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Primena periočipa sa hlorheksidinom u terapiji parodontopatije

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The Use of Subgingival Chlorhexidine Chip in the Treatment of Periodontal Disease

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KRATAK SADRŽAJ

U lečenju parodontopatija se lokalno se primenjuju različiti medikamenti, kao efikasna dopuna konvencionalnoj mehaničkoj terapiji. Međutim, koncentracija ovih lekova na mestu primene, posebno u funkciji vremena, ostavlja otvorenim pitanje o svrsishodnosti njihove primene.U novije vreme na tržištu su se pojavili novi sistemi lekova za lokalnu primenu u predelu parodontalnih i gingivalnih džepova. Ovi sistemi omogućavaju postepeno oslobađanje terapijskog agensa u inflamiranom parodontalnom džepu i održavaju koncentraciju leka koja je 10 do 100 puta veća od koncentracije koja se postiže u džepu nakon sistemske primene antibiotika.

U kontrolisanim kliničkim istraživanjima je ispitivano nekoliko različitih sistema sa lokalnim oslobađanjem leka – vlakna, gelovi, čipovi. Lekovi koji se najčešće koriste u navedenim sistemima su antibiotici (tetraciklin, minociklin), hemoterapeutici (metronidazol) i antiseptici (hlorheksidin diklukonat).

U ovom radu su analizirani rezultati studija koje su se bavile ispitivanjem efikasnosti subgingivalno primenjenog periočipa sa hlorheksidinom i prikazana je metoda njihove primene.

Ključne reči: parodontopatije, hlorheksidin diglukonat, lokalna primena leka

SUMMARY

Due to the infective nature of periodontal disease several local devices have been used to overcome the limited efficacy of convencional periodontal treatment. However, local concentration of these medicaments, especially over time, raises the question of expediency of their use. Local delivery systems allow the therapeutic agents to be targeted to the diseased site for a long time. These systems, when retained in the periodontal pocket, can release the antimicrobial agents at levels that are 10- to 100-fold higher than the levels that can be delivered by systemic antibiotics.

Several different drug delivery systems have been used in controlled clinical trials: fibers, gels and chips. The most frequently used antimicrobials are antibiotics (tetracycline, minocycline), hemotherapeutics (metronidazole), and antiseptics (chlorhexidine dicluconate).

In the present paper the method of chlorhexidine chip application is analyzed. We discussed the results of studies that evaluated the efficacy of a controlled- release of biodegradable chlorhexidine chip when used as an adjuct to scaling and root planing (SRP) in adult periodontitis.

Key words: periodontitis, chlorhexidine / therapeutic use

Aktuelno shvatanje etiologije i patogeneze parodontopatija zasnovano je na konceptu da bolest počinje dejstvom specifičnih bakterija iz dentalnog plaka. Podaci mnogobrojnih istraživanja sugerišu da su првенствено

Current paradigm of etiology and pathogenesis of periodontitis is based on the concept that specific microorganisms in dental biofilm initiate periodontal disease. Numerous multi-center studies have shown that gram

gram – negativne, anaerobne bakterije dentalnog plaka odgovorne za nastanak i progresiju oboljenja parodoncijuma. Pored direktnog delovanja, ove bakterije stimulišu imunobiološki odgovor domaćina, čije su reakcije velikim delom odgovorne za destrukciju tkiva parodoncijuma. Stoga je osnovni princip u lečenju parodontopatije uklanjanje supra- i subgingivalnog dentalnog plaka, kao i odstranjivanje svih faktora koji omogućavaju njegovu akumulaciju.

Lečenje obolelih od parodontopatije je poslednjih godina značajno napredovalo, posebno u smislu uvođenja brojnih metoda regenerativne parodontalne hirurgije. Međutim, osnovna terapijska metoda i dalje je obrada parodontalnih džepova. Kod dubljih parodontalnih džepova, posebno kod osoba sa oslabljenim imunitetom, obrada mekog i tvrdog zida parodontalnih džepova nije dovoljna metoda da se eliminišu sve bakterije iz džepova. [1,2,3] S obzirom na infektivnu prirodu parodontopatije, a u cilju prevazilaženja ograničenih efekata konvecionalne terapijske metode, opravdana je primena antibakterijskih sredstava, antiseptika i antibiotika.

Antimikrobna sredstva (antiseptici i antibiotici) se koriste kao pomoćna sredstva u lečenju kako početnih tako i razvijenih formi parodontopatija. Mogu se primeniti sistemski ili lokalno. Sistemska primena antibiotika zahteva primenu relativno visokih doza u cilju postizanja dovoljnih koncentracija leka u sulkusnoj tečnosti, što može dovesti do razvoja rezistentnih bakterijskih sojeva, pojavu hipersenzitivnosti, toksičnih i drugih sporednih efekata. Noviji terapijski izazov predstavlja mogućnost uspešne lokalne primene antimikrobnih lekova u različitim sistemima sa mogućnošću protrahiranog oslobađanja leka.

