

Therapeutic effects of local drug delivery systems - PerioChip® in the treatment of periodontal disease

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Abstract

The primary goal of periodontal treatment is to stop periodontal disease progression and reduce future risks in disease recurrence. In order to overcome the limitations of the conventional treatment, controlled drug delivery systems for application in periodontal pockets have been developed. Their use offers several advantages: the therapeutic agent is targeted directly to the disease site and concentrations are 10-100 folds higher than the concentrations achieved by systemic administration, with low incidence of side effects.

The PerioChip® is a local controlled-release biodegradable delivery system containing chlorhexidine digluconate. Several multicenter clinical trials have shown that the application of the PerioChip® in periodontal pockets as adjunct to the conventional periodontal treatment significantly improved the clinical parameters. In this article, the results from controlled clinical studies aimed to evaluate the clinical and microbiological efficacy of the PerioChip®, are discussed.

Keywords: periodontal disease, local controlled-release delivery systems, PerioChip®

Introduction

Chronic periodontal disease is an infectious disease characterized by progressive attachment loss, bone loss, periodontal pocket formation and/or recession of the gingiva which is a result of the host's response to a periopathogenic bacterial infection (Kalsi et al., 2011). It is well known that periodontal disease disturbs the integrity of oral mucous membranes. In this way periodontal pathogens can enter the circulation causing serious health problems such as septicemia, organ abscesses, endocarditis, coronary artery disease, cerebrovascular diseases and stroke. Undoubtedly, periodontal disease is a major burden and oral health

is a WHO priority topic in the 21st century (Petersen et al., 2005; Petersen, 2005).

The main goal of periodontal therapy is to restore the homeostatic relationship between the periodontal tissue and its polymicrobial dental-plaque community (Darveau, 2010). This includes elimination of periodontal pathogens, halting disease progression, obtaining host healing and gain in clinical attachment level. The oldest and most widely applied periodontal treatment, scaling and root planning (SRP), consists of mechanical removal of dental plaque, calculus and stain from the roots and crown of teeth (Tariq et al., 2012). Clinical investigations have shown that SRP effectively reduces the microbial levels in periodontal pockets and improves clinical parameters such as bleeding on probing; probing depths and clinical attach-

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ment level (Haffajee & Socransky, 2005). However, this procedure can be often difficult to perform due to the complex and unfavorable root morphology in deep periodontal pockets, it can be time consuming and unpleasant for the patient (Obeid et al., 2004). Additionally, SRP is not able to eliminate the periodontal pathogens present on oral mucous membranes or in deeper periodontal pockets where instruments are difficult to reach. In this context, it is evident that local or systemic therapy with an antimicrobial agent would be a valuable adjunct to mechanical therapy (Horz & Conrads, 2007; Darveau, 2010). Systemic antimicrobial therapy is especially important in the treatment of severe forms of periodontitis or in cases where the clinical outcome is potentially compromised by the patient's systemic health. Although this is an acceptable route of delivery for the patient, the use of systemic antibiotics is limited by the fact that doses needed to achieve therapeutic concentration of antimicrobials in the periodontal environment might be associated with undesirable side effects such as gastrointestinal disturbances, hypersensitivity and bacterial resistance (Horz & Conrads, 2007; Paolantonio et al., 2008a; Krayer et al., 2010).

Local drug delivery systems for the treatment of periodontal disease

In order to overcome the disadvantages associated with the administration of systemic antimicrobial therapy, systems for controlled release of antibiotics and antiseptics in periodontal pockets have been intensively studied. The main goal of these systems is to maintain effective drug concentrations at the site of action for adequate periods of time, despite the drug loss from gingival crevicular fluid clearance. Various local periodontal drug delivery systems have been designed: fibers, strips, films, gels and microparticles made of both biodegradable and non-biodegradable polymers (Schwach-Abdellaou et al., 2000). According to the duration of the drug release, they can be divided into two categories, "sustained release formulations", which deliver the agent for less than 24 hours and "controlled delivery devices", which release the therapeutic agent over an extended period of time (Srivastava et al., 2009). Several antimicrobial agents have been tested for their clinical and microbiological efficacy in periodontal treatment. Basically, we can distinguish two broad categories of antimicrobial agents: antibiotics such as tetracycline, doxycycline, minocycline and metronidazole and antiseptics such

as chlorhexidine.

