Sustained Local Delivery of Chlorhexidine in the Treatment of Periodontitis: A Multi-Center Study

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The safety and efficacy of a degradable, subgingivally placed drug delivery system containing 2.5 mg chlorhexidine (CHX) were evaluated in a randomized, blinded, multi-center study of 118 patients with moderate periodontitis. A split-mouth design was used to compare the treatment outcomes of scaling and root planing (SRP) alone with the combined use of SRP and the CHX in pockets with probing depths of 5 to 8 mm. The two maxillary quadrants were used for the two treatment arms of the study. Scaling and root planing was performed at baseline only, while the CHX was inserted both at baseline and at 3 months. Clinical and safety measurements including probing depth (PD), clinical attachment level (CAL), and bleeding on probing (BOP) as well as gingivitis, plaque, and staining indices were recorded at baseline, and at 1, 3, and 6 months. The average PD reduction in the CHX-treated sites was significantly greater than in the sites receiving SRP alone at both 3 and 6 months with a mean difference of 0.42 mm ($P \leq 0.01$) at 6 months. The reduction in CAL at the treated sites was greater than at the SRP sites, although the difference was statistically significant at the 6-month visit only. An analysis of patients with initial probing depths of 7 to 8 mm (n = 56) revealed a significantly greater reduction in PD and CAL in those pockets treated with CHX compared to SRP at both 3 and 6 months. The mean differences between test and control sites at 6 months were 0.71 mm and 0.56 mm PD and CAL respectively. *J Periodontol 1997;68:32–38.*

Key Words: Chlorhexidine/therapeutic use; drug delivery systems; multi-center studies; periodontitis/drug therapy.

The treatment of chronic periodontitis focuses on arresting the destruction of the periodontal support of the teeth by eliminating the pathogenic bacteria present in the inflamed pocket. This is performed routinely in the dentist's office by mechanical scaling and root planing (SRP), in which subgingival calculus is removed together with most of the bacteria. The efficacy of this procedure is well documented.[1–4] However, variation in the ability of the therapist to gain access to deep and tortuous pockets often results in substantial variation in the effectiveness of SRP. This has led to the adjunctive use of antibacterial agents, usually in the form of irrigants or systemic antibiotics, to overcome the limited efficacy of the conventional treatment. Systemic antibiotics have proved to be effective in certain forms of chronic inflammatory periodontal disease such as juvenile periodontitis and refractory periodontitis.[5,6] The use of short-term pocket irrigation using antibacterial agents has not proven to have any lasting effect.[7,8]

Recently a new approach using local delivery systems containing antibiotic or antiseptic drugs has been introduced. These systems allow the therapeutic agents to be targeted to the diseased site with minimal systemic effects. The new approach also addresses the critical concern of unnecessarily exposing the patient to large amounts of systemic antibiotics which can result in bacterial resistance.

Several different drug delivery systems have been de-

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veloped and used in controlled clinical trials: 1) a subgingivally introduced fiber that releases tetracycline;[9–12] 2) a minocycline gel that is introduced subgingivally;[13] 3) a subgingivally injectable gel that releases metronidazole;[14–16] and 4) a subgingivally placed chip that releases chlorhexidine digluconate.[17] The latter two drugs are not antibiotics and have minimal potential for inducing bacterial resistance.[18–20]

The present study analyzes the results of a 6-month clinical trial using a recently developed degradable subgingivally placed drug delivery system[1] containing 2.5 mg chlorhexidine[21] (hereafter referred to as CHX) as an adjunct to scaling and root planing in the treatment of adult type periodontitis.

MATERIALS AND METHODS

Study Design

This was a randomized, blinded, controlled, split-mouth, multi-center study conducted at 3 centers: Royal Air Force Base, Halton, UK; Newcastle, UK; and Jerusalem, Israel, from July 1993 to November 1994. Institutional review board approval and voluntary informed patient consent were obtained at each center. The study was conducted under the guidelines of good clinical practice (GCP) as defined by the European Economic Community with pre-review of the study protocol by the British Medicine Control Agency (MCA).

Clinical measurements were carried out by a single examiner at each center. Prior to study initiation each examiner was calibrated for intra-examiner repeatability using duplicate measurements of a minimum of 50 sites in at least 5 patients. At two of the centers kappa values $>$ 0.7 were required of the examiner prior to commencing the study. At the third center the kappa statistic was not calculated but absolute agreement between measurements was obtained at 64% of the sites and agreement within 1 mm at 98% of sites. No inter-center calibration was carried out for the clinical measurements; however, scaling and root planing procedures were reviewed in a pre-study investigator training session to ensure uniformity at all centers.