Dva bitna uslova u uspešnom lečenju parodontopatija su postizanje dovoljne koncentracije leka na obolelom mestu i to u dovoljnom dugom vremenskom periodu.[4] Antimikrobna sredstva lokalno primenjena u džepu, mogu postići koncentraciju leka koja je 10 do 100 puta veća nego koncentracija koja se postiže u džepu nakon sistemske primene. Lokalnom primenom leka se izbegavaju neželjeni efekti sistemski primenjenog leka, čime se izbegava nepotrebno izlaganje pacijenta visokim dozama antibiotika, a time i mogućnost nastanka bakterijske rezistencije.[5] Još jedan razlog za uvođenje sistema koji omogućavaju produženo oslobađanje leka, u ovom slučaju antiseptika, je taj što nije dokazano da upotreba antimikrobnih sredstava za ispiranje parodontalnih džepova ima dugotrajniji efekat. [6,7]

Zato su u ove svrhe uvedena sredstva sa lokalnim, protrahiranim oslobađanjem a sadrže antibiotike ili antiseptike. Ova sredstva olakšavaju terapijskim agensima da deluju direktno u inflamiranom području, a da pritom daju minimalne štetne efekte.

negative, anaerobic microorganisms possess the ability to invade gingival tissues and also are resposible in iniatiation and progression of periodontitis. These periodontopathogenic bacteria stimulate immunobiological host responses responsible for periodontal tissues destruction. Therefore, the most important goal of periodontal therapy is to eliminate supra- and subgingival microorganisms associated with periodontal disease.

The last decades have seen the significant improvement in treatment of periodontal disease,especially because numerous sofisticated methods have been introduced in regenerative periodontal surgery. However, scaling and root planing (SRP) has been a basic treatment for chronic periodontitis. During SRP, subgingival calculus is removed together with most of the pathogenic bacteria. Although mechanical treament significantly decreases the levels of subgingival microorganisms, it does not necessarily eliminate all pathogens. [1,2] Also, as probing depth increases, the effectiveness of SRP decreases, leaving subgingival plaque and calculus on root surfaces. [3] Due to the infective nature of periodontal disease, this has led to the adjunctive use of antibacterial agents, to overcome the limited efficacy of conventional treatment.

Antimicrobials, both antibiotics and antiseptics, have been used in cases of moderate to severe periodontitis to aid in eradication of plaque bacteria. Systemic antibiotics, however, require the administration of large doses in order to gain sufficient local concentrations at disease site and exhibit potential threat for the development of bacterial resistence, inconsistent patient compliance, side effects or drug interactions. Late therapy challenge represents prosperous local application of drugs in different vehicles. Local delivery systems allow therapeutic agents to be targeted into the disease site for a long time.

Targeting the antimicrobial agent directly to the infected site and maintaining effective levels for a sufficient period of time are two necessary conditions for a successful treatment. [4] These systems, when retained in the periodontal pocket, can release the antimicrobial agents at levels that are 10- to 100-fold higher than the levels delivered by systemic antibiotics. This approach also addresses the critical concerns of unnecessary exposing the patient to large amounts of systemic antibiotics, which can result in bacterial resistance. [5] One more reason for using these systems is that solutions, whether administrated as topical rinses or irrigants, have generally been poorly effective in the treatment of periodontitis, presumably due to the inability to obtain biologically significant concentrations of drug for sufficient lengths of time within the confines of the periodontal pocket. [6,7]

The inherent limitations of systemic or topical chemotherapies led to development of local delivery systems for the administration of antimicrobial, both antibiotics and antiseptics. These slow-release devices allow antimicrobials to be introduced directly to periodontal pockets,with minimal systemic effects.

U kontrolisanim kliničkim ispitivanjima se koristi nekoliko različitih sistema sa lokalnim oslobađanjem leka:

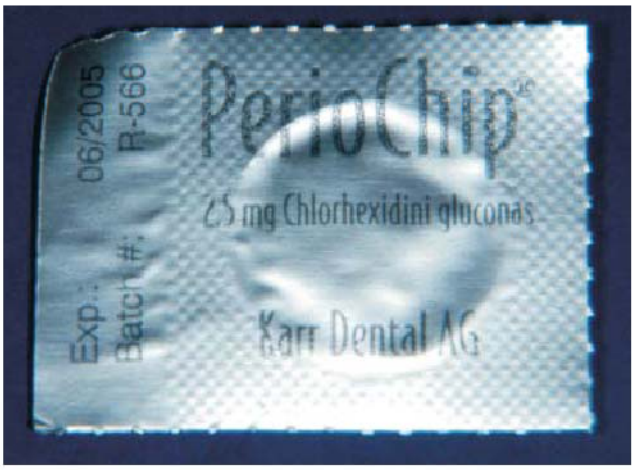
- tetraciklinska vlakna [8,9]
- gel sa antibioticima (metronidazol[10],minociklin[11] i doksiciklin[12])
- periočip sa hlorheksidin diklukonatom [4,13,14,15,16]

Svi navedeni sistemi se aplikuju subgingivalno. Hlorheksidin je dosad najproučavaniji i najdelotvorniji antiseptik u prevenciji nastanka plaka.[17]

Several different drug delivery systems have been used in controlled clinical trials:

- a subgingivally introduced fiber (that releases tetracycline)[8,9]
- a subgingivally introduced gel (that releases metronidazole[10], minocycline[11] and doxycycline[12])
- ubgingivaly placed chip (that releases chlorhexidine dicluconate) [4,13,14,15,16]

Chlorhexidine is one of the most widely studied antiseptic. It is regarded as the "gold standard" antiplaque treatment.[17]



