lokalni antiinflamatorni lekovi, antiseptici, antibiotici, orabaze, keratinocitni faktor rasta (stimuliše proliferaciju i diferencijaciju epitelnih ćelija), interferon, Lysobact, miks fiziološkog rastvora i sode bikarbone, veštačka pljuvačka i različiti čajevi.

Bolesnici sa lošom oralnom higijenom i karijesnim zubima imaju veću učestalost mukozitisa i teže kliničke simptome, nego bolesnici sa dobrom oralnom higijenom i popravljenim zubima.

Kserostomija

Otok i bol pljuvačnih žlezdi, uz smanjeno lučenje pljuvačke, koja je gusta i lepljiva, javljaju se već nekoliko sati nakon zračenja. Ove tegobe, u većini slučajeva, prestaju za nekoliko dana[27]. Nakon par dana primene radioterapije dolazi do oštećenja seroznih acinusa pljuvačnih žlezda, pa je pljuvačka viskozna. U daljem toku radioterapije oštećuju se i mukozne ćelije acinusa pljuvačnih žlezda, pa je smanjen ukupan volumen izlučene pljuvačke. Ukoliko je došlo do trajnog i ireverzibilnog funkcionalnog oštećenja parenhima pljuvačnih žlezda, nastaje kserostomija[27].

Iako vrednosti radiotolerantne doze za parotidnu žlezdu nisu precizno definisane, Emami i sar.[28] su, na osnovu rezultata brojnih studija i kliničkog iskustva, zaključili da vrednosti doza koje dovode do rizika pojave kserostomije, od 5% do 50% u toku 5 godina od sprovedenog zračenja, iznose 32 Gy i 46 Gy, a da kod skoro svih bolesnika čije su parotidne pljuvačne žlezde u celosti ozračene dozom od 50 Gy do -60 Gy, dolazi do kompletnog i ireverzibilnog prestanka lučenja pljuvačke[29].dozom od 50-60 Gy, dolazi do kompletnog i ireverzibilnog prestanka lučenja pljuvačke[29].

The oral mucositis therapy

The oralmucositis therapy protocol includes wide range of drugs and procedures: local anesthetics, systemic or local anti-inflammatory drugs, antiseptic drugs, antibiotics, keratinocyte growth factor (stimulates proliferation and epithelial cells differentiation), interferon, Lysobact, mix of saline solution and baking soda, artificial saliva and different types of tea.

The higher percentage of mucositis and severe clinical symptoms could be found in patients with poor oral hygiene and dental decay, than in patients with good oral hygiene and dental fillings.

Xerostomia

Swelling and pain in the salivary glands, together with reduced secretion of the saliva, which is thick and sticky, manifest as soon as few hours after the radiotherapy. In most cases, these symptoms disappear in a few days[27]. The serous acini of salivary glands damage occur a couple of days from the start of radiotherapy, and the saliva becomes viscous. In the further course of radiotherapy, mucous cells of salivary gland acini get damaged so the total volume of saliva is reduced. In the case of complete and irreversible functional damage of salivary glands parenchyma, xerostomia is manifested[27].

Although radiotolerance dose values for parotid gland are not precisely defined, Emami et al.[28] concluded, based on results of numerous studies and clinical experience, that dose values which cause xerostomia from 5% to 50% during 5 years from being under radiotherapy were 32Gy and 46Gy, and in patients where salivary glands were under radiotherapy from 50-60Gy came to complete and irreversible stopping of saliva production[29].

Disgeuzija

Disgeuzija, se odnosi na poremećaj osećaja ukusa i čest je klinički problem sa kojim se susreću bolesnici oboleli od raka[30]. Prema nekim procenama, 50% – 75% bolesnika obolelih od raka, koji primaju zračnu terapiju ili hemoterapiju, ili oba, imaju disgeuziju[31]. Interesantno je to da bolesnici na zračnoj terapiji (uglavnom glave i vrata) imaju goru disgeuziju nego bolesnici na hemoterapiji., Težina ovog oboljenja u korelaciji je sa kumulativnom dozom zračenja. Ustvari, 15% bolesnika na zračnoj terapiji ima poremećen osećaj ukusa nakon završetka njihovog tretmana[31]. Etiologija disgeuzije je multifaktorijalna, ali postoje jednostavni tretmani, uključujući savetovalište o ishrani i lečenje oralne infekcije, koji bi se smanjili loš uticaj ovog oboljenja na kvalitet života bolesnika[32]. Za lečenje idiopatske disgeuzije neke studije predlažu preparate cinka, konkretno u studiji Halyard i sar.[33] koristili su cink-glukonat, koji je poboljšao osećaj ukusa, apetit i raspoloženje bolesnika. Fink i sar.[34] predlažu vitamin D, kao suplement u terapiji ove oralne komplikacije.

Oralna kandidijaza

Candida albicans je gljivica koja je komensal i u normalnim uslovima koegzistira u usnoj duplji sa drugim oralnim mikroorganizmima i ne uzrokuje oboljenje. Kolonizacija i infekcija dešavaju se kada su sistemski ili lokalni faktori oštećeni, uključujući imunosupresiju, hiposalivaciju, oštećenje tkiva i / ili poremećaje flora, kod obolelih od raka koji su pod terapijom. U pregledu literature Lalla i sar.[35], procenat bolesnika obolelih od gljivičnih infekcija, koji su inače podvrgnuti hemoterapiji i zračnoj terapiji glave i vrata, bio je 7,5% pre tretmana, 40% tokom tretmana, i 30% nakon tretmana. Pseudomembranozna kandidijaza (Slika 1), hronična (atrofična) eritematozna kandidijaza i angularni heilitis najčešće su kliničke forme ovog oboljenja, dok je hronična hiperplastična forma (nodularna kandidijaza) retko prijavljena.

Dysgeusia

Dysgeusia is a taste disturbance and it is a frequent clinical symptom in cancer patients[30]. According to some estimates, 50% to 75% of cancer patients who receive radiotherapy or chemotherapy or both have dysgeusia[31]. It is interesting that patients undergoing radiotherapy (mostly head and neck) have greater risk of dysgeusia than patients undergoing chemotherapy, the severity of disease is in correlation with cumulative radiation dose. Actually, 15% of patients undergoing radiotherapy have taste disturbances after the end of their treatment[31]. Etiology of dysgeusia is multifactorial, but the treatment is simple, includes nutrition counseling and treating of oral infection to decrease the negative impact of this disease on the quality of life of patients[32]. For treating of idiopathic dysgeusia some studies recommend zinc supplements; specifically in their study, Halyard et al. used zinc gluconate, which improved taste sensation, appetite and mood of patients[33]. Fink suggests vitamin D, as supplement in the treatment of this oral complication[34].

Oral candidiasis

Candida albicans is a fungus, which is commensal and in normal circumstances coexists with other microorganisms in oral cavity not causing disease. Colonization and infection occur when systemic and local factors are impaired, including immunosuppression, hyposalivation, tissue damage and/or disturbed flora in patients undergoing cancer therapy. Lalla et al.[35] found that percent of candidiasis in patients undergoing chemotherapy and radiotherapy for head and neck were 7.5% before treatment, 40% during treatment and 30% after treatment. Pseudomembranous candidiasis (Figure 1), chronic (atrophic) erythematous candidiasis and angular cheilitis are the most frequent clinical forms of this disease, while the chronic hyperplastic form (nodular candidiasis) is rarely reported.

Virusne infekcije

Oralne virusne infekcije, uključujući *herpes simplex virus (HSV), varicella zoster virus* (VZV), Epstein–Barr virus (EBV) i cytomegalovirus (CMV), česte su komplikacije kod bolesnika obolelih od raka. Teške infekcije mogu dovesti do dehidratacije, malnutricije i komplikacija opasnih po život, uključujući encefalitis i diseminovanu infekciju. Kod imunokompromitovanih bolesnika ispoljavanje HSV može biti atipično i može se pomešati sa mukozitisom i aftoznim stomatitisom.

U najvećem broju slučajeva, HSV infekcija je rezultat reaktivacije virusa. Elad i sar.[36] su zabeležili prevalenciju HSV infekcije kod neutropeničnih bolesnika tokom tretmana hematoloških maligniteta u oko 50% slučajeva. Kod bolesnika koji su na zračnoj terapiji glave i vrata HSV je zastupljen 0% . Kod bolesnika koji su kombinovali radioterapiju i hemoterapiju zastupljenost je blizu 40%. Ovi podaci pokazuju da je imunosupresija zbog hemoterapije glavni faktor HSV infekcije. Neutropenični bolesnici sa hematološkim malignitetima izloženi su najvećem riziku.

Vlasasta leukoplakija je, česta manifestacija Epstein–Barr virusa koja se viđa kod HIV pozitivnih bolesnika. Primarno se nalazi na bočnim stranama jezika, mada i druge površine jezika mogu biti zahvaćene: dorzalna i ventralna povšina jezika, bukalna mukoza ili gingiva. Može se pomešati sa hroničnom hiperplastičnom kandidijazom. Javlja se kod bolesnika obolelih od raka, zbog imunokompromitovanog domaćina. Zabeležena je kod bolesnika sa akutnom mijeloidnom leukemijom, akutnom limfocitnom leukemijom i muliplim mijelomom, koji su podvrgnuti hemoterapiji[37-39], kao i kod bolesnika sa stromalnim gastrointestinalnim tumorom[40], koji su na pronizonu.

Bakterijske infekcije

Normalnu oralnu floru čine mnoge bakterije, koje mogu postati patogene kod imune supresije. Rautemaa i sar.[41] tvrde da *Viridans* streptococci, *Prevotellae, Fusobacterium, Actinobacillus actinomycetemcomitans i Actinomyces*vrste mogu biti uzrok oralne mukozne infekcije. Takve infekcije su obično lokalizovane i mogu biti lečene kombinacijom penicilina i metronidazola.