The first local drug delivery system in periodontal treatment was Acticite™, a hollow nonabsorbable fiber containing tetracycline. Although quite effective, the placement of this system in the periodontal pockets required additional skills and a second visit to the dentist in order to be removed. The disadvantages of the non-resorbable systems led to the development of resorbable systems for antimicrobial delivery. The first resorbable local delivery system was ATRIDOX™, gel containing 10 % doxycycline hyclate. Improvements in the formulation of local delivery systems resulted in the manufacture of ARESTIN™, sustained release product containing minocycline hydrochloride and Elyzol™, 25% metronidazole gel (Krayer et al., 2010).

Compared to antibiotics, antiseptic agents have much broader spectrum of antibacterial activity due to multiple intracellular targets which reduce the possibility of development of bacterial resistance (Slots, 2002). The most widely used and studied antiseptic in oral diseases is chlorhexidine (Fig. 1)

Chlorhexidine shows high affinity towards bacteria because of the interaction between the positively charged parts of the molecule and the negatively charged phosphate groups of lipopolysaccharides on the bacterial cell walls (Attin et al., 2006). The main advantages of chlorhexidine application during SRP or surgical periodontal treatment include improved wound healing and general plaque control (Imfeld, 2006; Horz & Conrads, 2007). However, despite the advantages, the application may result in staining of the teeth, taste disturbances and increase of calculus formation (Zanatta et al., 2010).

PerioChip® is a controlled-release drug delivery system that delivers chlorhexidine in the periodontal pockets. It is the only locally applied antiseptic approved by the FDA as adjunct to SRP procedures for the reduction of probing pocket depth or as a part of a routine periodontal maintenance treatment (Ryan, 2005). PerioChip® was developed by Dexcel Pharma (Jerusalem, Israel). It contains 2.5 mg chlorhexidine digluconate in a biodegradable matrix of gelatin and glutaraldehyde which releases 40 % of chlorhexidine within the first 24 hours and the rest over the one week treatment period. While the chip is degraded, chlorhexidine is released gradually for approximately 7-10 days with concentrations above 125 µg mL⁻¹ in gingival crevicular fluid (GCF). When in situ, there is an initial burst in concentration of 2000 µg mL⁻¹ chlorhexidine in GCF. After 2-4 days the concentration of drug reaches

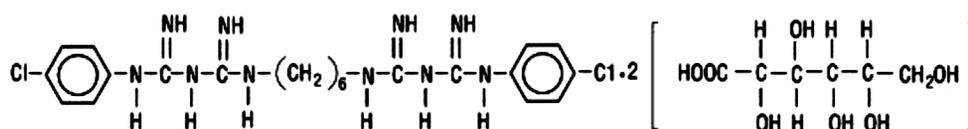


Fig. 1 Chemical structure of chlorhexidine digluconate.

1300 $\mu\text{g mL}^{-1}$ and then decreases but remains above 125 $\mu\text{g mL}^{-1}$ in the first 7 days (Soskolne et al., 1998). Another *in vivo* study on 12 patients reported chlorhexidine concentrations of 800-1000 $\mu\text{g mL}^{-1}$ in GCF in the first 48 hours after chip placement. This first burst was followed by lower concentrations of 100-500 $\mu\text{g mL}^{-1}$ in the next 6 days. Concentrations above the minimal inhibitory concentration (MIC) were observed for at least 7 days (Schwach-Abdellaou et al., 2000).

Clinical studies performed to assess the effectiveness of PerioChip® in periodontitis compared two treatment modalities: SRP as monotherapy and SRP+ PerioChip®. They were designed so that the target sites in experimental group of patients received PerioChip® whereas the same sites in the control group SRP only. Patients included in the studies were considered eligible if they had periodontal pockets ≥ 5 mm in depth that bled on probing. The clinical parameters used to evaluate the treatment were the following: plaque index, bleeding on probing, probing depth and clinical attachment level.