Slika1. Periochip
Figure 1. Periochip

Antiseptik deluje protiv velikog broja Gram pozitivnih i Gram negativnih bakterija, gljivica i virusa (HBV i HIV).Mehanizam delovanja hlorheksidina zasniva se na njegovom vezivanju za ćelijske membrane bakterija. Moguće je da se jedan katjon molekula pripaja uz pelikulu zuba, a druga katjonska molekula deluje sa bakterijama.[18] Kada se jednom adsorbuje, za razliku od drugih antiseptika, počinje da deluje bakteriostatski, što traje i duže od 12 sati.[19]

U cilju usavršavanja sistema za subgingivalnu primenu lekova vršena su opsežna ispitivanja. Od sistema sa lokalnim oslobađanjem najviše istraživano sredstvo za primenu je PerioChip (Perio Products, Jeruzalem, Izrael), razgradiva želatinska pločica koja sadrži 2,5 mg hlorheksidina. Periočip oslobađa ovaj antiseptik u parodontalnom džepu u vremenskom intervalu od 7 do 10 dana, održavajući prosečnu koncentraciju leka veću od 125 μg/ ml tokom 7 dana u gingivalnoj tečnosti.[13] Oslobađanje je najveće u prvih 24 časa od aplikovanja.U prvih 2 sata nakon primene beleže se koncentracije do 2000 μg/ ml gingivalne tečnosti u džepu. Nakon dva do četiri dana koncentracije dostižu vrednosti do 1300 μg/ ml, da bi posle tog vremena lagano opadale ali ostale iznad 125 μg/ ml u prvih 8 dana. Napred navedena koncentracija je minimalna inhibitorna koncentracija (MIK) za više od 99 % subgingivalnih mikroorganizama izolovanih iz parodontalnih džepova.[20]

U svim obavljenim studijama koje su analizirane kao metodološki koncept je korišćen metod podeljenih usta.

It has a broad spectrum of antibacterial activity against both Gram - positive and Gram - negative bacteria, anti-micotic (against candida) and anti-viral (against HBV and HIV). The target site of chlorhexidine is the cytoplasmic membrane of microbes. It is possible that one kation of chlorhexidine interacts with tooth pelicule and the other kation interacts with membrane of bacteria.[18] When absorbed, in contrast to the other antiseptics, it acts as if bacteriostatic more than 12 hours. [19]

Recently a new approach using local delivery systems containing antiseptics has been introduced. One such product PerioChip (Perio Products, Jeruzalem, Izrael), is biodegradable, local delivery system that contains 2.5 mg of chlorhexidine gluconate in a cross-linked, hydrolised gelatin vehicle. In its present formulation the chip biodegrades and releases chlorhexidine within the pocket over 7 to 10 days, maintaing an average concentration of chlorhexidine in the gingival crevicular fluid (GCF) greater than 125 μg/ ml for 7 days. [13] When in situ, there is an initial peak of concentration of 2000 μg/ ml chlorhexidine in GCF. After 2 to 4 days the concentration of drug reaches 1300 μg/ ml, and than decreases but remains above 125 μg/ ml in first 8 days. Drug concentrations remains above the minimum inhibitory concentration (MIK) for more than 99 % of periodontal pocket flora.[20]

This device is used after etiotropic phase of periodontitis that is performed on patients with chronic periodontal disease. Split-mouth design is used. All the studies that

Preparat se primenjuje nakon sprovedene kauzalne terapije parodontopatija. Ispitivanje je obavljano u okviru dve grupe: **kontrolne** (koju čine parodontalni džepovi dubine 5 do 8mm u jednoj strani vilice kod kojih je primenjena klasična metoda obrade parodontalnih džepova) i **eksperimentalne** (parodontalni džepovi iste dubine druge strane vilice kod kojih je pored obrade parodontalnih džepova aplikovan i periočip). Kliničko stanje parodontalnih tkiva je verifikovano sledećim kliničkim parametrima:

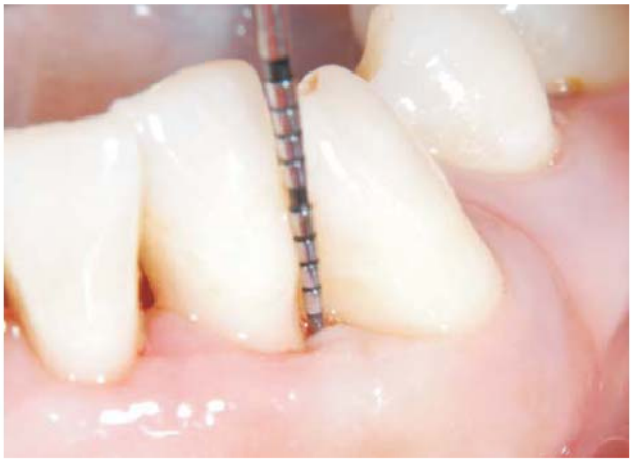
1. plak indeks (Silness & Loe) – PI
2. indeks krvarenja gingive (Muhlemann) – IKG
3. dubina parodontalnih džepova – DPDŽ
4. nivo pripojnog epitela – NPE

Parametri su beleženi nakon 1, 3, 6 i/ili 9 meseci (u zavisnosti od istraživanja). Na kontrolnom pregledu posle 3 meseca, sprovedeno je uklanjanje svih čvrstih i mekih supragingingivalnih naslaga i u eksperimentalne parodontalne džepove, kod kojih je zabeležena dubina veća od 5 mm ponovo je aplikovan periočip. Pacijentima je savetovano da ne koriste zubni konac ili bilo koji rastvor za ispiranje usta u periodu od 10 dana, da ne bi došlo do pomeranja čipa u parodontalnom džepu.