Viral infections

Oral viral infection including *herpes simplex virus (HSV), varicella zoster virus* (VZV), Epstein–Barr virus (EBV) and cytomegalovirus (CMV) are the most frequent complications in patients with cancer. Severe infections could lead to dehydratation and malnutrition and life-treating complication including encephalitis and disseminated infection. In immunocompromised patients, presentation of HSV could be atypical and could be mixed with mucositis and aphthous stomatitis.

In most cases, HSV infection is a result of virus reactivation. Elad et al.36 recorded prevalence of HSV infection in nearly 50% of neutropenic patients during cancer hematologic treatment. In patients under radiotherapy for head and neck prevalence of HSV was 0%. In patients under radiotherapy and chemotherapy prevalence was nearly 40%. These data showed that immunossuppresion caused by chemotherapy was the main factor of HSV infection. Neutropenic patients with hematologic malignancies were classified in the highest risk category.

Hairy leucoplakia, frequent manifestation of Epstein–Barr virus, is seen in HIV positive patients. Primarily, it is found on the sides of the tongue, although other surfaces of the tongue can be affected, like dorsal and ventral surface of the tongue, as well as buccal mucosa and gingiva. It can be substituted with chronic hyperplastic candidiasis. It is found in cancer patients because of the immunocompromised host. It has been reported in the patients undergoing chemotherapy with acute myeloid leukemia, acute lymphocyte leukemia and multiple myeloma[37-39], as well as in patients with a stromal gastrointestinal tumor receiving prednisone[40].

Bacterial infections

Normal oral flora contains different types of bacteria, which can become pathogenic under immunosuppression. Rautemaa et al.[41] claim that *Viridans Strep, Prevotellae, Fusobacterium, Actinobacillus actinomycetemcomitans and Actinomyces* species can be cause of oral mucosal infections. Usually, such infections can be localized and treated only with combination of penicillin and methronidazol.

Karijes zuba

Zabeležena je prevalencija od približno 6% inficiranih zuba / apcesa tokom hemoterapije[42]. Bolesnici koji su bili na zračnoj terapiji zbog maligniteta glave i vrata imali su veći procenat pokvarenih / ekstrahiranih/plombiranih zuba nego bolesnici koji su bili na antineoplastičnoj terapiji. Rautemaa i sar.[41] predložili su upotrebu proizvoda koji sadrže fluorimid i vodice za ispiranje koje sadrži hlorheksidin.

Zaključak

Uprkos značajnim poboljšanjima u tretmanu bolesnika obolelih od raka, oralne komplikacije su česte i dovode do nelagodnosti, pogoršanja kvaliteta života i povremeno do teških malnutricija i infekcija, koje su problemi opasni po život ovih bolesnika. Mada, postoje uspešne terapeutske metode koje mogu da ublaže ove tegobe, potrebna su dalja istraživanja koja će uticati na njihovo poboljšanje i koja će imati za cilj smanjenje neželjenih efekata radio-terapije i hemoterapije bolesnika obolelih od raka. Onkološki tim bi trebalo da uključi doktora stomatologije radi prevencije i tretmana oralnih komplikacija pre, nakon i posle zračne terapije i hemoterapije.

Koflikt interesa

Autori nemaju nikakvu finansijsku korist ili sukob interesa.

Tooth decay

The prevalence is reported to be approximately 6% of the tooth infection/abscess during chemotherapy[42]. Patients undergoing radiotherapy for head and neck malignancies have a larger percentage of teeth decay/extracted/seal teeth than patients undergoing antineoplastic therapy. Rautemaa et al.[41] suggest using of fluoride products and chlorhexidine mouthwash.

Conclusion

Despite significant improvements in treatment of cancer patients, oral complications are frequent and lead to discomfort,decrease in the quality of life and sometimes severe malnutrition and infections which are life-treating. Although successful therapeutic methods can reduce these problems, further research is necessary forimprovement of the quality of life and reduction of side effects of radiotherapy and chemotherapy in cancer patients. The dentist should be an active member of oncology team for prevention and treatment of oral complications, before, during and after radiotherapy and chemotherapy.

Conflict of interest

The authors have no any financial benefit or conflict of interests.

LITERATURA /REFERENCES

1. Lalla RV, Bowen J, Barasch A, Elting L, Epstein J, Keefe DM, et al. MASCC/ISOO clinical practice guidelines for the management of mucositis secondary to cancer therapy. Cancer 2014; 120:1453-1461.
2. Marinković I. Grupisanje zemalja prema vodećim uzrocima smrti u svetu početkom 21. veka. Stanovništvo 2010;48(1):75-101.
3. Topić B, Cekić-Arambašin A. Oral mucositis. Acta Med Acad 2006;35:40-49.
4. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo, et al. Cancer incidence and mortality worldwide: Sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer, 2015;136(5):E359-E386.
5. Hashim D, Genden E, Posner M, Hashibe M, Boffetta, P. Head and neck cancer prevention: from primary prevention to impact of clinicians on reducing burden. Ann Oncol 2019;30(5):744-756.
6. Dautović S. Tumori. In: Malić M, editor. Oralna medicina. Sarajevo: Stomatološki fakultet Univerziteta u Sarajevu; 2001:371-404.
7. Levi LE, Lalla RV. Dental treatment planning for the patient with oral cancer. Dent Clin 2018;62(1):121-130.
8. Orlov S, Mirković B, Kojović D, Kesić Lj, Petrović D, Pešić Z. Oralna medicina. Europrint: Niš; 2007:92-93.
9. Sroussi HY, Epstein, JB, Bensadoun RJ, Saunders DP, Lalla RV, Migliorati CA, et al. Common oral complications of head and neck cancer radiation therapy: mucositis, infections, saliva change, fibrosis, sensory dysfunctions, dental caries, periodontal disease, and osteoradionecrosis. Cancer Med 2017;6(12):2918-2931.
10. Oronsky B, Goyal S, Kim MM, Cabrales P, Lybeck M, Caroen S, et al. A review of clinical radioprotection and chemoprotection for oral mucositis. Transl Oncol 2018;11(3):771-778.
11. Sonis ST. Oral mucositis in head and neck cancer: risk, biology, and management. Am Soc Clin Oncol Educ Book 2013;33:e236-e240.
12. Blijlevens, N, Schwenkglenks M, Bacon, P, D'Addio A, Einsele H, Maertens J, et al. Prospective oral mucositis audit: Oral mucositis in patients receiving high-dose melphalan or BEAM conditioning chemotherapy–European Blood and Marrow Transplantation Mucositis Advisory Group. J Clin Oncol 2008;26:1519–1525.
13. Basile D, Di Nardo P, Corvaja C, Garattini SK, Pelizzari G, Lisanti C, et al. Mucosal Injury during Anti-Cancer Treatment: From Pathobiology to Bedside. Cancers 2019;11(6):857.
14. Meraw SJ, Reeve CM. Dental considerations and treatment of the oncology patients receiving radiation therapy. J Am Dent Assoc. 1998;129(2):201-5.
15. Ray-Chaudhuri A, Shah K, Porter RJ. The oral management of patients who have received radiotherapy to the head and neck region. Br Dent J 2013;214(8):387.
16. Vissink A, Burlage FR, Spijkevert FK, Jansma J, Coppes PR. Prevention and treatment of the consequences of head and neck radiotherapy. Crit Rev Oral Biol Med 2003;14(3):213-25.
17. ESC Guidelines. Guidelines on the prevention, diagnosis, and treatment of infective endocarditis Eur Heart J 2009;30:2369–2413.
18. Silverman S Jr. Oral cancer. 3rd ed. Atlanta: American Cancer Society; 1990.
19. Sonis ST, Fazio RC, Fang L. Principles and practice of oral medicine. 2nd ed. Philadelphia: Saunders;1995:46-54.
20. Villa A, Connell CL, Abati S. Diagnosis and management of xerostomia and hyposalivation. Ther Clin Risk Manag 2015;11:45.
21. Dhanda, J, Pasquier D, Newman L, Shaw R. Current concepts in osteoradionecrosis after head and neck radiotherapy. Clin oncol 2016;8(7):459-466.
22. Rice N, Polyzois I, Ekanayake K, Omer O, Stassen LF. The management of osteoradionecrosis of the jaws–a review. The surg 2015;13(2):101-109.
23. Mosel D, Bauer R, Lynch D, Hwang S. Oral complications in the treatment of cancer patients. Oral Dis 2011;17:550–559.
24. Brailo V. Oralne komplikacije zračenja glave i vrata. Hrvat Stomatol Vjesn 2006; 13(2): 12-5.
25. Konjhodžić-Prcić A, Cekić-Arambašin A, Malić M. Incidence of radiation induced mucositis in Bosnian population. Oral Dis 2006;12(1):13-30.
26. Scully C, Epstein J, Sonis S. Oral mucositis: a challenging complication of radiotherapy, chemotherapy and radiochemotherapy. Part 2: Diagnosis and management of mucositis. Head Neck. 2004; 26(1): 77-84.
27. Nutting CM, Morden JP, Harrington KJ, Urbano TG, Bhide SA, Clark C, et al. Parotid-sparing intensity modulated versus conventional radiotherapy in head and neck cancer (PARSPORT): a phase 3 multicentre randomised controlled trial.

Lancet Oncol 2011;12(2):127-136.