Male and female patients, aged 30 to 65 years, with moderate periodontitis and in good general health were accepted into the study. At a screening visit which was scheduled for no more than 2 weeks prior to the baseline visit, general oral and full mouth periodontal examinations were carried out. Patients were considered eligible if they had at least one pocket, 5 to 8 mm in depth, that bled on probing, in each of the two maxillary quadrants.

All eligible patients received a full mouth scaling and root planing. In all instances the subgingival instrumentation was carried out after recording the baseline measurements. The two quadrants of the upper jaw were randomized to the two treatment arms using a predetermined computer generated randomization scheme; SRP alone (control quadrant) or SRP plus CHX (test quadrant). All remaining maxillary pockets with a PD between 5 to 8 mm at the baseline visit were entered into the study. CHX was inserted into each pocket of 5 to 8 mm in the designated quadrant. Clinical measurements including PD, CAL, and BOP, as well as gingivitis, plaque, and staining indices were recorded at 1, 3 and 6 months. At the 3-month visit, a full mouth supragingival prophylaxis was undertaken according to clinical needs and the CHX inserted into each test pocket that remained with 5 to 8 mm PD.

No dietary limitations were imposed during or after treatment. Normal oral hygiene procedures were permitted except for the use of chemotherapeutic mouthrinses and oral irrigation devices.

Clinical Evaluation

At the screening visit the periodontal examination was carried out with the manual North Carolina Probe. Probes were taken from the same batch to assure accuracy and consistency for all clinical measurements.[22] The measurements were carried out at four sites around each tooth (mesio-buccal, mid-buccal, disto-buccal, and mid-palatal). Impressions were taken for fabrication of acrylic stents. Based on this charting the target sites were identified and their position marked by a vertical groove on pre-prepared individualized stents to assure repeatable positioning of the probe.

At the baseline visit an oral examination was undertaken and the clinical parameters associated with the target teeth recorded. Full mouth supra-and subgingival scaling was then carried out by a hygienist. Extensive supragingival deposits, if such existed, were removed prior to the baseline visit. The total time provided for this treatment did not exceed 1 hour. Oral and periodontal examinations were carried out at baseline prior to placement of the CHX, and at 1, 3, and 6 months. The measurements were recorded on case report forms (CRFs) and double-entered into a computer.

The primary efficacy variable was PD which was measured to the nearest millimeter from the free gingival margin to the base of the pocket. Clinical attachment levels were recorded from the margin of the stent to the base of the pocket. Bleeding on probing (BOP) to the depth of the pockets,[23] a modified gingival index (GI)[24] plaque index (PI),[25] and a supragingival stain index (SI) based on a subjective score of 0 to 3 (where 0 represented no detectable stain, 1 = slight staining, 2 = moderate staining, and 3 = severe staining) were also recorded.

[1]Perio-Chip, Perio Products, Jerusalem, Israel.

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Table 1. Baseline Recordings for Probing Depths (PD), Gingival Index (GI), Bleeding on Probing (BOP), Plaque Index (PI), and Staining Index (SI)

		Clinical Indices				
Treatment	N(n)*	PD ± SE	GI ± SE	BOP ± SE	PI ± SE	SI ± SE
CHX + SRP	118 (474)	5.99 ± .05	1.42 ± .03	2.00 ± .05	0.75 ± .02	0.40 ± .03
SRP	118 (485)	6.01 ± .05	1.44 ± .03	2.03 ± .05	0.77 ± .02	0.37 ± .02

*N = number of patients; (n) = number of pockets.

Statistical Analysis

At the 1, 3, and 6 month visits the change from baseline for PD and CAL for each site was calculated. A mean value was then calculated for each treatment quadrant. The proportion of pockets per patient that were ≤ 4 mm, 5 to 6 mm, or ≥ 7 mm was calculated for each of the two treatment quadrants at the baseline, and 1, 3, and 6 month visits. In addition the proportions of sites within a patient showing an improvement from baseline, of PD or CAL of ≥ 2 mm, 1 mm, or 0 mm were recorded.

PD and CAL changes from baseline and BOP, GI, PI, and SI scores were analyzed with a univariate analysis of variance model (ANOVA). The model consisted of terms for the investigator/study site, examination visit, treatment, 2-way and 3-way interactions and patient within center. As the variance in the clinical parameters per patient changes in proportion to the number of pockets in a quadrant, weighted least squares were used to take this into account. The results reported are the estimated marginal means (least squares means) based on this model. They estimate the expected observations as if all patients and all centers had supplied equal amounts of complete data. The comparability between the two treatment groups at baseline was determined with an ANOVA model which consisted of terms for center, patient within center, treatment group, and center by treatment interaction. No statistically significant treatment differences were found to indicate an imbalance at baseline.

PD and CAL improvements were each characterized for each treatment, at each visit. A multivariate analysis of variance (MANOVA) model, identical to the ANOVA model, was used as the weighted least squares estimation. Statistical significance levels for the multivariate tests were derived from Wilk's lambda statistic. Residuals were examined to assess the suitability of the model for valid statistical inferences and it was determined that the untransformed data gave a suitable fit.