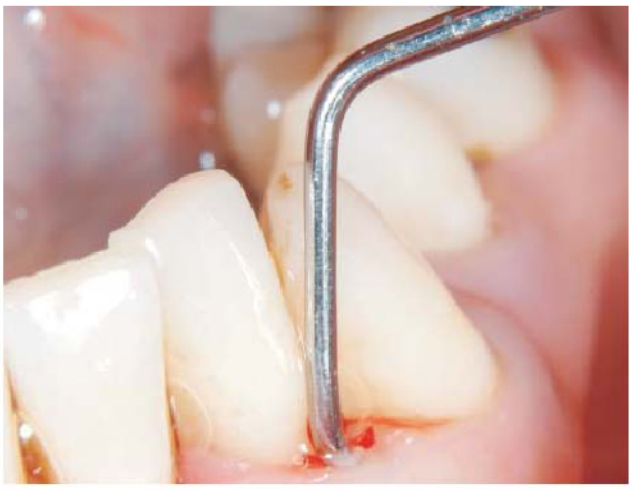
evaluated effectiveness of subgingivally placed periochip were performed for comparison of two treatments: scaling and root planing alone (SRP) versus SRP plus periochip. Patients were considered eligible if they had periodontal pockets ≥5mm in depth that bled on probing. The following clinical parameters were recorded at baseline and after 1, 3,6 and/or 9 months:

1. Plaque index (Silness & Loe) – PI
2. Bleeding on probing (Muhlemann) – BOP
3. Probing depth – PD
4. Clinical attachment level – CAL

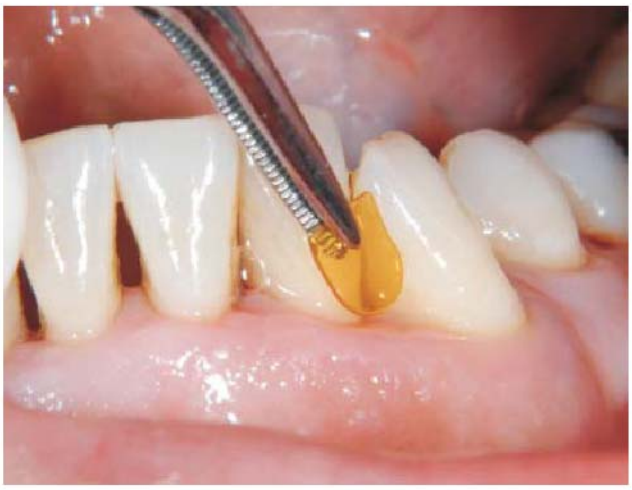
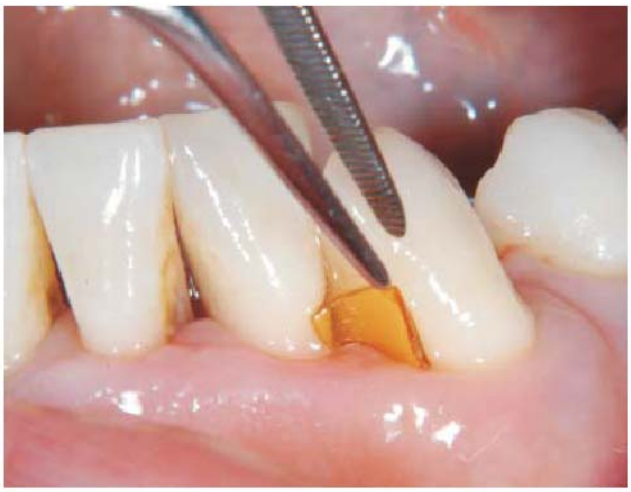
At 3 months recall visit, all the pockets that remained 5 mm or more in depth received subgingival re-treatment. Additionally, tha target sites of the experimental group received a new chlorhexidine chip. Patients were asked not to use dental floss for 10 days to avoid displacement of the chlorhexidine chip, or any kind of chemotherapeutic mouthrinses or oral irrigation devices during the study period.



Slika 2. Sondiranje parodontalnog džepa graduisanom parodontalnom sondom
Figure 2. Periodontal pocket probing using a graduated periodontal probe



Slika 3. Obrada parodontalnog džepa kiretom
Figure 3. Scaling and root planing

Slike 4,5 Aplikovanje periočipa sa hlorheksidinom u parodontalni džep 33 mezijalno
Figures 4,5 Chlorhexidine periochip aplication in the mesial periodontal pocket 33