28. Emami B, Lyman J, Brown A et el. Tolerance of normal tissue to therapeutic radiation. lnt J Radiat Oncol Biol Phys 1991; 21: 109 - 122.
29. Hazuka MB, Martel MK, Marsh L, Licther AS, Wolf GT. Preservation of parotid function after external beam irradiation in head and neck cancer patients: a feasibility study using 3dimensional (3-D) treatment planning. lnt J Radiation Oncology Biol Phys 1993; 27: 731-737.
30. Cowart B (2011). Taste dysfunction: a practical guide for oral medicine. Oral Dis 2011;17:2–6.
31. Hovan AJ, Williams PM, Stevenson-Moore P et al (2010). A systematic review of dysgeusia induced by cancer therapies. Support Care Cancer 18: 1081–1087.
32. Ohrn KE, Wahlin YB, Sjoden PO (2001). Oral status during radiotherapy and chemotherapy: a descriptive study of patient experiences and the occurrence of oral complications. Support Care Cancer 9: 247–257.
33. Halyard MY. Taste and smell alterations in cancer patients – real problems with few solutions. J Support Oncol 2009;7: 68–69.
34. Fink M. Vitamin D deficiency is a cofactor of chemotherapy-induced mucocutaneous toxicity and dysgeusia. J Clin Oncol 2011;29:e81–e82.
35. Lalla RV, Latortue MC, Hong CH et al. A systematic review of oral fungal infections in patients receiving cancer therapy. Support Care Cancer 2010;18:985–992.
36. Elad S, Zadik Y, Hewson I, Hovan A, Correa MEP, Logan R, et al. A systematic review of viral infections associated with oral involvement in cancer patients: a spotlight on Herpesviridea. Support Care Cancer 2010;18:993–1006.

37. Syrjanen S, Laine P, Niemela M, Happonen RP. Oral hairy leukoplakia is not a specific sign of HIV-infection but related to immunosuppression in general. J Oral Pathol Med 1989;18: 28–31.
38. Blomgren J, Back H (1996). Oral hairy leukoplakia in a patient with multiple myeloma. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 1996;82:408–410.
39. Nicolatou O, Nikolatos G, Fisfis M et al. Oral hairy leukoplakia in a patient with acute lymphocytic leukemia. Oral Dis 1999;5:76–79.
40. Piperi E, Omlie J, Koutlas IG, Pambuccian S. Oral hairy leukoplakia in HIV-negative patients: report of 10 cases. Int J Surg Pathol 2010;18:177–183.
41. Rautemaa R, Lauhio A, Cullinan MP, Seymour GJ. Oral infections and systemic disease – an emerging problem in medicine. Clin Microbiol Infect 2007;13:1041–1047.
42. Hong CH, Napenas JJ, Hodgson BD, Stokman MA, Mathers-Stauffer V, Elting LS, et al. A systematic review of dental disease in patients undergoing cancer therapy. Support Care Cancer 2010;18:1007–1021.

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SISTEMSKE NEŽELJENE REAKCIJE NA LOKALNE ANESTETIKE

SYSTEMIC ADVERSE REACTIONS TO LOCAL ANESTHETICS

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Sažetak

Uvod:*Lokalni anestetici su najčešće korišćeni lekovi u svakodnevnoj stomatološkoj i medicinskoj, a sve češće i u kozmetičkoj praksi. Danas postoji veliki broj lokalnih anestetika koji su prema strukturi podeljeni na dve grupe: estarske i amidne lokalne anestetike. Iako je njihova primena u svakodnevnom radu uglavnom bezbedna, nije isključena mogućnost pojave negativnih reakcija koje mogu biti psihogene, toksične, imunološke i specifične neželjene reakcije.*
Cilj: *ovog rada je da ukaže na mehanizam nastanka i simptomatologiju mogućih negativnih reakcija na lokalne anestetike.*
Zaključak:*Ukoliko dođe do pojave sistemske neželjene reakcije na lokalni anestetik, najveći problem, u kliničkoj praksi, predstavlja prepoznavanje prirode negativne reakcije i pružanje adekvatne terapije u vezi sa nastalom reakcijom.Brzina i sigurnost u prepoznavanju neželjene reakcije na lokalni anestetik, nekada mogu biti od životnog značaja za bolesnika.*

Ključne reči:*lokalni anestetici, toksičnost, alergija*

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Abstract

Introduction: *Local anesthetics are the most commonly used drugs in everyday dental and medical and increasingly in cosmetic practice. Today there are a number of local anesthetics that are divided into two groups based on their structure: ester and amide local anesthetics. Although their use in everyday work is generally safe, there is a possibility of adverse reactions that may be psychogenic, toxic, immunologic and specific adverse reactions.*
The aim *of this work is to highlight the mechanism of occurrence and symptoms of possible adverse reactions to local anesthetics.*
Conclusion: *If you experience systemic adverse reactions to the local anesthetic, the biggest problem in clinical practice, is a recognition of the nature of adverse reactions and providing appropriate therapy in conjunction with the resulting reaction. Speed and security to identify adverse reactions to local anesthetic can be of vital importance for the patient.*

Key words:*local anesthetics, toxicity, allergy*

Uvod

Lokalni anestetici su supstance koje, na mestu primene, privremeno i reverzibilno sprečavaju sprovođenje impulsa kroz nervno vlakno. Predstavljaju najčešće korišćeni lek u svakodnevnoj stomatološkoj i medicinskoj praksi, a danas se sve češće koriste i u kozmetičke svrhe. Prema načinu primene lokalna anestezija može biti površinska i infiltraciona. Procenjuje se da oko šest miliona ljudi svakodnevno primi neki lokalni anestetik[1].

Početak zvanične primene lokalnih anestetika vezuje se za 1884. godinu, kada je rastvor kokaina upotrebljen kao lokalni anestetik za izvođenje oftalmološke hirurške intervencije, a ubrzo iza toga započeta je upotreba istog lokalnog anestetika i u stomatologiji[2,3]. Danas postoji veliki broj lokalnih anestetika, koji su prema strukturi, odnosno vrsti veze kojom je lipofilni aromatični prsten spojen sa alifatičnim lancem i supstituisanom hidrofilnom amino grupom na drugom kraju molekula, podeljeni na dve grupe: estarske i amidne lokalne anestetike. Estarski lokalni anestetici metabolišu se preko krvne plazme, pomoću pseudoholinesatraze do paraaminobenzoeve kiseline, dok se amidni lokalni anestetici metabolišu u jetri do neaktivnih supstanci.

Primena lokalnih anestetika u svakodnevnoj praksi uglavnom je bezbedna i do negativnih rekacija retko dolazi, naročito kada se oni aplikuju pravilno i u propisanim dozama. Međutim, pojava negativnih reakcija ipak je moguća.U neželjene reakcije na lokalne anestetike spadaju sistemske toksične reakcije, lokalne reakcije, specifične neželjene reakcije na određene lokalne anestetike, alergija i zavisnost[4].

Autonomne- psihogene reakcije

Ovaj tip reakcija predstavlja najčešće negativne reakcije na lokalne anestetike, koje nisu vezane za dejstvo samog anestetika. Kod određenog broja bolesnika intolerantnih na strah, bol ili neprijatne mirise u ordinaciji, može doći do ekscitacije vegetativnog nervnog sistema, simpatikusa i parasimpatikusa sa vazovagalnom manifestacijom. Nadražaj je zapravo osećaj straha koji kao nervni impuls iz kore velikog mozga, preko limbičkog sistema (*corpus amygdaloideum i area reticularis superficialis ventrolateralis*) silazi na simpatičke ganglije,odnosno jezgara vagusa,izazivajući njihovu aktivaciju.

Introduction

Local anesthetics are substances that temporarily and reversibly inhibit conduction through the nerve fiber. They represent the most commonly used drug in everyday dental and medical practice, and are now increasingly used for cosmetic purposes. According to the method of applying local anesthesia can be superficial and infiltration. An estimated six million people daily receives some local anesthetic[1].

Official application of local anesthetic binds to 1884, when the solution cocaine was used as a local anesthetic to perform ophthalmic surgery, and soon after that the same local anesthetic was used in stomatology[2,3]. Today, there are a large number of local anesthetics which are divided into two groups: ester and amide local anesthetics, based on the structure or the type of connection by which the lipophilic aromatic ring is fused with an aliphatic chain and the hydrophilic substituted amino group at the other end of the molecule. Ester local anesthetics are metabolized by the blood plasma by using pseudo cholinesterase to para amino benzoic acid, whereas amide local anesthetics are metabolized in the liver to inactive substances.

Application of local anesthetics in everyday practice is generally safe and negative reactions occur rarely, especially when they are applied properly and within the prescribed doses. However, the occurrence of adverse reactions is still possible. Adverse reactions to local anesthetics include systemic toxic reactions, local reactions, specific adverse reactions to certain local anesthetics, allergy and addiction[4].

Autonomous - psychogenic reactions

This type of reaction is the most frequent adverse reaction to local anesthetics, the effect is not related to the anesthetics. A number of patients who are intolerant to fear, pain or unpleasant odors in the office, there may be excitae of vegetative nervous system, sympathetic and parasympathetic nervous system with vasovagal event. Irritation is actually a sense of fear that as a nerve impulse from the cortex of the brain, via the limbic system (corpus amygdaloideum and area reticularis superficialis ventrolateralis) is moving in sympathetic ganglia or nuclei of the vagus, causing their activation. The stimulation of the vagal centers is reflected in the clinical

Stimulacija vagusnih centara ogleda se u kliničkoj slici: osoba je bleda, znojna i obično bradikardična, ali ako je jače nadražen simpatikus javlja se tahikardija. Pad krvnog pritiska nastaje zbog vagusne vazodilatacije splanhničkog dela krvotoka. Zbog hipoksije kore velikog mozga, dolazi do kratkotrajnog gubitka svesti. Gubitku svesti mogu prethoditi zamagljenje vida, osećaj mučnine i dispneja. Psihogena reakcija praćena je, uznemiranošću, znojenjem, vrtoglavicom, dok vazovagalna reakcija u stvari predstavlja progresiju psihološke napetosti, praćenu padom krvnog pritiska, bradikardijom i bledilom, odsustvom reagovanja na spoljne nadražaje sa reverzibilnim gubitkom svesti[5].

Toksične reakcije na lokalne anetetike

Toksične reakcije na lokalni anestetik mogu biti posledica reakcije na sam lokalni anestetik ili na vazokonstriktor, koji se uobičajeno nalazi u lokalnim anestetičkim rastvorima.

