A Systematic Review on the Effects of the Chlorhexidine Chip When Used as an Adjunct to Scaling and Root Planing in the Treatment of Chronic Periodontitis

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Background: Several local antimicrobial agents, such as a bioabsorbable chlorhexidine chip, have been developed to enhance the outcome of non-surgical periodontal therapy.

Methods: Electronic (MEDLINE and Cochrane Oral Health Group Specialized Trials Register) and manual searches were performed to detect studies concerning the use of the chlorhexidine chip as an adjunct to scaling and root planing in the treatment of chronic periodontitis. Only full-text randomized controlled trials published in English up to June 2005 were included.

Results: Five studies were finally selected following independent screening by two reviewers. Due to considerable heterogeneity in study design, a qualitative data analysis was performed. Multicenter studies have indicated significantly higher pocket reductions and clinical attachment gains following a combination of mechanical debridement and repeated chlorhexidine chip administration in comparison to scaling and root planing alone. However, some recent studies failed to confirm the additional value of the chlorhexidine chip. A number of interstudy disparities with respect to methodological quality and study design may account for this lack of accordance.

Conclusions: The clinical and microbiological data currently available on the chlorhexidine chip are limited and conflicting. More research is needed to elucidate the additional value of the chlorhexidine chip when used as an adjunct to scaling and root planing. *J Periodontol 2006;77:257-264.*

KEY WORDS

Chlorhexidine; dental scaling; periodontitis; root planing; subgingival; systematic review.

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Scaling and root planing (SRP) are effective means of treating and controlling periodontitis.[1-6] However, the ability of the therapist to gain access to deep pockets or furcations often results in a substantial variation in its effectiveness.[7-9] Consequently, this has led to the adjunctive use of antimicrobials, assuming that chemical aids would compensate for technical limitations and prevent early microbial recolonization to ultimately ensure the best chance for clinical improvements. Even though systemic and locally applied antibiotics have been proven to be effective, the risk of developing bacterial resistance is a contraindication for using them routinely.[10-14] Topical antiseptics, among which chlorhexidine (CHX) remains one of the most effective ones reported to date, have been successfully used for treating plaque-related gingivitis.[15-17] However, subgingival irrigation using CHX solutions or even CHX gels turned out to be poorly effective in the treatment of periodontitis, presumably due to the inability to retain biologically significant concentrations of the drug for sufficient lengths of time within the confines of the periodontal pocket.[18-23] Hence, "slow-release devices" have been developed, among which are "sustained-release devices" delivering the drug for <24 hours and "controlled-delivery devices" (CDDs) releasing the agent over

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an extended period of time.[24] In the early 1980s, the first slow-release device containing CHX incorporated in a non-degradable matrix was introduced. Studies on release kinetics[25] and "proof of principle" when using the vehicle as an adjunct to SRP[26-29] and conventional maintenance therapy[30] were published. A second-generation slow-release device, notably a bioabsorbable chip containing 2.5 mg CHX in a cross-linked hydrolyzed gelatin matrix,† was developed and pharmacokinetically tested in vitro.[31] When placed in an isolated pocket, the chip serves as a CDD slowly releasing its CHX while simultaneously biodegrading, maintaining over a 7 to 10 day period an average concentration of <125 μg/ml in the crevicular fluid[32] reported to be inhibitory to 99% of bacteria isolated from periodontal pockets.[33,34]

Studies have been published evaluating the effectiveness of the CHX chip when used as an adjunct to SRP. This study addressed the question of whether there is sufficient evidence to support the administration of the CHX chip, adjunctive to SRP, as a means to enhance the treatment outcome of initial periodontal therapy.

METHODS

Study Selection

Only full-text randomized controlled trials (RCTs) published in English were considered. Furthermore, studies had to be based on chronic periodontitis patients. To be as inclusive of articles as possible, neither age limits nor study duration were considered as selection criteria. Study protocols had to enclose comparative clinical data on SRP alone and a combination of SRP followed by the administration of the CHX chip.