Soskolne i sar.[4] su ispitivali efikasnost resorptivnog periočipa sa hlorheksidinom primenjenog u parodontalne džepove. Ispitivanje je sprovedeno na 118 odraslih pacijenata sa parodontopatijom. Rezultati istraživanja su pokazali da je smanjenje dubine parodontalnih džepova (DPDŽ), nakon 3 i 6 meseci bilo značajno veće (što je i statistički potvrđeno) kod džepova gde je uz konvencionalnu metodu primenjen hlorheksidinski periočip, nego kod džepova gde je primenjena samo konvencionalna metoda. Vrednosti nivoa pripojnog epitela (NPE) posle 3 i 6 meseci su bile manje u džepovima gde je primenjen hlorheksidinski periočip nego tamo gde nije primenjen. Ta značajnost razlika je i statički potvrđena za nivo p=0,05. Na kontrolnom pregledu, godinu dana kasnije, utvrđeno je i značajno poboljšanje vrednosti NPE u džepovima gde nije primenjen periočip. U toku eksperimenta, nakon 3 i 6 meseci, došlo je do smanjenja dubine parodontalnih džepova, a time i promene njihove distribucije u smislu povećanja broja džepova manje dubine, što je i statistički potvrđeno (p < 0,0001). U zaključku istraživanja navodi se da je procenat parodontalnih džepova, čija je dubina smanjena za 2 i više mm, bio veći tamo gde je korišćen periočip.Statističke značajnosti razlika ovih vrednosti uočene su i posle 3 i posle 6 meseci. Što se tiče vrednosti indeksa krvarenja gingive (IKG) uočen je njihov mali pad, ali bez statistički značajnih razlika.

Jeffcoat i sar.[14] su sproveli istraživanje na 447 pacijenata obolelih od parodontopatije. Rezultati njihovog istraživanja nakon 9 meseci pokazuju statistički značajno veće smanjenje vrednosti DPDŽ (p < 0,001) u džepovima gde je primenjen periočip nego kod džepova gde je primenjena samo konvencionalna metoda ili džepova gde je uz konvencionalnu metodu primenjen placebo čip. Vrednosti NPE u džepovima gde je primenjen periočip su na kraju eksperimentalnog perioda manje nego u džepovima gde on nije primenjen. Značajnost razlika je potvrđena statistički za nivo p <0,05. Navedeni rezultati, koji se tiču vrednosti DPDŽ i NPE su u saglasnosti sa rezultatima studije

Soskolne et al.[4] were evaluated the safety and efficacy of a degradable, subgingivally placed drug delivery system containing chlorhexidine in a multi-center study of 118 patients with moderate periodontitis. At 3 and 6 months the pockets in test quadrants showed a significantly greater reduction in periodontal pocket depth (PPD) than the pockets treated by SRP alone (p <0.0001). CAL showed a similar, but less marked improvement over the study period. The improvement in CAL obtained with the chlorhexidine was greater than obtained by SRP alone at 3 and 6 monts. The differences reach significance at the 6 –month visit only *(p <0.05)*. One year later, greater improvements were found in CAL values in the group with pockets that received SRP alone. The probing depth distribution per patient was similar both treatment groups. This shift was significantly greater in the chlorhexidine treated sites at 3 and 6 monts (p < 0.0001). There was a significant reduction in the percentage of sites with visible bleeding on probing for both groups, but they did not reach significant difference.

Jeffcoat et al.[14] performed two duble-blind, randomized, placebo controlled multi-center clinical trials on 447 patients. Significant reduction of probing depth at 9 months was observed in the chlorhexidine chip plus SRP treatment group compared with both control treatment groups, SRP alone and placebo chip plus SRP *(p< 0.001)*. A significant improvement in CAL was observed at 9 months in the chlorhedine chip plus SRP treatment group compared to both control treatment groups *(p <0.05)*. These results in those sites that received SRP plus chlorhexidine chip was in accordance with the results reported by Soskolne et al[4]. There was a statistically significant reduction in BOP in control group compared to test group at 9 months *(p <0.05)*, that was in accordance to Grisi et al [16].

In the study by Grisi et al [16] it was reported that the gingival recession (GR) obtained by the SRP plus chlo-

Soskolne i sar [4]. Medjutim,vrednosti IKG u džepovima su posle 9 meseci bile statistički značajno manje u džepovima ($p < 0,05$) gde hlorheksidinski periočip nije bio primenjen u odnosu na džepove u kojima je on bio primenjen. ($p < 0,05$), što su potvrdili i Grisi i sar [16] i objasnili lokalnom mehaničkom iritacijom periočipom.