Lokalni anestetici se deponuju u blizinu ciljanih nervnih struktura,ali se značajne količine ubrizganog anestetika uklanjaju sa mesta ubrizgavanja putem sistemske cirkulacije i dospevaju do udaljenih organa. Manje od 3% ubrizganog anestetika prodire u ciljani nerv, dok više od 90% dospeva u sistemsku cirkulaciju u roku od 30 minuta[6]. Distribucija lokalnog anestetika u organe zavisi od njihove prokrvljenosti, tako da su gusto vaskularizovani organi, kao što su mozak, srce, pluća, jetra i bubrezi, najviše izloženi delovanju nemetabolisanog lokalnog anestetika. Dotok venske krvi bogate anestetikom u pluća, donekle ublažava uticaj anestetika na ostale organe, ali je sposobnost pluća da brzo ekstrahuju lokalni anestetik ograničena. Najveći deo apsorbovanog anestetika metaboliše se pri prolasku kroz jetru i zavisi od količnika hepatičkog izlučivanja i protoka krvi kroz jetru. Sa druge strane količnik hepatičkog izlučivanja zavisi od odnosa slobodnog anestetika ianestetika vezanog za proteine plazme. Lokalni anestetici vezuju se za plazma proteine, smanjuju slobodnu frakciju LA, što ima klinički značaj, jer su jedini slobodni ili nevezani deo LA. Aktivne koncentracije α_1-acid glikoproteina (AAG), za koji se vezuje LA, povećavaju se kod onkoloških bolesnika, infarkta miokarda, traume, hirurških intervencija, uremije, što utiče na količinu anestetika koji će se metabolisati u jetri, kao i na njegovu toksičnost[7]. Sistemska oboljenja sa smanjenom funkcijom jetre i ekskretornom funkcijom bubrega, povećavaju mogućnost

presentation: person is pale, sweaty and usually bradycardic, but if sympathetic is highly irritated tachycardia occurs. The fall in blood pressure is due to vasodilation vagal splanchnic work bloodstream. Because of hypoxia cortex, there is a brief loss of consciousness. Loss of consciousness may be preceded by blurred vision, nausea and dyspnea. Psychogenic reaction is followed by disturbance, sweating, dizziness, while vasovagal reaction is in fact a progression of psychological tension accompanied by a drop in blood pressure, bradycardia and pallor, lack of response to external stimuli with reversible loss of consciousness5.vagus causing their activation. it is pale, sweaty and usually bradycardic, but if severe

Toxic reactions to local anesthetics

Toxic reactions to a local anesthetics can be caused by a reaction to the local anesthetic itself or vasoconstrictor which is commonly found in local anesthetic solutions.

Local anesthetics are deposited near the target neural structures, but significant amounts of injected anesthetic are removed from the injection site through the circulatory system and reach the distant organs. Less than 3% of the injected anesthetic penetrates the target nerve, while more than 90% reaches the systemic circulation within 30 minutes6. Distribution of local anesthetic to the organs depends on their blood supply, so that densely vascularized organs such as brain, heart, lungs, liver and kidneys, are the most exposed to the influence of unmetabolized local anesthetic. The flow of venous blood rich in anesthetic, to the lungs, somewhat mitigates the impact of anesthetic to other organs, but ability of the lungs to extract a local anesthetic quickly is limited. Most of the absorbed anesthetic is metabolized through passage in the liver and depends on the ratio of hepatic extraction and blood flow through the liver. On the other hand hepatic extraction ratio depends on the ratio of free and anesthetic bound to plasma proteins. Local anesthetics bind to plasma proteins, reduce the free fraction of the LA, which has clinical significance because it is the only free or unbound part of LA. The active concentrations of α1-acid glycoprotein (AAG) to which LA is bound, are elevated in patients with cancer, myocardial infarction, trauma, surgical intervention, uremia, which affects the quantity of anesthetic to be metabolized in the liver and its toxicity its toxicity[7].

nastanka sistemskih toksičnih reakcija. Kod osoba sahepatičkom disfunkcijom, koncentracija anestetika dvostruko se povećava u odnosu na zdrave osobe[8]. Lidokain, koji se umereno vezuje za proteine, ima visok količnik hepatičke ekstrakcije 70%−75%, dok dugodelujući LA−bupivakain i ropivakain, koji se u visokom procentu vezuju za proteine imaju <50% hepatičke ekstrakcije[9]. (Tabela 1. Farmakološki parametri lokalnog anestetika)[10]. Kod starijih bolesnika funkcija jetre je značajno smanjena i u 65 godini života ona iznosi svega oko 60% vrednosti u odnosu na funkciju jetre u mladosti[11]. U toku trudnoće dolazi do niza fizioloških promena koje mogu povećati rizik za ispoljavanje toksičnog efekta lokalnog anestetika. Vezivanje LA za proteine plazme značajno je smanjeno[12], pojačana cirkulacija dovodi do brže apsorpcije anestetika, a progesteron može povećati osetljivost aksona na blokadu[13].

Toksični potencijal lokalnog anestetika direktno zavisi od njegove liposolubilnosti. Sa porastom liposolubilnosti lokalnog anestetika sužava se bezbedna granica između poželjnog kliničkog dejstva i neželjenih reakcija. Stepen depresije perifernog nervnog sistema i centralnog nervnog sistema (CNS) u direktnoj su vezi sa koncentracijom, lokalnog anestetika u krvi. Lidokain se u manjim serumskim koncentracijama koristi u kliničkoj praksi za supresiju srčanih aritmija, ali u većim koncentracijama indukuje napade. Pri manjim dozama svi lokalni anestetici deluju antikonvulzivno i sedativno[14].

Visoka koncentracija lokalnog anestetika u serumu, izaziva kratkotrajnu stimulaciju, pa depresiju centralnog nervnog sistema. Stimulacija se manifestuje razdražljivošću, nervozom i preteranom govorljivošću bolesnika. Zavisno od nadraženosti nervnih centara javljaju se tremor, glavobolja, mučnina, produbljeno disanje, kao i najteža komplikacija tonično klonični grčevi. U fazi depresije bolesnikmože osećati vrtoglavicu, bol u prekordijumu, dezorijentisan je i gubi sposobnost govora, a zatim i svest. Puls je bradikardičan, mada se može javiti i kompenzatorna tahikardija,dok na kraju pada do nemerljivih vrednosti, što vodi akutnom zastoju srca. Disanje je u početku usporeno i plitko, može i potpuno prestati. Različiti lokalni anestetici pokazuju različiti stepen kardiotoksičnosti. Kratkodelujući lokalni anestetici, kojima pripada lidokain, retko dovode do negativnih reakcija i njihova kardiotoksičnost je manja od kardiotoksičnosti dugodelujućih lokalnih anestetika[15].

Systemic diseases with reduced liver function and excretory function of kidneys, increase the possibility of systemic toxic reactions. In patients with hepatic dysfunction, the concentration of the anesthetic is increased twice in comparison to a healthy person[8]. Lidocaine, which is moderately bound to proteins, has a high hepatic extraction ratio of 70-75%, while a long acting LA- bupivacaine and ropivacaine, which are bound to proteins in high percentage, have <50% of hepatic extraction[9]. (Table 1. The pharmacological parameters of the local anesthetic)[10]. In elderly patients liver function is significantly reduced and in the 65-th year of life it is only about 60% of the value in relation to the function of the liver in youth[11]. During pregnancy, there are a number of physiological changes which can increase the risk for manifestation of the toxic effect of the local anesthetic. LA binding to plasma proteins is significantly decreased[12] increased blood circulation leads to faster absorption of the anesthetic, and progesterone can increase the sensitivity of the axon to the blockade[13].

The toxic potential of local anesthetic directly depends on its liposolubility. With increasing liposolubility of the local anesthetic the safe border between the desirable clinical effects and adverse reactions is narrowed. The degree of depression of the peripheral nervous system and the central nervous system (CNS) is directly related to the concentration of the local anesthetic in the blood. Lidocaine in smaller serum concentrations is used in clinical practice to suppress cardiac arrhythmias, but in higher concentrations induce attacks. At low doses, all local anesthetics act anticonvulsant and sedative[14].

The high concentration of local anesthetic in serum induces a short-term stimulation and central nervous system depression. The stimulation is manifested by irritability, nervousness and excessive speech of the patient. Depending on the excitability of nerve centers, tremor, headache, nausea, deepened breathing and one of the most severe complications - tonic clonical spasms occur. At the stage of depression, the patient may feel dizziness, precordial pain, disorientation and loss of the ability to speak and then consciousness. Pulse is bradycardic, compensatory tachycardia can occur, eventually dropping to undetectable levels and leading to cardiac arrest. Breathing is initially slow and shallow, and can completely stop. Various local anesthetics exhibit varying degrees of cardiotoxicity.

Tabela1. Farmakološki parametri lokalnog anestetika
Table 1. Pharmacological parameters of local anesthetic

Lokalni anestetik Local anesthetic	Klirens (L/min) Clearance (L / min)	Polu-život (min) Half life (min)	Količnik hepatičke ekstrakcije Hepatic Extraction Ratio
Lidokain	0.95	96	0.72
Etidokain	1.11	162	0.74
Mepivakain	0.78	114	0.51
Bupivakain	0.58	162	0.40
Ropivakain	0.73	111	0.40
Levobupivakain	0.47	108	0.67

Od kliničkog je značaja da su doze koje izazivaju toksičnost CNS-a vrlo blizu dozama koje izazivaju ireverzibilni kardio-vaskularni kolaps[16]. Simptomi toksičnosti CNS-a ne moraju se razvijati postepeno, već može odmah doći do kome i respiratornog zastoja, što se najčešće javlja nakon intraarterijske aplikacije anestetika, ali ovo je retka pojava u praksi. Lokalni anestetici ne dovode do trajnog oštećenja CNS-a, pa se funkcija ovog sistema vraća sa padom koncentracije lokalnog anestetika u krvi. Do trajnog oštećenja može doći samo usled dugotrajne hipoksije nastale usled gubitka svesti, respiratornog zastoja i konvulzija. Kod pojedinih tehnika lokalne anestezije u usnoj duplji, kao što su intraligamentarna i intraosealna tehnika, brzina prodora anestetika u cirkulaciju jednaka je kao i kod intravazalnog ubrizgavanja[11].Kako bi preventirali pojavu toksičnih reakcija na lokalni anestetik, treba imati u vidu maksimalne preporučene doze lokalnog anestetika(Tabela2)[10].