Soskolne et al., evaluated the safety and efficacy of the PerioChip® in a multicenter study of 118 patients with moderate forms of periodontitis. After 3 and 6 months, the selected pockets in the experimental quadrants showed significant reduction in periodontal pocket depth compared to the pockets treated with SRP only ($p < 0.0001$). Clinical attachment level showed similar, but less marketed improvement over the study period, although the gain was greater compared to the pocket that received SRP only. One year later, greater improvements were found in clinical attachment level values in the group with pockets that received SRP as the only treatment. The probing depth distribution per patient was similar in both treatment groups. There was a significant reduction in the number of sites with visible bleeding on probing, but they did not reach significant difference (Soskolne et al., 1997).

Jeffcoat et al., performed two double-blind, randomized, placebo controlled multi-center clinical trials on 447 patients. Significant reduction of probing depth at 9 months was observed in the PerioChip® group + SRP compared both with control treatment group, SRP alone and placebo chip + SRP ($p < 0.001$). A significant improvement in clinical attachment level was observed at 9 months in the PerioChip® + SRP treatment group compared to the other treatment groups ($p < 0.05$). These results in those sites that received SRP + PerioChip® were in accordance with the results reported by Soskolne et al. There was a statistically significant reduction in bleeding on probing in the control group compared to the test group at 9 months ($p < 0.05$) (Jeffcoat et al., 1998).

In a study conducted by Heasman et al., the efficacy of PerioChip® in maintenance patients was evaluated. 26 patients (non-smokers) were enrolled in the study. Important clinical parameters were recorded at baseline and after 1, 3 and 6 months. The study suggests that the application of the PerioChip® is beneficial for patients on main-

tenance therapy although the benefit is not apparent until six months after placement (Heasman et al., 2001).

In the study by Grisi et al., it was observed that the gingival recession obtained by SRP + PerioChip® treatment was greater than the one obtained by SRP alone. That may be related to greater reduction in gingival margin inflammation, as well as to the mechanical trauma caused by additional applications of the chip after 3 and 6 months. Both treatment groups presented marketed reduction in the percentage of sites with visible bleeding on probing throughout the study. The pocket depth reduction in the group treated with SRP + PerioChip® was even greater than the one observed in the studies performed by Soskolne et al., and Jeffcoat et al. The study also reported that there were no statistically significant differences between the SRP and SRP + PerioChip® groups for clinical parameters after a 9-month period. This might be due to the lack of the statistical power of the study as a result of the insufficient number of subjects enrolled which might lead to statistical errors. The overall conclusions of this study indicate that application of the PerioChip® as adjunct to SRP may be beneficial in improving clinical periodontal parameters and may help reduce the risk of disease recurrence during routine supportive periodontal treatment (Grisi et al., 2002).

Salvi et al., reported an immediate effect of PerioChip® on the total bacterial count, proposing a greater potential for reduction of bacterial colonization soon after the application of this type of local delivery system. However, Salvi reported that the dimensions of the PerioChip® may not allow efficacy in the deepest pockets; this may explain why, in the presence of thorough SRP, the deeper pockets did not show better results than all of the experimental sites together (Salvi et al., 2002).

The efficacy of PerioChip® on the clinical parameters and on GCF matrix metalloproteinase (MMP)-8 levels in chronic periodontitis patients was evaluated in the study conducted by Azmak et al. 20 patients with chronic periodontitis were screened for 6 months. In each patient, PerioChip® was inserted into a randomly selected site following scaling and root planing (SRP + PerioChip®), while the other selected site received only SRP. Probing depth, clinical attachment level, plaque index, and papilla bleeding index were recorded at baseline and at 1, 3, and 6 months. GCF MMP-8 levels were analyzed at baseline; 2 and 10 days; and at 1, 3, and 6 months. At baseline, there were no statistically significant differences in the mean probing depth, clinical attachment level, papilla bleeding index and plaque index scores between SRP + PerioChip® and SRP alone groups. At 1, 3, and 6 months, all clinical parameters in each group significantly decreased ($P < 0.0167$) when compared to baseline. The reduction of probing depth and improvement in attachment level were higher in the SRP + PerioChip® group compared to SRP alone at 3 and 6 months. However, the differences between the 2 groups were not statistically significant. Papilla bleeding and plaque index scores were not signifi-

cantly different between SRP+ PerioChip® and SRP alone groups at any visit. GCF MMP-8 levels were similar in both groups at baseline. Intragroup analysis showed significant decreases in the GCF MMP-8 level for the SRP+ PerioChip® group between baseline and 1, 3, and 6 months ($p < 0.01$). Intergroup analysis demonstrated significantly lower mean levels of GCF MMP-8 at 1 month in the SRP + PerioChip® group compared to the SRP alone group ($p < 0.05$). These data suggest that PerioChip® application following SRP is beneficial in improving periodontal parameters and reducing GCF MMP-8 levels for 6 months' duration. The use of a chairside MMP-8 dipstick periodontitis test might be a useful adjunctive diagnostic tool when monitoring the course of PerioChip® treatment (Azmaq et al., 2002).