Sličnu metodologiju ispitivanja su primenili i Grisi sar.[16] u cilju procene efikasnosti primene periočipa. U ovoj studiji je zabeležen veći porast vrednosti recesije gingive (RG) u parodontalnim džepovima gde je primenjen periočip sa hlorheksidinom u odnosu na džepove gde on nije primenjen. Ove rezultate autori studije objašnjavaju većim smanjenjem eksudativne inflamacije gingive i sledstvenim smanjenjem DPDŽ u grupi gde je primenjen periočip nego u džepovima gde nije primenjen. Mogući razlog ovakvim rezultatima je i mehanička trauma uzrokovana ponovnom primenom periočipa u parodontalnim džepovima nakon 3 i 6 meseci. Značajno smanjenje vrednosti IKG je zabeleženo u parodontalnim džepovima gde nije primenjen periočip.Smanjenje vrednosti DPDŽ u džepovima sa primenjenim periočipom (1,7mm u odnosu na početak ispitivanja) je bilo veće u ovoj studiji u poređenju sa vrednostima koje su dobili Soskolne i sar.[4] (0,84mm) i Jeffcoat-a i sar.[14] (0,80mm). Razlike u dobijenim rezultatima se mogu objasniti donekle različitom metodologijom ispitivanja, tj. ponovnom aplikacijom hlorheksidinskog periočipa posle 3 i 6 meseci u ispitivanju Soskolnog. Srednja vrednost NPE u džepovima gde je primenjen periočip je iznosila 0,60 mm, i slična je rezultatima NPE koje su objavili Soskolne i sar.[4](0,47mm) i Jeffcoat-a i sar[14] (0,74 mm). Posle verifikovanja kliničkih parametara, urađen je mikrobiološki test – BANA (N- benzoyl-DL – arginine-2- naphthylamide). Ovaj test se koristi za dokazivanje prisustva bakterija *Bacteroides forsythus, Treponema denticola* i /ili *Porphyromonas gingivalis*.Dobijeni rezultati BANA testa odstupaju od očekivanih. Test je bio pozitivan, tj. ukazivao je na prisustvo navedenih mikroorganizama već posle 3 meseca. Autori smatraju da je test bio pozitivan zbog neefikasno sprovedenog konvencionalnog lečenja ili zbog rekolonizacije mikroorganizama iz susednih lokaliteta kao što su jezik i tonzile.[21]

Rezultati dobijeni nakon primene periočipa se ne razlikuju značajno u odnosu na rezultate studija u kojima je ispitivana efikasnost primene sistema sa lokalnim oslobađanjem antibiotika, kao što je tetraciklin[9,22] ili minociklin.[11] Stoga, izgleda da vrsta antibakterijskog sredstva nije odlučujući faktor za postizanje boljih kliničkih rezultata. Prednost upotrebe antiseptika, kao što je hlorheksidin jeste da je mogućnost nastanka bakterijske rezistencije pri njegovoj primeni minimalna. [6,7]

U slučajevima kada dubina parodontalnog džepa dostiže vrednost od 5 mm i više, obrada parodontalnog džepa postaje manje efikasna metoda u lečenju. [1,2,3,6] Dopunska primena antimikrobnih sredstava doprinosi postizanju boljih terapijskih rezultata. Dokazano je da je sistemska primena antibiotika efikasna u agresivnim

rhexidine chip treatment was greater than obtained by SRP alone. That may be related to greater reduction in the gingival margin inflammation, as well as to the mechanical trauma caused by additional applications of the chlorhexidine chip after 3 and 6 months. Both treatment groups presented marked reduction in the percentage of sites with visible BOP throughout the study. A greater reduction in BOP values was shown in favour of control group, $p < 0.05$. The PD reduction in the SRP plus chlorhexidine chip group (1.7 mm) was greater than observed in studies by Soskolne et al. [4] (0.84mm) and Jeffcoat-a et al. [14] (0.80mm). The majority of pockets received a second application of chlorhexidine at 3 and 6 months, while the controls only received a supragingival profilaxis. Therefore, differences in results may be explained by different metodology of investigation. The mean attachment gain of 0.60 mm in those sites that received SRP plus chip was in accordance with the results reported by Soskolne et al.[4](0.47mm) and Jeffcoat-a et al.[14] (0.74 mm). After recording clinical parameters, a microbial chairside test, BANA test (N- benzoyl-DL – arginine-2- naphthylamide) was used to verify the presence of *Bacteroides forsythus, Treponema denticola and/or Porphyromonas gingivalis*. The data of the present investigation were in contrast to the expected finding that the adjunctive use of the chip plus SRP would provide greater improvement in the results. This result should be considered with some caution because the first re-evaluation was performed only 3 monts after the baseline. The interval of 3 months between the treatment and the first re-evaluation did not allow to determine whether the percentage of BANA positive results was due to an infective treatment or to a recolonisation of the target pockets by those periodontopathogenic microorganisms, such as tongue, tonsils and mucous membranes. [21]

The presenting results concerning the subgingival placement of a chlorhexidine chip are in accordance with previous studies, which demonstrated that local delivery antibiotics, such as tetracycline [9,22] or minocycline.[11] Therefore, it seems that the choice of the antibacterial agent is not critical to the clinical result. The use of an antiseptic such as chlorhexidine, however, has the advantage of having a minimal, if any, potential to induce resistant bacterial resistance. [6,7]

As the depth of periodontal pockets increases more than 5 mm, SRP becomes progressively less effective.[1,2,3,6] For periodontal pockets ≥5 mm, the adjunctive use of an antimicrobial may be necessery to enhance the therapeutic effect. This has led to he adjunctive use of antibacterial agents, usually in the form of irrigants or systemic antibiotics, to overcome the limited efficacy of the convencional treatment. Systemic antibiotics have proved to be effective in aggressive periodontal diseases. Systemic antibiotics require the administration of large doses and show potential for the development of bacterial resistance. Even the local delivery of antibiotics may have the potential for the

formama parodontopatija. Medjutim, posle dugotrajne sistemske primene antibiotika postoji mogućnost razvoja bakterijske rezistencije, nekih sporednih efekata i interakcije među lekovima.Nastanak bakterijske rezistencije je opisan i posle lokalne primene antibiotika[23].