Short acting local anesthetics, including lidocaine, rarely lead to adverse reactions and their cardiac toxicity is lower than in long-acting local anesthetics[15]. Of clinical importance is that the doses inducing CNS toxicity are very close to doses that cause irreversible cardiovascular collapse[16]. Toxicity symptoms of the CNS do not have to develop gradually, but may immediately cause coma, and respiratory arrest, which often occurs after the intra-arterial application of anesthetic, but is rare in practice. Local anesthetics do not cause permanent damage to the CNS, so the function of this system returns with a decrease in the concentration of local anesthetic in the blood. Permanent damage may occur only due to long-term hypoxia caused by loss of consciousness, respiratory paralysis and convulsions. In some techniques of local anesthesia in the oral cavity, such as intra-ligament and intraosseous technique, the speed of penetration of the anesthetic in the circulation is the same as in intravascular injection[11]. In order to prevent the occurrence of toxic reactions in the local anesthetic, it is necessary to bear in mind the maximum recommended dose of a local anesthetic (Table 2)[10].

Tabela 2.Maksimalne preporučene doze lokalnih anestetika[10]
Table 2. Maximum recommended doses of topical anesthetics[10]

Lokalni anestetik Local anesthetic	Maksimalna doza sa vazokonstriktorom Maximum dose with a vasoconstrictor	Maksimalan broj ampula od 1.8ml sa vazokonstriktorom Maximum number of 1.8ml ampoules with vasoconstrictor maximum dose without vasoconstrictor	Maksimalna doza bez vazokonstriktora Maximum dose without vasoconstrictor
Lidokain	7 mg/kg (do500mg)	13	4.5 mg/kg (do300mg)
Artikain	7 mg/kg (do500mg)	7	/
Mepivakain	6.6 mg/kg (do400mg)	11	4 mg/kg (do300mg)
Bupivakain	2 mg/kg (do200mg)	10	1.5 mg/kg (do150mg)
Prilokain	8 mg/kg (do500mg)	8	7 mg/kg (do400mg)
Etidokain	5.5 mg/kg (do400mg)	/	4 mg/kg (do300mg)
Ropivakain	/	/	2.5 mg/kg (do150mg)

Toksične reakcije na vazokonstriktor

Većina lokalnih anestetika sadrži vazokonstriktor adrenergičkog tipa koji smanjuje resorpciju lokalnog anestetika, smanjuje toksičnost i produžava njegovo dejstvo. Neželjeni toksični efekti vazokonstriktora javljaju se češće nego toksični efekti samih lokalnih anestetika. Treba napomenuti da povišene vrednosti endogenih kateholamina koji se luče direktno u krvotok u slučaju stresa, koji je prisutan u većini stomatoloških, a pogotovo oralnohirurških intervencija, uz unošenje dodatnih količina vazokonstriktora, mogu dovesti do toksičnih koncentracija u krvi. Toksične reakcije na vazokonstriktor ne predstavljaju klasične toksične reakcije već neželjene efekte povećane ekscitabilnosti kardiovaskularnog sistema[8]. Adrenalin je najčešće korišćeni vazokonstriktor u lokalnim anestetičkim rastvorima i deluje kao agonist alfa, beta-1 i beta-2 receptora. Submukozno tkivo sadrži manje krvne sudove u kojima se nalaze samo alfa receptori. Veće sistemske arterije koje utiču na krvni pritisak sadrže daleko više beta-2 receptora, i sa apsorpcijom adrenalina i manje doze izazivaju dilataciju ovih krvnih sudova[17].Najveći uticaj adrenalina najčešće se uočava 5–10 minuta posle injekcije lokalnog anestetičkog rastvora koji sadrži adrenalin, i on naglo opada usled brze razgradnje putem katehol-O-metiltransferaze. Eliminacioni poluživot većine kateholamina (u koje spada i adrenalin) svega je minut do tri minuta, i njihov hemodinamski uticaj kompletno opada 10–15 minuta posle ubrizgavanja[18]. Toksično dejstvo vazokonstriktora klinički se manifestuje stimulacijom CNS-a: tahikardijom, porastom krvnog pritiska, palpitacijama, fibrilacijom, glavoboljom i vrtoglavicom. skraćenim dahom, strahom i prisustvom panike, znojenjem, bledilomibolom u sredogruđu[5,8].

Specifične neželjene reakcije na određene lokalne anestetike

Kod malog broja bolesnika može doći do razvoja methemoglobinemije, vrlo retkog, ali potencijalno fatalnog oboljenja[19-21]. Methemoglobinemija je retka neženljena reakcija na pojedine lokalne anestetike u kojoj dolazi do razvoja cijanozi sličnog stanja uz odsustvo kardioloških ili respiratornih nepravilnosti.

Toxic reactions to vasoconstrictor

Most local anesthetics contain adrenergic type of vasoconstrictor that reduces the absorption of local anesthetic, reduces toxicity and extends its effect. Undesired toxic effects of vasoconstrictor occur more frequently than toxic effects of local anesthetics themselves. It should be noted that the elevated levels of endogenous catecholamines which are secreted directly into the bloodstream in the event of stress that is present in most of the dental and oral surgery, especially with the introduction of additional quantities of the vasoconstrictor, may lead to toxic levels in blood. Toxic reaction to the vasoconstrictor is not a typical toxic reaction, but a side effect of increased excitability of cardiovascular system[8]. Adrenalin is the most commonly used vasoconstrictor in local anesthetic solutions and acts as agonists of alpha, beta-1 and beta-2 receptors. Submucosal tissue contains smaller blood vessels containing only alpha receptors. Higher systemic arteries which affect blood pressure include far more beta-2 receptors, and with an absorption of adrenaline lower doses cause dilation of these blood vessels[17]. The biggest effect of adrenaline is usually observed 5-10 minutes after the injection of local anesthetic solution containing adrenalin, and it declines rapidly due to rapid degradation by catechol-o-methyltransferase. Elimination half-life of most of catecholamines (which include adrenaline) is only 1-3 minutes, and their hemodynamic effect decreases completely after 10-15 minutes after injection[18]. Toxic effect of vasoconstrictors is clinically manifested in stimulation of the CNS: tachycardia, increase in blood pressure, palpitations, fibrillation, headaches and dizziness, shortness of breath, fear and panic, sweating, paleness, pain in chests[5,8].

Specific adverse reactions to certain local anesthetics

In small number of patients methemoglobinemia can be developed, very rare, but potentially fatal disease[19-21]. Methaemoglobinemia is a rare side effect to the particular local anesthetics which leads to production of cyanosis similar conditions and absence of cardiac or respiratory irregularities.

Dva lokalna anestetika, prilokain i artikain, koja, kada se ubrizgavaju u velikim dozama mogu dovesti do pojave methemoglobinemije, kao što to može učiniti i benzokain koji se koristi za površinsku anesteziju. Methemoglobinemija je uzrokovana metabolitima ovih anestetika-metabolit prilokaina o-toluidin oksidiše gvožđe u hemoglobinu (iz Fe2+ u Fe3+) i tako izmenjen hem ne vezuje kiseonik a neizmenjeni hemovi na molekulu hemoglobina ne otpuštaju vezani kiseonik. Ovakav oblik hemoglobina naziva se methemoglobin, a stanje kada je prisutan u koncentraciji većoj od 1% naziva se methemoglobinemija. Bolesnik postaje cijanotičan i simptomi se javljaju kada je methemoglobinprisutan u koncentraciji većoj od 15%[22]. Stanje životno ugrožava bolesnika kada nivo hemoglobina pređe 50%−60%. Simptomi methemoglobinemije obično se javljaju 3−4 časa posle primene većih doza prilokaina (600mg) ili artikaina. Simptomi variraju u zavisnosti od nivoa methemoglobina, ali se kod većine bolesnika javljaju letargičnost i poremećaj disanja, mukoza i nokti postaju cijanotični, a koža pepeljasta. Dijagnoza methemoglobinemije postavlja se na osnovu prisustva cijanoze koja ne reaguje na primenu čistog kiseonika, a karakteristična je arterijska krv braon boje. Definitivni tretman podrazumeva sporu intravensku primenu jednoprocentnog metilenaplavog (interesantno je da veće količine izazivaju methemoglobinemiju). Methemoglobinemija uobičajeno se ne javlja kod zdravih bolesnika ukoliko su primenjene doze lokalnih anestetika u granicama preporučenih doza. Kod bolesnikasa urođenom methemoglobinemijom primena artikaina i prilokaina predstavlja relativnu kontraindikaciju[17] i kod njih se preporučuje upotreba drugih lokalnih anestetika.

U specifične neželjene reakcije može se ubrojati i pojava trizmusa kod pojedinih bolesnika nakon primene etidokaina[23].

Alergijske reakcije na lokalne anestetike

Alergijske reakcije na lokalne anestetike vrlo su retke.

Estarski lokalni anestetici imaju veći alergijski potencijal od amidnih, zbog svog metabolita–paraaminobenzoeve kiseline, koja ima određeni antigeni potencijal. Danas se uglavnom primenjuju u vidu gelova i krema za površinsku anesteziju ili kao dodaci medikamentima za topikalnu primenu.