Mizrak et al., conducted a randomized, single blind study in order to determine the effect of a PerioChip® on crevicular prostaglandin E₂ (PGE₂) levels and on the clinical and microbiological parameters of periodontitis when used as adjunctive therapy to SRP in patients with chronic periodontitis. Clinical indices, microbiological samples and GCF samples were evaluated at baseline and after 1, 3, and 6 months. Microbiological samples were evaluated under a light microscope. Significant improvements could be found for all clinical variables in both groups over the study period. The mean changes in probing depth obtained by SRP plus PerioChip® were greater than those obtained by the SRP alone group at 3 and 6 months. In the test group, there was also significant gain in clinical attachment level at 6 months. When data were combined from all groups, significant reductions in GCF PGE₂ levels and number of microorganisms were noted at all time points. However, in the test group, reduction was greater at 6 months for crevicular PGE₂ level and at 3 and 6 months for proportions of spirochetes. Based on the findings of this study, the PerioChip® reduced GCF PGE₂ levels and had positive effects on clinical parameters and subgingival flora when used as adjunctive therapy to SRP in patients with chronic periodontitis (Mizrak et al., 2006).

The objective of the study conducted by Rodrigues et al., was to evaluate the effectiveness of a PerioChip® clinically, in sites still showing signs of disease during periodontal maintenance therapy. Forty-two maintenance non-smoking patients (previously treated with SRP), presenting at least one probing depth of 5-8 mm, and bleeding on probing at single-rooted teeth were assigned randomly to two groups: treated with a PerioChip® (CHIP group) and treated with SRP (SRP group). Patients were assessed for plaque index, gingival index, bleeding on probing, probing depth, clinical attachment level and gingival recession at baseline, 6 weeks, and 3 and 6 months. Both treatments resulted in improvements in all parameters evaluated. After 6 months, a reduction in pocket depth of 2.64 +/- 0.02 mm and 2.12 +/- 0.02 mm was observed for CHIP and SRP groups, respectively ($p > 0.05$). The observed gain in CAL was 2.19 +/- 0.87 mm and 2.07 +/- 1.53 mm for CHIP and SRP groups, respectively ($p > 0.05$). In deep pockets, depth

reduction was 3.60 +/- 0.70 mm for CHIP group and 2.83 +/- 0.62 mm for SRP group ($p = 0.01$). Both treatments were equally effective in periodontal health reestablishment in inflamed single-root sites of maintenance patients. However, for deep pockets, the PerioChip® was more effective than SRP in reducing probing depth (Rodrigues et al., 2007).

A randomized, single-blind, controlled, split mouth study conducted by Paolantonio et al., investigated the effects of PerioChip® on the clinical parameters and the levels of alkaline phosphatase in GCF. The results from the controlled study confirmed significant reduction of pocket depth with administration of the PerioChip®; this treatment yielded significantly lower pocket depth values at the 6-month evaluation in comparison with SRP alone. Similar trends were observed for clinical attachment level. These results suggest that the PerioChip® can be used to improve clinical results obtained by SRP (Paolantonio et al., 2008a).

In order to provide with further data on clinical and microbiological effects of PerioChip® when used as an adjunct to SRP, a multicenter study, by Paolantonio and co-workers, was carried out at four Italian universities. The main clinical effects of periodontal treatment depend mainly on a reduction in the subgingival bacterial mass. In this regard, an effective subgingival chemical device is expected to affect the amount and/or the composition of the subgingival microbiota. In the present study, the SRP + PerioChip® treatment resulted in total bacterial count that was significantly lower than that of SRP alone at 15 days and after 1 month of therapy. In conclusion, the adjunctive use of PerioChip® with SRP resulted in a clinically meaningful improvement in pocket depth reduction and clinical attachment gain compared to SRP alone. These results were concomitant with the significantly greater effect that the SRP + PerioChip®, treatment exerted on the subgingival microbiota compared to SRP alone. These clinical and microbiological effects were obtained by a single episode of chip placement inside the periodontal pocket (Paolantonio et al., 2008b).