U lečenju gingivitisa i parodontopatija dugo se koriste lokalna sredstva, kao efikasna dopunska antimikrobna terapija. Međutim,rastvori hlorheksidina, koji se koriste kao sredstva za ispiranje usta, nedovoljno su efikasni u lečenju parodontopatija, zbog nemogućnosti da održe biološki značajne koncentracije leka u dovoljno dugom vremenskom intervalu u parodontalnom džepu [7]. Osim toga, kada se hlorheksidin koristi kao sredstvo za ispiranje usta u vremenskom periodu dužem od 2 nedelje dovodi do brojnih lokalnih neželjenih efekata: prebojavanje zuba i jezika, promene ukusa, a zabeleženi su i slučajevi alergijskih reakcija u vidu erozija oralne sluznice i obostranog oticanja parotidnih pljuvačnih žlezda.[23] Opisani neželjeni efekti ograničavaju njegovu dugotrajnu upotrebu.

Prvi sistemi za lokalno oslobadjanje lekovitih supstanci u parodontalnom džepu su bili nerazgradljivi: akrilne trake, etil-celulozni polimer filmovi, etil-vinil- acetatne trake i monolitička vlakna. Nerazgradljivi sistemi imaju brojne nedostatke: dugo vreme aplikacije, nepotpuno oslobađanje lekovitih svojstava i mogućnost zaostajanja delova sistema za lokalnu isporuku leka, što može da pogorša stanje inflamiranog tkiva. Navedeni problemi su rešeni uvodjenjem razgradljivih sistema. Prednost razgradljivih sistema je u tome što ne zahtevaju uklanjanje sa mesta postavljanja, a iskorišćavanje lekovite supstance je poboljšano.Primena čipa u parodontalnom džepu u trajanju od 3 dana je pokazala kratkoročne efekte.[25] Međutim, kontinuirana primena hlorheksidina u trajanju od 6 do 9 dana ima dugotrajnije antibakterijske efekte i kliničke rezultate.[4,7] Utvrđeno je da i tetraciklini zahtevaju približno isto vreme primene.[8] Stoga, sistemi sa oslobađanjem koji otpuštaju aktivne sastojke u kratkom vremenskom intervalu, zahtevaju ponavljanu primenu. Prethodne studije su pokazale da su antimikrobni efekti kratkoročni nakon trodnevne primene perio- čipa, ali se održavaju i do 11 nedelja posle primene od 6 do 9 dana. Najčešći neželjeni efekti uzrokovani primenom hlorheksidinskog periočipa su bili: nelagodnost, bol i osećaj stranog tela u gingivi, svrab kao i edem gingive, prolazna zubobolja, apsces gingive. Ovaj poslednji neželjeni efekat je bio neznatan i prolazan, sa spontanom rezolucijom u toku nekoliko dana.

Kliničke studije su pokazale da je primena periočipa kao pomoćnog sredstva u toku obrade parodontalnih džepova efikasnija u poređenju sa obradom parodontalnih džepova kao jedinom metodom.[4,13,14,15,16] Rezultati ispitivanja u grupi sa periočipom su bili izraženiji kada je on zamenjen u džepu svakih 3 meseca.[4,14] Pored toga, sredstva sa lokalnim oslobađanjem leka se mogu primeniti i u toku faze održavanja postignutih terapijskih rezultata, kada dolazi do poboljšanja ostalih kliničkih znakova parodontopatije.[15]

development of bacterial resistance.[23] Several different local drug delivery systems have been developed and used in controlled clinical trials, including antibiotics (tetracycline, minocycline), metronidazole and chlorhexidine.

Due to the infective nature of periodontal disease several local devices have been used to overcome the limited efficacy of convencional periodontal treatment. Pocket irrigation with antibacterial agents, such as chlorhexidine solution, is less effective in the treatment of periodontitis becuse it has been short term end episodic.[7] Local, reversibile side effects to chlorhexidine mouthrinse use for more than 2 weeks may occur, primarily brown staining of the teeth, tongue and transient impairment of taste perception and some cases of allergic reactions (erosions of oral mucosa and parotid gland) swelling. [23] For that reason, these side effects limit its long term of application.

At first, there were numerous nonbiodegradable systems for subgingival use such as: acrylic strips, ethylcelulous polimer films, ethyl-vinil acetate strips and monolythic fibers. Disadvantages of nonbiodegradable systems are: a long aplication time and uncomplete delivery of antimicrobial agent. Removing these systems have to be complete because residual particles may induce systemic effects. Because it is biodegradable, the chlorhexidine chip does not have to be removed. Additionally, the subgingival bacterial flora were markedly supressed, effects which were evident up to 11 weeks after administration.[13,14] The duration of pocket exposure to the drug is probably the most critical factor in determing the efficacy of treatment. The sustained exposure of the pocket enviroment to chlorhexidine for 3 days showed a short-term antibacterial effect. [25] However, a continious 6 to 9 day exposure gave long-lasting antibacterial and clinical results. [4,7] Tetracycline seems to require a similar time of exposure. [8]

The most frequent adverse events observed in the chlorhexidine chip treatment group were discomfort, pain, local irritation,toothache, aching, throbbing and gingival oedema.Gingival abscessus were found [16], however, this side effect was minor and transient, with resolution usually complete within a few days, and requiring no intervention or medication.