Two local anesthetics prilocaine and articaine, which when injected in high doses can cause methemoglobinemia, and benzocaine which is used for topical anesthesia. Methemoglobinemia is caused by the metabolites of these anesthetics - prilocaine metabolite o-toluidine oxidizes iron in hemoglobin (Fe2 + from Fe3 + in) and thus changed hem does not bind oxygen and unmodified hems on hemoglobin molecule do not release the bound oxygen. This form of hemoglobin is called methemoglobin, and condition when it is present in a concentration greater than 1% is referred to as methemoglobinemia. The patient becomes cyanotic and symptoms occur when methemoglobin at a ratio greater than 15% lifetime[22]. This condition endangers the patient when hemoglobin levels exceed 50-60%. Methaemoglobinemia symptoms usually appear 3-4 hours after having higher doses of prilocaine (600mg) or articaine. Symptoms vary depending on the level of methemoglobin, but in most patients lethargy and impaired breathing, mucosa occurs, nails become cyanotic, and skin ashens. Methaemoglobinemia diagnosis is made based on the presence of cyanosis, which does not respond to the use of pure oxygen, and arterial brown blood is characteristic. A definitive treatment involves a slow intravenous administration of 1% methylene-blue (it is interesting that larger amounts cause methemoglobinemia). Methaemoglobinemia does not normally occur in healthy subjects if administered doses of local anesthetics are within the recommended dose. In patients with congenital methemoglobinemia application of articaine and prilocaine represents the relative contraindication[17] and they are advised to use other local anesthetics.

Specific adverse reactions also include the occurrence of trismus for some patients after the administration of etidocaine[23].

Allergic reactions to local anesthetics

Allergic reactions to local anesthetics are very rare.

Ester local anesthetics have a larger allergic potential than amide local anesthetics, due to its metabolites-para-amino-benzoic acid that has a specific antigenic potential. It is generally applied in the form of gels and creams for topical anesthesia, or as an adjunct medicament for topical administration.

Kreme protiv hemoroida ili neke kreme za sunčanje sadrže benzokain. Smatra se da oko 5% bolesnika koji primenjuju ove preparate razvija neku od reakcija preosetljivosti na njih[24]. Kod topikalne primene estarskih lokalnih anestetika načešće se razvija IV tip reakcije preosetljivosti tj. kontaktni dermatit koji se manifestuje eritemom, svrabom, makulo-papuloznom ospom ili pojavom vezikula[25]. Ovaj tip odložene alergijske reakcije dešava se posredstvom T limfocita u periodu od 12h−72h od izloženosti alergenu, mada se prvi simptomi mogu pojaviti već 2 sata nakon od izloženosti. Kod primene amidnih lokalnih anestetika ovaj tip reakcije javlja se znatno ređe. Ako se radi o infiltracionoj anesteziji javijaju se eritem i edem mekog tkiva na mestu uboda.

Anafilaktička reakcija, tj. prvi tip alergijske reakcije razvija se posredstvom IgE, koji dovodi do degranulacije mastocita i bazofila sa oslobađanjem histamina i ostalih vazoaktivnih supstanci. Anafilaktička reakcija najopasnija je komplikacija primene lokalnih anestetika i javlja se u manje od 1% slučajeva[15]. Zbog relativno retke pojave, lekar može podsvesno zanemariti ovu mogućnost i usredsrediti se na lečenje druge nuspojave, što u nekim slučajevima može ugroziti život bolesnika. Postoje slučajevi sa smrtnim ishodom kao posledicom anafilakse posle primene lokalne anestezije[26]. Simptomatologija podseća na sinkopu, ali bez gubitka svesti – vrtoglavica, bledilo, vlažna koža i suve sluzokože, glavobolja, mučnina, povraćanje, opšta slabost, dispneja, slab puls. Pojava edema mekih tkiva, periorbitalno, usana i jezika može biti praćena edemom laringsa i unutrašnjih organa koji vodi fatalnom ishodu.

Alergija se najčešće javlja kao reakcija na neku od komponenti lokalnog anestetičkog rastvora: stabilizirajuće sredstvonatrijum-bisulfit ili metilparaben, antiseptik ili fungicide i lateks iz instrumenata za anesteziju. Metilparaben je metilestar parahidrobenzoeve kiseline. Estarski lokalni anestetici metabolišu se u plazmi, pomoću pseudoholinestaraze do paraaminobenzoeve kiseline, pa bolesnici koji su alergični na estarske lokalne anesteičke rastvore mogu imati ukrštenu reakciju na amidne lokalne anestetike koji sadrže metilparaben. Osim toga, paraaminobenzoeva kiselina je čest sastojak kozmetičkih preparata. Na natrijum metabisulfit, kao stabilizirajuće sredstvo, naročito su osetljive osobe sa astmom.

Hemorrhoidal creams or some sunscreens contain benzocaine. It is believed that about 5% of patients who use these preparations develop a reaction of hypersensitivity to it[24]. Topical application of ester local anesthetics most commonly develop type IV of hypersensitivity reactions, i.e. contact dermatitis, which is manifested by erythema, itching, macula or the appearance of vesicles[25]. This type of delayed allergic reactions occurs through T cells over a period of 12h-72h of exposure to the allergen, although the first symptoms may appear after only 2 hours of exposure. When using amide local anesthetic this type of reaction occurs less often. In the case of infiltration anesthesia, erythema and edema of the soft tissue at the injection site occur.

Anaphylactic reaction, the first type of allergic reaction is developed through IgE , which leads to degranulation of mast cells and basophils with a release of histamine and other vasoactive substances. The most dangerous complication of local anesthetics and occurs in less than 1% cases[15]. Because of the relatively rare phenomenon, the doctor may unconsciously ignore this feature and focus on the treatment of other side effects, which in some cases can endanger the patient's life. There are cases with fatal outcome as a result of anaphylaxis after administration of local anesthesia[26]. Symptomatology reminiscent of syncope but without loss of consciousness. Dizziness, paleness, clammy skin and dry mucous membranes, headache, nausea, vomiting, weakness, dyspnea, weak pulse. Periorbital edema of soft tissue, on lips and tongue can be accompanied by edema of the larynx and the viscera leading to a fatal outcome.

Allergies often occur as a reaction on one of the components of a local anesthetic solution: stabilizing appliance -Na-bisulfite, methyl paraben or, antiseptic or fungicide. Methyl paraben is methyl para-dihydrobenzo acid. Ester local anesthetics are metabolized by plasma, by means of pseudo holinestarase to para- amino- benzoic acid, and patients who are allergic to an ester local anesthetic solutions can have the cross-reaction to an amide local anesthetics containing methyl paraben. In addition, para-amino-benzoic acid is a common ingredient of cosmetic products.

To a sodium meta-bisulfite, as the stabilizing agent, are particularly vulnerable persons with asthma.

Povećan senzibilitet na metabisulfit svakako je i posledica njegove upotrebe u agronomiji, gde se koristi kao antioksidans naprskan na sveže voće i povrće, kako bi se očuvala njihova svežina i izgled. Bolesnici koji navode alergiju na takvu hranu mogu imati ukrštenu reakciju sa lokalnim anesteticima koji sadrže i vazokonstriktor[17]. Senzibilitet na bisulfite može biti prisutan kod atopičnih i astmatičnih bolesnika kod kojih se može razviti teži oblik reakcije (bronhospazam)[27,28].

Dostupni podaci ukazuju da se skoro na svaki amidni lokalni anestetik u praksi pojavljuje alergijska reakcija, sa određenom rastućom stopom[29-36]. U slučaju sumnje na alergiju na lokalne anestetičke rastvore, preporučuje se primena čistog lokalnog anestetika, bez prisustva stabilizatora koji je mogući antigen, ili upotreba drugog anestetika. Estarski lokalni anestetici imaju ukrštenu reakciju pa stoga alergija na jedan podrazumeva moguću alergiju na drugi anestetik ove grupe. Postoje različiti stavovi po pitanju zamene amidnog lokalnog anesteika koji je izazvao alergijsku reakciju. Nema sigurnih podataka u literaturi da li postoji ukrštena reakcija između anestetika amidne grupe. Ipak postoji verovatnoća da je mogući antigen metaksilen, koji je deo aromatičnog prstena skoro svih amidnih lokalnih anestetika[37]. Osobama senzibilnimna lidokain, kao pogodna zamena preporučivan je mepivakain, ali se pokazalao da i on daje ukrštenu reakciju sa lidokainom, verovatno zbog prisustva metaksilena u aromatičnom radikalu[38-42]. Artikain se čini kao sigurnija zamena kod osoba senzibilnih na lidokain, verovatno zato što u svom aromatičnom prstenu umesto metaksilena sadrži tiofen[37,43].

Difenhidramin je antihistaminik koji deluje kao antiholinergik, antitusik, antiemetik i sedativ, a poseduje i svojstva lokalnog anestetika[45]. Kod bolesnika sa dokazanom alergijom na lokalne anestetike, može se primeniti rastvor difenhidramin-hlorida sa sličnim dejstom kao jednoprocentni lidokain[46,47]. Međutim njegovu primenu ograničavaju bolna aplikacija, blag otok na mestu uboda i moguća prolazna ošamućenost koja prati parenteralnu primenu. Neka istraživanja ukazuju na to anestetički efekat difenilhidramina ipak nije zadovoljavajući [48].

Osim imunoloških reakcija preosetljivosti, žmomentalni tip reakcije na amidne lokalne anestetike može biti pseudoanafilaksa-anafilaktoidna reakcija ili neimunološki tip anafilakse[49,50].

Increased sensitivity to meta-bisulfite is certainly the result of its use in agriculture, where it is used as an antioxidant sprayed on fresh fruits and vegetables, in order to preserve their freshness and appearance. Patients who confirm to have that food allergy may have a cross-reaction with local anesthetic agents containing vasoconstrictor[17]. Sensibility to the bisulfite can be present in atopic patients and asthmatic patients and may cause a more severe form of the reaction (bronchospasm)[27,28].