In a study performed by Machtei et al., the safety and efficacy of frequent application of the PerioChip® and Flubiprofen Chip® (FBP) in chronic periodontitis patients was examined. The frequent application of PerioChip® and FBP Chips resulted in a pocket depth reduction, gain in clinical attachment level and decrease in bleeding on probing. The PerioChip® gave greater response compared to FBP chip. The principal findings of this study would tend to suggest that if both chips are used consecutively or simultaneously, it might result in even greater improvement in clinical parameters compared to when each of them is used individually (Machtei et al., 2011).

The efficacy of the PerioChip® for a period of three months has been analyzed by Puri and coworkers. The three month interval was chosen because of the effects of locally delivered chlorhexidine which has been shown effective for eleven weeks and 3 months corresponds to a

typical recall interval for patients after periodontal treatment. In this study, the higher improvement in the clinical parameters was found to be attributed to PerioChip®, which is known to inhibit microbial proteases from periodontal pathogens, which play a key role in the destruction of periodontal tissues during disease progression. Although, the use of systems for local delivery does not replace the need for SRP, the use of the PerioChip® along with SRP represents a simple and non-invasive technique adjunctive to classical treatment. In addition it reduces and delays the recurrence of periodontal pathogens in periodontal pockets (Puri et al., 2013).

Jagadish et al., evaluated the efficacy of two chlorhexidine containing systems for local delivery, namely EC40 CHX varnish and PerioChip®, over SRP for a period of three months. The study indicated that the application of the PerioChip® as adjunct to SRP produced clinically significant reduction of pocket depth, bleeding on probing and gains in clinical attachment level compared to baseline although the results weren't statistically significant. However, the small sample size and a single application/insertion of the PerioChip® could be considered as limitations of this study (Jagadish et al., 2013).

Overall, PerioChip® application has a well documented safety profile and does not cause any visible staining of the teeth. The most frequently observed adverse effects in clinical trials were mild to moderate toothache which resolved spontaneously in most cases and required no further medical treatment (Ryan, 2005).

Summary

The adjunctive use of controlled-release drug delivery systems represents a valuable treatment modality which improves the effects of the conventional periodontal treatment.

The results from numerous studies have shown that the application of the PerioChip® results in markedly suppressed subgingival bacterial flora, with effects evident up to 11 weeks after administration. The additional benefits are even more evident when this local drug delivery system is replaced every 3 months, during the course of maintenance phase therapy. Therefore, the use of the PerioChip® as adjunct to SRP represents a simple and non-invasive treatment modality to enhance periodontal health. Furthermore, the platform of the PerioChip® provides a technology of delivering other chemotherapeutic agents in the periodontal pockets.

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Резиме

Терапевтски ефекти од примената на системи со контролирано ослободување за локална апликација - PerioChip® во третманот на пародонталната болест

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Клучни зборови: пародонтопатија, формулации со контролирано ослободување за локална апликација, PerioChip®

Основната цел на третманот на пародонталната болест е да се запре прогресијата на болеста, како и да се спречи нејзина повторна појава. Со цел да се надминат ограничувањата на конвенционалниот третман, развиени се формулации со контролирано ослободување наменети за локална апликација во пародонталните џебови. Примената на овие формулации нуди низа предности: терапевтскиот агенс се ослободува во пародонталниот џеб со што се постигнуваат концентрации 10-100 пати повисоки од оние кои би се постигнале по системска администрација на истиот и истовремено значително е намалена појавата на несакани ефекти.

PerioChip® претставува формулација со контролирано ослободување која содржи хлорхексидин диглуконат. Голем број на мултицентрирани клинички студии покажуваат дека апликацијата на PerioChip® заедно со конвенционалниот третман резултира со значително подобрување на клиничката слика. Во овој труд ќе биде направен преглед на резултатите од контролирани клинички студии што ги проценуваат клиничките и микробиолошките ефекти од примената на PerioChip®.