Outcome Variables

The primary outcome variables were changes in probing depth (PD) and clinical attachment level (CAL). Microbiological effects also were scrutinized.

Search Strategy

An electronic search was performed in the MEDLINE and Cochrane Oral Health Group Specialized Trials Register databases, using June 2005 as the final date. The selection strategy was based on a combination of *types of studies* AND *disease* AND *therapy*, using free text words. MeSH terms (*) were adopted for the MEDLINE search.

Types of Studies

Longitudinal studies* OR comparative study* OR clinical trial* OR controlled clinical trial* OR randomized controlled trial*.

Disease

Periodontitis* OR periodontal diseases*.

Therapy

(((Chlorhexidine* OR chlorhexidine gluconate*) AND (chip OR slow-release OR controlled-release)) OR (periochip OR perio chip)) AND (subgingival curettage* OR dental scaling* OR root planing* OR dental prophylaxis*).

To minimize publication bias, a complementary manual search that included a revision of the past two decades up to June 2005 was made of the following journals: *Journal of Periodontology*, *Journal of Clinical Periodontology*, and *Journal of Periodontal Research*. Additionally, reference lists of the retrieved articles were scrutinized following a preliminary selection by the electronic and manual search.

Assessment of Methodological Quality

The methodological quality of the papers was assessed, mainly focusing on four points: the adequacy of the method of randomization, the allocation concealment, the existence of blinding, and the existence and management of lost cases.

Qualitative Data Analysis

Considerable heterogeneity in experimental characteristics was found after a preliminary evaluation of the selected articles. Consequently, a quantitative synthesis by means of a meta-analysis was not possible. Therefore, an attempt was made to tabulate the data from a descriptive point of view.

RESULTS

Search Results

All search strategies resulted in the identification of 54 publications. Independent screening by two reviewers (JC and IW) led to the rejection of 49 articles for the following reasons: only abstract and no full-text available;[35-40] follow-up instead of randomized controlled study;[41,42] case series instead of randomized controlled study;[43] interim reports presenting preliminary data that are also implemented in larger studies;[44,45] published in Chinese;[46] evaluation of other treatment regimens;[47-68] administration of the first generation slow-release non-degradable chip;[26-28,30] use of the CHX chip prior to periodontal regeneration;[69] application of the CHX chip during supportive periodontal care;[70,71] pharmacokinetic evaluation of the CHX chip;[31,32] report describing ease of use of the chip;[72] economic evaluation of a CHX chip implemented treatment strategy;[73,74] and narrative reviews.[75-77]

The Cohen's κ value for interreviewer agreement for study inclusion was 0.88 (P <0.001; 95% confidence interval [CI]: 0.64 to 1.12) indicating strong agreement. Disagreement was resolved by discussion, which finally led to five eligible publications.

Methodological Quality of Included Studies

In only one study, the method of randomization was provided and found adequate.[78] The allocation concealment was not described in any of the papers.

† PerioChip, Perio Products, Jerusalem, Israel.

Double blinding was achieved in three studies.[78-80] Single blinding was assumed in two studies knowing that masking for the patient may not have been possible given the nature of parallel-designed trials.[81,82] In four studies, patients were lost during the follow-up period.[78,79,81,82] Statistical analysis took into account the losses to follow-up in two studies.[79,81] In one study, this issue remained unclear.[78] In addition, data analysis was found inaccurate in one study that ignored the fact that response parameters measured on different occasions are repeated measures from a statistical point of view.[82]

Only two studies employed a model of parallel groups of independent patients,[81,82] whereas the other three used an intrasubject split-mouth design.[78-80] Needless to say, sites within a patient are not completely independent. Furthermore, there is variation in the number of sites used to evaluate treatment effects, ranging from one site[78,80] to multiple sites.[79,81,82] Including multiple sites per patient for each treatment can be considered a prerequisite for a proper study. Indeed, Timmerman et al.[83] indicated that data derived from one site may not be representative. Cautiousness in data interpretation seems imperative knowing that study populations were small in all but the multicenter studies (N < 30) and thereby compromising statistical power.[78,80,82] Study populations were well defined in all papers presenting the age range of the patients. In all but one study,[80] long-term clinical effects were reported. In one paper, no longitudinal clinical data were available on the primary outcome variables PD and CAL.[80] Microbiological tests were conducted in only two studies.[80,82] These tests consisted of bacterial culturing[80] and the N-benzoyl-DL-arginine-naphthylamide (BANA) test.[‡,82]