Available data indicate that almost every amide local anesthetic in practice causes allergic reaction, with a specific growing pace[29-36]. In the case of suspected allergy to the local anesthetic solutions use of pure local anesthetic is recommended, without the presence of a stabilizer which is a potential antigen, or use of a different anesthetic. Ester local anesthetics have a cross-reaction and allergy involves a possible allergy to other anesthetic in this group. There are different views on the issue of replacing the amide local anesthetic that caused an allergic reaction. There are no reliable data in the literature whether there is a cross-reaction between the anesthetics of the amide groups. Yet there is a possibility that a possible antigen is metaksilen, which is part of the aromatic ring of almost all amide local anesthetic[37]. Persons sensitized to lidocaine as a suitable replacement is widely recommended mepivacaine, but it resulted that it provides cross-reaction with lidocaine, probably due to the presence of the aromatic radical metaksilena[38-42]. Articaine seems like a safer substitute for persons sensitized to lidocaine, probably because it contains thiophene instead metaksilena in its aromatic ring[37,44].

Diphenhydramine is an antihistamine which acts as an anticholinergic, antitussive, antiemetic and sedative, and it also has the properties of a local anesthetic[45]. In patients with known allergy to local anesthetics a solution of diphenhydramine chloride can be applied, with similar effect as 1% lidocaine[46,47]. However its application is limited because of severe application, mild swelling at the injection site and possible transient dizziness that accompanies parenteral use. Some studies suggest that the anesthetic effect of diphenhydramine is not satisfactory[48].

In addition to immunological hypersensitivity reactions, type of reactions to amide local anesthetics may be pseudo anaphylaxis - anaphylactoid reactions or non-immunological type anaphylaxis[49,50].

Ovaj tip reakcije preostljivosti dešava se bez posredstva IgE i razvija se već pri prvom kontaktu sa antigenom. Simptomi liče na pravu anafilaksu. Naročitu preosetljivost i sklonost anafilaktoidnoj reakciji, koja se dešava bez posredstava IgE, imaju bolesnici koji boluju od sisitemske mastocitoze[51]. Kod ovog oboljenja nepoznate etiologije, postoje mastocitni infiltrati u koži, koštanoj srži i unutrašnjim organima. Zbog otpuštanja histamina iz obilja mastocita razvijaju se simptomi anafilakse.

U kliničkoj praksi, veliki problem može da predstavlja prepoznavanje prirode negativne reakcije na aplikovani anestetik. Često se dešava da samibolesnici svoju psihogenu reakciju, koja je praćena prolaznim nadržajnim simptomima, proglase alergijskom. Kod bilo koje sumnje na alergijsku reakciju na lokalni anestetik, lekar mora uputiti bolesnika na alergološka ispitivanja, zbog sličnosti simptoma koji prate psihološke i toksične reakcije sa alergijskim. Ukoliko se dokaže alergijska reakcija na aplikovani anestetik, akupunktura i hipnoza mogu tada biti od koristi, kao alternativne ili dopunske metode lokalne anestezije, kako bi izbegli uvođenje bolesnika u opštu anesteziju.

Zaključak

Negativne reakcije na lokalne anestetike uglavnom su privremenog karaktera i reverzibilne prirode. U najvećem broju slučajeva javljaju se do 2 sata nakon aplikovanja anestetika[52],pa autori smatraju da je u ovom vremenskom periodu neophodno paratiti bolesnika. U kliničkoj praksi, naročito je važno utvrditi prirodu negativne reakcije, kako bi se pružila odgovorajuća pomoć u vezi sa nastalom reakcijom, i preporučila odgovarajuća alternativa datom lokalnom anestetiku. U tom smislu, naročito je važno razlikovati psihogenu reakciju na anestetik od toksične i alergijske reakcije, što u praksi predstavlja najveći problem.

This type of sensitivity reaction occurs without using IgE and develops already at the first contact with the antigen. Symptoms of anaphylaxis resemble the real one. Particular sensitivity and tendency to anaphylaxis reaction that occurs without using IgE, have patients suffering from systemic mastocytosis[51]. In this disease of unknown etiology, there are mast cell infiltrated in the skin, bone marrow and internal organs. Due to the release of histamine from mast cells abundance, symptoms of anaphylaxis are developed.

In clinical practice, the big problem may represent a recognition of the nature of the negative reaction to an anesthetic. It often happens that patients themselves declare their psychogenic reaction, which is accompanied by transient irritable symptoms, as allergic. In any suspicion of an allergic reaction to a local anesthetic, the doctor should refer the patient to the allergy testing, because of the similarity of symptoms associated with psychological and toxic reactions with allergic. If the allergic reaction to the applied anesthetic is confirmed, acupuncture, and hypnosis may then be used as an alternative or additional method for local anesthetic.

Conclusion

Negative reactions to local anesthetics are generally temporary and reversible. In the majority of cases, they occur up to 2 hours after application of anesthetic[52], so authors believe that at this time it is necessary to watch on the patient. In clinical practice, it is particularly important to determine the nature of the adverse reactions, in order to provide aid in connection with the resulting reaction, and recommend an alternative to the given local anesthetic. In this regard it is particularly important to distinguish psychogenic reaction to the anesthetic from toxic and allergic reactions, which in practice is the biggest problem.

LITERATURA /REFERENCES

1. Lukawska J, Caballero R, Tsabouri S, Dugué P. Hypersensitivity to local anaesthetics 6 facts and 7 myths. Curr Allergy Clin Immunol 2009; 22(3): 117-20.
2. Tijanić M. Historical development of local anestheticsused in stomatology. Acta Stom Naissi 2003; 19 (44).
3. Leonard M, Koller C. Mankind's greatest benefactor? The story of local anesthesia. J Dent Res 1998; 77(4): 535-538.
4. Chan SK., Karmakar MK, Chui PT. Local anesthesia outside the operating room.HKMJ 2002;8(2): 106-13.
5. Todorović Lj, Petrović V, Strajčić Z, Avramović K. Anestezija u stomatologiji. Beograd: Nauka; 2003.
6. Berde C. Local anesthetics in infants and children: an update. Paediatr Anaesth 2004; 14: 387-93
7. Varagić V. Lokalni anestetici u: Varagić V, Milošević M. Farmakologija. IX izdanje Beograd, Medicinska knjiga 1991;str: 118-24
8. Vučović D, Pavlović A.Sistemske toksične reakcije na lokalne anestetičke rastvore. In: Urgentna medicina u stomatološkoj praksi, Beograd, Don Vas, 2011: 114-7.
9. Dillane D, Finucane B.T. Local anesthetic systemic toxicity. J Can Anesth 2010;57: 368-80.
10. Rosenberg PH, Veering BT, Urmey WF. Maximum recommended doses of local anesthetics: a multifactorial concept. Reg Anesth Pain Med 2004; 29: 564-75.
11. Meechan J: How to avoid local anesthetic toxicity. BDJ 1998;184(7): 334-5.
12. Santos AC, Pederson H, Harmon TW, et al. Does pregnancy alter the systemic toxicity of local anesthetics? Anesthesiology 1989; 70: 991-5.
13. Butterworth JF 4th, Walker FO, Lysak SZ. Pregnancy increases median nerve susceptibility to lidocaine. Anesthesiology 1990;72: 962-5.
14. Borgeat A. Toxicity of local anesthetics. Proceedings of 1st Slovenian con- gress of regional anesthesia. Ljubljana 2010.
15. Butterworth JF. Models and mechanisms of local anesthetic cardiac toxicity: a review. Reg Anesth Pain Med 2010; 35(2):167-76.
16. Reiz S, Nath S. Cardiotoxicity of local anesthetic agents. Br J Anaesth 1986;58: 736-46.
17. Becker D.E, Reed K.L. Local anesthetics: review of pharmacological considerations. Anesth Prog 2012; 59: 90-102.
18. Hersh EV, Giannakopoulos H, Levin LM, et al. The pharmacokinetics and cardiovascular effects of highdose articaine with 1: 100,000 and 1: 200,000 epinephrine. J AmDentAssoc 2006;137: 1562-71.
19. Benz EJ. Disorders of hemoglobin. In: Longo DL, Kasper DL, Jameson JL, et al, eds. Harrison's Principles of Internal Medicine. 18th ed. New York, NY: McGraw Hill;2012.
20. Soto-Aguilar M, de Shazo R, Dawson E. Approach to the patient with suspected local anesthetic sensitivity. Immunology and Allergy Clinics of North America 1998; 18(4): 851-65.
21. Dahshan A, Donovan GK. Severe methemoglobinemia complicating topical benzocaine use during endoscopy in a toddler: a case report and review of the literature. Pediatrics 2006; 117(4): e806-9.
22. Moos DD, Cuddeford JD. Methemoglobinemia and benzocaine. Gastroenterology Nursing 2007; 30:342-345.
23. Sambrook PJ, Smith W, Elijah J, Goss AN. Severe adverse reactions to dental local anaesthetics: systemic reactions. Aust Dent J 2011;56(2):148–53.
25. Finucane BT. Allergies to local anaesthetics – the real truth. Can J Anaesth 2003; 50 (9): 869-874.
26. Thyssen JP, Menne T, Elberling J, Plaschke P, Johansen JD. Hypersensitivity to local anaesthetics--update and proposal of evaluation algorithm. Contact Dermatitis 2008; 59(2):69–78.
27. Boren E, Teuber SS, Naguwa SM, Gershwin ME. A critical review of local anesthetic sensitivity. Clin Rev Allergy Immunol 2007; 32(1):119–128.
28. Kean T, McNally M. Latex hypersensitivity: a closer look at considerations for dentistry. J Can Dent Assoc 2009;75(4):279-82.
29. Mackley CL, Marks JG Anderson BE. Delayed-type hypersensitivity to lidocaine. Arch Dermatol 2003;139(3):343-6.
30. Chiu CY, Lin TY, Hsia SH, Lai SH, Wong KS. Systemic anaphylaxis following local lidocaine administration during a dental procedure. Pediatr Emerg Care 2004; 20 (3):178-80.
31. Araújo LM, Amaral JL. Allergy to lidocaine: case report. Rev Bras Anestesiol 2004; 54(4):672–676.
32. Guttman, Cheryl . Be aware of lidocaine allergic contact dermatitis. Dermatology Times 2007; 28 (2): 44.
33. Calderon AL, Diot N, Benatir F, Christin F, Hautin E, Truc C, Allaouchiche B, Boselli E. Immediate allergic cross-reactivity to levobupivacaine and ropivacaine. Anaesthesia 2013;68(2):203-5.
34. Jenerowicz D, Polańska A, Glińska O, Czarnecka-Operacz M, Schwartz RA. Allergy to lidocaine injections: comparison of patient history with skin testing in five patients. Postepy Dermatol Alergol 2014;31(3):134-8.
35. Presman B, Vindigni V, Tocco-Tussardi I. Immediate reaction to lidocaine with periorbital edema during upper blepharoplasty. Int J Surg Case Rep 2016;20:24-6.
36. Venemalm L, Degerbeck F, Smith W. IgE-mediated reaction to mepivacaine. J Allergy Clin Immunol 2008; 121(4):1058-9.
37. Ing Lorenzini K, Gay-Crosier Chabry F, Piguet C, Desmeules J. Meta-xylene: identification of a new antigenic entity in hypersensitivity reactions to local anesthetics. J Allergy Clin Immunol Pract 2016;4(1):162-4.
38. Fuzier R, Lapeyre-Mestre M, Mertes PM, Nicolas JF, Benoit Y, Didier AAlbert NMontastruc JLFrench Association of Regional Pharmacovigilance Centers Immediate- and delayed-type allergic reactions to amide local anesthetics: clinical features and skin testing. Pharmacoepidemiol Drug Saf 2009;18(7): 595-601.
39. Duque S, Fernández L. Delayed-type hypersensitivity to amide local anesthetics. Allergol Immunopathol (Madr) 2004; 32(4):233-4.
40. Juan Luis Estrada-Rodriguez, Angel Rodríguez-Paredes, Margarita Latasa and Jose Luis Perez-Laiz. Delayed Hypersensitivity to Lidocaine Cross-Reactivity with Others Amide-Type Anesthetics. Int J Aller Medcations 2015; 1:2