The results of previous studies therefore have showed the chlorhexidine chip was an effective adjunct to SRP in the treatment of periodontal disease. [4,13,14,15,16] These additional benefits were even more evident when the chip was replaced every 3 months during maintenance phase therapy. [4,14,15]

Literatura / References

1. *Haffajee AD,Cuggini MA, Didbart S et al.*The effect of SRP on the clinical and microbiological parameters of periodontal diseases. *J Clin Periodontol* 1997;24:324-33
2. *Cuggini MA, Haffajee AD, Smith C et al.*The effect of SRP on the clinical and microbiological parameters of periodontal diseases,12 month results. *J Clin Periodontol* 2000;27:30-6
3. *Rabbani GM, Ash MM, Caffesse RS.* The effectiveness of SRP in calculus removal. *J Periodont*1981;52:119-23
4. *Soskolne WA, Heasman PA, Stabholz A et al.* Sustained local delivery of chlorhexidine in the treatment of periodontitis: a multi- center study. *J Periodontol* 1997;68:32-8
5. *Loeshe WJ.* The antimicrobial treatment of periodontal disease: Changing the treatment paradigm. *Crit Rev Oral Biol Med* 1999;10:245-75
6. *Greenstein G.* Effects of subgingival irrigation on periodontal status. *J Periodontol* 1987 ; 58:827-36
7. *Banting D, Bosma M, Bollimer B.* Clinical effectiveness of a 0.12 % chlorhexidine mouthrinse over two years. *J Dent Res* 1989 ; 68(Spec.Issue): 1716-8
8. *Goodson JM, Haffajee A. Socransky S.S.*Periodontal therapy by local delivery of tetracycline. *J Clin Periodontol* 1979;6:83-92
9. *Drisko CL, Cobb CM, Killoy WJ et al.* Evaluation of periodontal treatments using controlled – release tetracycline fibers: Clinical response. *J Periodontol* 1995; 66: 692-9
10. *Ainamo J, Lie T, Ellingsen BH et al.* Clinical responses to subgingival application of metronidazole 25% gel compared to the effect of a subgingival scaling and root planning in adult periodontitis. *J Clin Periodontol* 1992; 19: 723-9
11. *Van Steenberghe, Bercy P, Kohl Jet al.*Subgingival minocycline hydrohloride ointment in moderate to severe chronic adult periodontitis: a randomized, double – blind, vehicle controlled, multicenter study.*J Periodontol* 1993;64:637-44
12. *Larsen T.* In vitro release of doxycicline from bioabsorbable materials and acrylic strips. *J Periodontol* 1990;61: 30-4
13. *Soskolne WA, Chajek T, Flasher M et al.* An in vivo study of the chlorhexidine release profile of the periochip ™ in the gingival crevicular fluid, plasma and urine. *J Clin Periodontol* 1998 ; 25: 1017-21
14. *Jeffcoat MK, Bray KS, Ciancio SG et al.* Adjunctive use of a subgingival controlled-release chlorhexidine chip reduces probing depth and improves attachment level compared with scaling and root planning alone. *J Periodontol* 1998; 69:989-97
15. *Heasman PA, Heasman L, Stacey F et al.* Local delivery of chlorhexidine gluconate (PerioChip ™) in periodontal maintenance patients. *J Clin Periodontol* 2001;28:90-5
16. *Grisi DC, Salvador SL, Figueiredo LC et al.* Effect of a controlled- release chlorhexidine chip on a clinical and microbiological parameters of periodontal syndrome. *J Clin Periodontol* 2002; 29: 875-81
17. *Jones CG.* Chlorhexidine: is it still the gold standard? In Addy M.,Moran J.M.,eds.Toothpaste, mouth rinse and other topical remedies in periodontics.*Periodontology* 2000; 15:55-62
18. *Jenkins S, Addy M, Wade W.* The mechanism of action of chlorhexidine: a study of plaque growth on enamel inserts in vivo.*J Clin Periodontol* 1988;15:415-24
19. *Schiott, CR, Löe H, Jensen SB et al.* The effect of chlorhexidine mouthrinses on the human oral flora. *J Periodont Research* 1970;5:84-9
20. *Stanley A, Wilson M, Newman HN.* The in vitro effects of chlorhexidine on subgingival plaque bacteria. *J Clin Periodontol* 1989;16:259-64
21. *Loeshe WJ, Bretz WA, Lopatin D et al.*Multicenter clinical evaluation of a chairside method of detecting certain periodontopathic bacteria in periodontal disease. *J Periodontol* 1990;61:189-96
22. *Newman MG, Korman KS, Doherty WM.* A 6-month multi center evaluation of adjunctive tetracycline fiber therapy used in conjuction with scaling and root planning in maintenance patients: clinical results. *J Periodontol* 1994;65:685-91
23. *Lindhe J, Karring T, Lang NP.* Klinička parodontologija i dentalna implantologija,Zagreb: Nakladni zavod globus, 2004: 476-87
24. *Goodson JM.* Antimicrobial strategies for treatment of periodontal diseases. *Periodontol* 2000 1994; 5; 142-168
25. *Soskolne A, Golomb G.* New sustained release dosage form of chlorhexidine for dental use.Use in periodontal therapy. *J Periodont Res* 1982;17:323-8

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