Clinical and Microbiological Findings

Table 1 shows the experimental characteristics and principal findings of five RCTs evaluating the surplus value of the CHX chip when used as an adjunct to SRP in ≥5 mm pockets in comparison to SRP alone. Large-scale multicenter studies were conducted in Europe and the United States in which the clinical efficacy and safety of the CHX chip were assessed.[79,81] Over a 6- to 9-month period, the use of the CHX chip in conjunction with SRP significantly reduced PD more than mechanical debridement alone: 0.46 mm additional pocket reduction favoring the test group in the study by Soskolne et al.[79] and, respectively, 0.30 mm in the study by Jeffcoat et al.[81] The improvements in CAL followed a similar course, yet, to a smaller extent, resulting in a significant additive gain of 0.16 mm in favor of the CHX chip.[79,81] Analogue results were found when a comparison was made between a placebo chip and the active chip pointing to a significant additional pocket reduction of 0.26 mm and, respectively, clinical attachment gain of 0.20 mm in favor of the latter.[81] To substantiate the clinical relevance of these results, the proportion of pockets showing a pocket reduction of ≥2 mm after 6 to 9 months was calculated: Soskolne et al.[79] reported 35.4% for the test group versus 21.3% for the control group and Jeffcoat et al.[81] reported 19.1% and 8.0%, respectively. Considering safety, most adverse effects were minor in nature, of short duration, and generally occurred at a similar incidence in the different treatment groups.[79,81]

In a single-center survey of 6 months, a trend toward higher pocket reductions and improvements in CAL for the test group was described, although without statistical consolidation.[78]

Furthermore, an exploratory study by Daneshmand et al.[80] failed to show a significant difference in total colony counts following cultivation after 2 and 4 weeks between sites treated with the CHX chip after SRP and those managed by mechanical debridement alone. In addition, there were no significant intergroup differences with respect to the proportion of three key periodontopathogens.

These results seem to be in accordance with those published by Grisi et al.[82] reporting long-term clinical and microbiological observations by using the commercially available BANA-test. A significant reduction in the proportion of BANA positive sites was found for both treatment strategies, although without intergroup differences at 3 and 9 months. Interestingly, at 6 months, the results favored the control group (25% more reduction of BANA positive sites). Furthermore, there was a trend toward higher pocket reductions in favor of the control group at all times. The latter even expressed a significantly greater improvement in CAL at 3 and 6 months in comparison to the test group (1 mm additional clinical attachment gain).

DISCUSSION

Despite the fact that CDDs ensure high subgingival levels of CHX maintained for a prolonged period of time, the treatment outcome of a CDD-implemented treatment strategy remains fairly disappointing in comparison to SRP alone. This observation might be a reflection of the extraordinary biochemical conditions reigning within the confines of the periodontal pocket.

The effectiveness of CHX as an active agent has been well established when used as a mouthrinse.[15-17] However, more research is needed to determine its antiseptic value in the subgingival area. Indeed, conflicting results have been published. Some papers described a low subgingival substantivity of

‡ Perioscan, Oral B Laboratories, Belmont, CA.

Table 1.