41. Sanchez-Morillas L, Martinez JJ, Martos MR, Gomez-Tembleque P, Andres ER. Delayed-type hypersensitivity to mepivacaine with cross-reaction to lidocaine. Contact Dermatitis 2005; 53(6):352-3.
42. Gunera-Saad N, Guillot I, Cousin F, Philips K, Bessard A, Vincent L, Nicolas JF Immediate reactions to local anesthetics: diagnostic and therapeutic procedures. Ann Dermatol Venereol 2007; 134(4 Pt 1):333-6
43. Khalid Al-Dosary, Ahmad Al-Qahtani, Abdullah Alangari. Anaphylaxis to lidocaine with tolerance to articaine in a 12 year old girl. Saudi Pharm J 2014; 22(3): 280–282.
44. Smith DW, Peterson MR, DeBerard SC (August 1999). Local anesthesia. Topical application, local infiltration, and field block. Postgrad. Med 1999; 106 (2): 57–60, 64–6.
45. Pavlidakey PG, Erin MD, Brodell E, Helms SE.Diphenhydramine as an Alternative Local Anesthetic Agent J Clin Aesthet Dermatol 2009; 2(10): 37–40.
46. Ernst AA, Marvez-Valls E, Mall G, et al. 1% Lidocaine versus 0.5% diphenhydramine for local anesthesia in minor laceration repair. Ann Emerg Med 1994; 23 (6):1328-1332.
47. Willett J, Reader A, Drum M, Nusstein J, Beck M. The anesthetic efficacy of diphenhydramine and the combination diphenhydramine/lidocaine for the inferior alveolar nerve block. J Endod 2008;34(12):1446-50.
48. Ring J, Franz R, Brockow K. Anaphylactic reactions to local anesthetics. Chem Immunol Allergy 2010; 95:190-200.
49. Ong C, Seymour R.A. pathogenesis of postoperative oral surgical pain. Anesth Prog 2003; 50:5-17.
50. Russell WJ, Smith WB. Pseudoanaphylaxis. Anaesth Intensive Care 2006; 34(6):801-3.
51. Grzanka A1, Misiołek H, Filipowska A, Miśkiewicz-Orczyk K, Jarząb J. Adverse effects of local anaesthetics - allergy, toxic reactions or hypersensitivity. Anestezjol Intens Ter 2010; 42(4):175-8.
52. Kaufman E, Goharian S, Katz Y. Adverse reactions triggered by dental local anesthetics: a clinical survey. Anesthesia progress 2000; 47(4): 134-138.

UPUTSTVA AUTORIMA

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

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

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Uvod: opisuje problem o kome se radi u radu

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Rezultati: opisuje primarno rezultate

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

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

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TABELE I FIGURE

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Priznanja i zahvalnosti prethode literaturi specificirajući generalnu podršku kao i odeljenje i ime šefa odeljenja, priznanja tehničkoj pomoći i konačno finansijskoj i materijalnoj pomoći. Navesti naziv i broj projekta, odnosno naziv programa u okviru koga je nastao članak i naziv institucije koja je finansirala projekat, u posebnoj napomeni pri dnu prve strane članka

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2. Organizacija kao autor: Federation Dentaire Internationale. Technical Report No. 28. Guidelines for antibiotic prophylaxis of infective endocarditis for dental patients with cardiovascular disease. Int Dent J 1987;37:235.

3. Nije dat autor: Coffee drinking and cancer of the pancreas (editorial).BMJ 1981;283:628

4. Volumen sa suplementom: Magni R, Rossoni G, Berti R, BN52021 protect guinea pig from heart anaohylaxis. Pharmacol Res Commun 1988; 20 Suppl 5:75–8.

Knjige ili druge monografije

5. Lični autor (i): Tullman JJ, Redding SW. Systemic Disease in Dental Treatment. St.Louis: The CV Mosby Company;1983:1–5.

6. Poglavlje u knjizi: Rees TD. Dental management of the medically compromised patient. In: McDonald RE, Hurt WC,Gilmore HW, Middleton RA, eds.Current Therapy in Dentistry, vol.7. St. Louis: The CV Mosby Company; 1980:3–7.

7. Disertacije i teze: Teerakapong A. Langerhans Cells in human periodontally healthy and diseased gingiva. (Thesis). Houston, TX: University of Texas; 1987.92 p.

Ostali publikovani materijal

8. Novinski članak: Shaffer RA.Advances in chemistry are starting to unlock mysteries of the brain. The Washington Post 1989 Ang 7; Sect. A:2 (col. 5).

Reference-elektronski citati

9. On line časopisi bez podataka o volumenu i strani. Berlin JA , Antman EM. Advantages and limitations of metaanalytic regressions of clinical trials data. Online J Curr Clin Trials (serial online). June 4;doc 134. Accessed July 20, 2000.

10. Online časopisi sa podacima o volumenu i strani. Fowler EB, Breault LG. Ridge augmentation with a folded acellular dermal matrix allograft: A case Report. J Contemp Dent Pract (serial online). 2001;2(3):31–40. Available from: Procter&Gamble Company, Cincinnat, OH. Accessed December 15, 2001.

11. World Wide Web.Centers for Disease Control and Prevention. Preventing emerging infectious diseases: Addressing the problem of antimicrobial resistance. Available at: http://www.cdc.gov/ncidod/emergplan/antiresist/. Accessed November 5, 2001.

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The title page should contain: a) the full title of the article (in upper case); b) first name, middle initial, and last name of each author without the academic degree; c) name of department and institutional affiliation for each author; d) running title of no more than 10 characters. At the bottom of the page, please indicate the name, academic degree and address (including E-mail, telephone and fax number) of the author responsible for correspondence.

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ACKNOWLEDGEMENTS

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2. Corporate author: Federation Dentaire Internationale. Technical Report No.28. Guidelines for antibiotic prophylaxis of infective endocarditis for dental patients with cardiovascular disease. Int Dent J 1987;37:235.

3. No author given: Coffee drinking and cancer of the pancreas (editorial). BMJ 1981;283:628

4. Volume with supplement: Magni R, Rossoni G, Berti R, BN52021 protect guinea pig from heart anaphylaxis. Pharmacol Res Commun 1988; 20 Suppl 5:75–8.

Books or other monographs:

5. Personal author(s): Tullman JJ, Redding SW. Systemic Disease in Dental Treatment. St. Louis: The CV Mosby Company; 1983:1–5.

6. Chapter in a book: Rees TD. Dental management of the medically compromised patient. In: McDonald RE, Hurt WC, Gilmore HW, Middleton RA, eds. Current Therapy in Dentistry, vol. 7. St. Louis: The CV Mosby Company; 1980:3–7.

7. Dissertations and thesis: Teerakapong A. Langerhans Cells in human periodontally healthy and diseased gingiva. (Thesis). Houston, TX: University of Texas; 1987.92 p.

Other published material:

8. Newspaper article: Shaffer RA.Advances in chemistry are starting to unlock mysteries of the brain. The Washington Post 1989 Ang 7; Sect.A:2 (col. 5).

References – electronic quotations:

9. Online journals without volume and page information. Berlin JA , Antman EM. Advantages and limitations of metaanalytic regressions of clinical trials data. Online J Curr Clin Trials (serial online). June 4; doc 134. Accessed July 20, 2000.

10. Online journals with volume and page information. Fowler EB, Breault LG. Ridge augmentation with a folded acellular dermal matrix allograft: A case Report. J Contemp Dent Pract (serial online). 2001;2(3):31–40. Available from: Procter&Gamble Company, Cincinnat, OH. Accessed December 15, 2001.

11. World Wide Web.Centers for Disease Control and Prevention. Preventing emerging infectious diseases: Addressing the problem of antimicrobial resistance. Available at: http://www.cdc.gov/ncidod/emergplan/antiresist/. Accessed November 5, 2001.

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