Experimental Characteristics and Results of RCTs Evaluating the Surplus Value of the CHX Chip as an Adjunct to SRP (results derived from tables and/or figures)

Author	Concept	N	Age (years)	Length of Study (months)	Experimental Sites (total amount and selection criteria)	Time Scheduled for SRP	CHX Chip Application Interval	Clinical Results*		Microbiological Results
								PD (mm)	CAL (mm)	
Soskolne et al.[79]†	Intrasubject split-mouth	118, 24‡	30 to 65	6	959 pockets (≥1 pocket/ modality/subject), PD = 5 to 8 mm, BOP	1 hour (full-mouth)	At baseline and 3 months if PD ≥5 mm	1 month: –0.04 3 months: 0.28‖ 6 months: 0.46‖	1 month: –0.04 3 months: 0.08 6 months: 0.16¶	–
Jeffcoat et al.[81]†	Intersubject parallel placebo chip controlled	447, 28‡ Test: 225, 14‡§ Control: 222, 14‡#	30 to 79	9	1,788 pockets (4 pockets/subject), PD = 5 to 8 mm, BOP	1 hour (full-mouth)	At baseline and 3 and 6 months if PD ≥5 mm	1 month: ? 3 months: 0.07 6 months: 0.17¶ 9 months: 0.30‖	1 month: ? 3 months: 0.01 6 months: 0.04 9 months: 0.16¶	–
Azmak et al.[78]	Intrasubject split-mouth	22, 2‡	36 to 62	6	44 pockets (1 pocket/ modality/ subject), mesial sites of anterior teeth: PD = 6 to 8 mm, BOP	5 minutes per tooth	1× at baseline	1 month: –0.05 3 months: 0.30 6 months: 0.30	1 month:–0.05 3 months: 0.35 6 months: 0.10	–
Daneshmand et al.[80]	Intrasubject split-mouth	13	30 to 79	1	26 pockets (1 pocket/ modality/subject), bilateral pockets: PD = 6 to 7 mm	3 hours (full-mouth)	1× at baseline	1 month: ?	1 month: ?	Cultivation at baseline, 2 weeks, and 1 month: no significant differences
Grisi et al.[82]	Intersubject parallel	20, 1‡ Test: 10 Control: 10, 1‡	35 to 56	9	84 pockets (≥4 pockets/subject), PD ≥5 mm, BOP	?	At baseline and 3 and 6 months if PD ≥5 mm	1 month: ? 3 months: –0.20 6 months: –0.30 9 months: –0.10	1 month: ? 3 months: –1.0‖ 6 months: –1.0‖ 9 months: –0.40	BANA* positive sites: –25%¶ at 6 months

BOP = bleeding on probing; ? = unknown.
* Intergroup difference: positive value in favor of SRP + CHX chip and negative value in favor of SRP alone.
† Multicenter study.
‡ Number of premature terminations.
§ Half managed by SRP + CHX chip and half by SRP alone.
‖ Intergroup differences: $P \leq 0.005$.
¶ Intergroup differences: $0.005 < P \leq 0.05$.
# Half managed by SRP + placebo chip and half by SRP alone.

CHX due to its poor adherence to root surfaces[84] and/or its high affinity for salivary or serum proteins and blood.[85-89] Moreover, there is some evidence that *Porphyromonas gingivalis* releases vesicles that bind to and inactivate CHX, protecting themselves and other bacteria from the agent.[90] However, it has also been reported that CHX can inhibit microbial proteases from potent periodontopathogens such as *Tannerella forsythensis*, *Treponema denticola*, and *Actinobacillus actinomycetemcomitans*.[91] Furthermore, Oosterwaal et al.[92] described a 99% reduction in periodontal pathogens when a 2% CHX gel was applied three times within 10 minutes in periodontal pockets. In this regard, not only the active agent should be questioned, but also the limitations of the vehicle itself should be properly addressed. Indeed, Salvi et al.[71] described that the dimensions of the CHX chip wafer may not allow efficacy in deep pockets. This view should be further investigated.

Multicenter trials have proven the effectiveness of the CHX chip in conjunction with SRP.[79,81] However, some recent studies failed to confirm these

results.[78,80,82] The following interstudy disparities with respect to methodological quality and study design may explain the conflicting results: first, the time scheduled for full-mouth SRP ranged from 1 hour in both multicenter trials to 3 hours in the study published by Daneshmand et al.[80] Assuming equally skilled and experienced clinicians among the trials, this time disparity may have induced a quality difference in mechanical debridement. Hypothetically, SRP was performed close to an optimal level in the single-center trials. Consequently, benefits would almost completely be the result of SRP alone, making every additive effect due to the CHX chip practically impossible to detect. Concurrently, the CHX chip may have compensated for less effective SRP in the large-scale multicenter trials. Unfortunately, because the effectiveness of mechanical debridement is a methodological variable that is fairly impossible to control in a clinical situation, it is very difficult to study the validity of this hypothesis. Further, test pockets with a residual PD ≥5 mm were not always equally dealt with at 3-month intervals. In the study by Azmak et al.,[78] the chip was once inserted at baseline, whereas in the other studies reporting long-term clinical effects,[79,81,82] residual test pockets were systematically retreated every 3 months using the CHX chip. In addition, management of residual control pockets differed among these trials. Grisi et al.[82] subjected them to corrective SRP, whereas Soskolne et al.[79] did not expose residual control sites to additional therapy. Jeffcoat et al.[81] also left these sites untreated or subjected them to placebo chips. This disparity in pocket management might become important taking into account that the clinical course of residual test pockets subjected to CHX chip insertion every 3 months could have been favored over non-treated residual control sites, even if one assumes that the CHX chip was ineffective. Indeed, by mechanically reinfiltrating and inserting a chip at non- or weakly responding sites, the biofilm would be disrupted, resulting in a temporary stagnation of the clinical status of these test sites or even in improvement, depending on the quality of corrective SRP and possible pharmacodynamic properties of the chip. Finally, the initial PD differed markedly among the trials: Grisi et al.[82] reported fairly low mean baseline values of 5.2 mm in contrast to the other studies (range: 5.63 to 7.07 mm). This observation might become imperative, taking into account that deeper sites have a higher potential for clinical improvements leaving more margin for differences to be detected.[71,93] Thus, more high-quality large-scale RCTs are needed to elucidate the additional value of a single application of the CHX chip as an adjunct to SRP. The effects of mechanical debridement at weakly responding sites should be properly studied by comparing a combination of repeated SRP and CHX chip administrations to repeated SRP alone. In addition, fundamental microbiological research that reinforces clinical findings is essential. At present, microbiological data with respect to the CHX chip are very limited and should be interpreted with caution. Indeed, in one study, culturing was performed on only 13 samples per treatment strategy, thereby identifying three periodontopathogens.[80] In another study, the commercial BANA test was used.[82] However, a high detection limit and the ability to identify only microorganisms sharing a trypsin-like enzyme confine its diagnostic value.[94]

In general, RCTs seek effectiveness, whereas in clinical practice, efficiency is more relevant. Indeed, efficiency is primarily based on the cost-effectiveness ratio of an intervention, taking costs on such grounds as economic data, adverse effects, and ease of use into consideration. Economic reports have indicated that the CHX chip may be a cost-effective treatment option for non-surgical therapy.[73,74] Indeed, a reduction of surgical treatment needs as a result of repeated chip therapy was reported. However, it has to be anticipated that reduced surgical needs were described at the expense of a significant increased need for maintenance care in one study[73] and considerable additional financial costs in another study.[74] These facts, concomitant with a lack of unambiguous clinical results in the literature, may have prevented the general use of the CHX chip in daily clinical practice.

CONCLUSIONS

Multicenter studies have promoted the CHX chip as a valuable treatment option for chronic periodontitis. However, more RCTs providing clinical and microbiological data are needed to elucidate the surplus value of the CHX chip as an adjunct to SRP. It is not possible to make any firm clinical recommendations based on a qualitative analysis of only five studies with considerable heterogeneity in terms of study design. Yet, we emphasize that all studies confirmed the primordial importance of SRP in the treatment of chronic periodontitis. Hence, if the CHX chip were to be used, it should be preceded by thorough mechanical debridement at all times. Indeed, mechanical debridement gives the best chance of removing subgingival accretions. Furthermore, a proper disruption of the biofilm is an important prerequisite for chemotherapy.

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