RESULTS

Of 131 patients screened 118 were found to be eligible after the baseline examination. The mean age of the patients was 47.5 years (range 30 to 65 years); 64% less than 50 years old. There were 60 males and 58 females. All eligible patients received the assigned therapy, in the predetermined quadrant, at baseline. The mean values of the clinical variables at baseline are given in Table 1. All

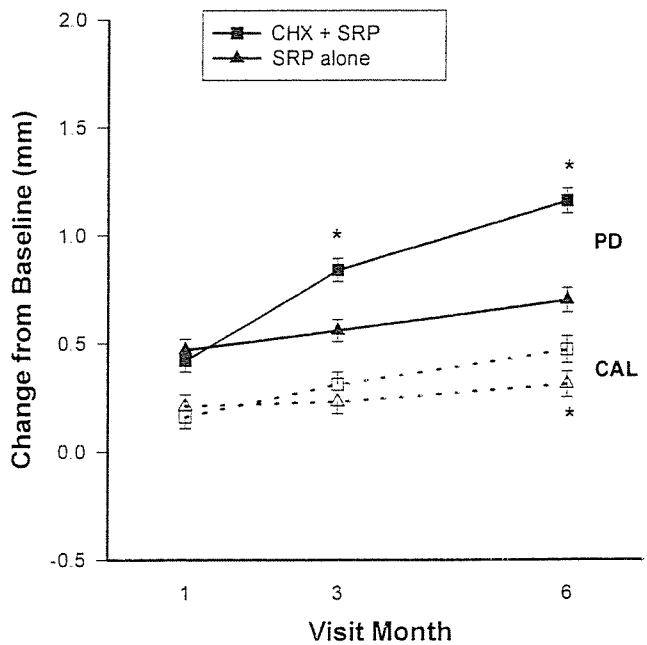

*Figure 1. Probing depth and clinical attachment level at 1, 3, and 6 months for all pockets. *Statistically significant difference between the two treatments (P ≤ 0.05).*

the patients presented for the 1-month examination, 111 for the 3-month examination and 94 for the final 6-month visit. Patients were excluded from the study due to the use of antibiotics or anti-inflammatory drugs during the study, loss to follow up, or withdrawal of consent.

A minimum of one site and a maximum of 16 sites were treated in each quadrant. The data for PD and CAL were analyzed for the total study population as well as for a subset of patients who had pockets ≥ 7 mm at baseline (n = 56). In the latter situation only data from the pockets ≥ 7 mm were used.

The mean changes in PD and CAL are shown in Figure 1. The improvement in PD at 1 month was similar for both treatments tested. At 3 months the pockets in the test quadrants showed a significantly greater reduction in PD than the pockets in the quadrants treated by SRP alone (0.84 mm ± 0.053 vs. 0.56 mm ± 0.051, $P \leq 0.0001$). At 6 months further improvement in PD had occurred at the CHX sites compared to controls (1.16 mm ± 0.058 vs. 0.70 mm ± 0.056, $P \leq 0.0001$). CAL showed a similar, but less marked, improvement over the study period. The improvement in CAL obtained with the CHX was

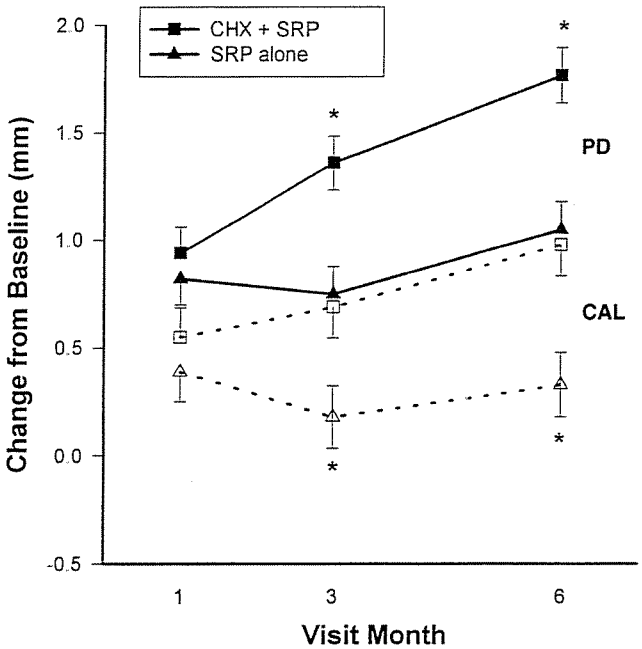

*Figure 2. Probing depth and clinical attachment level at 1, 3, and 6 months for pockets ≥ 7 mm. *Statistically significant difference between the two treatments (P ≤ 0.05).*

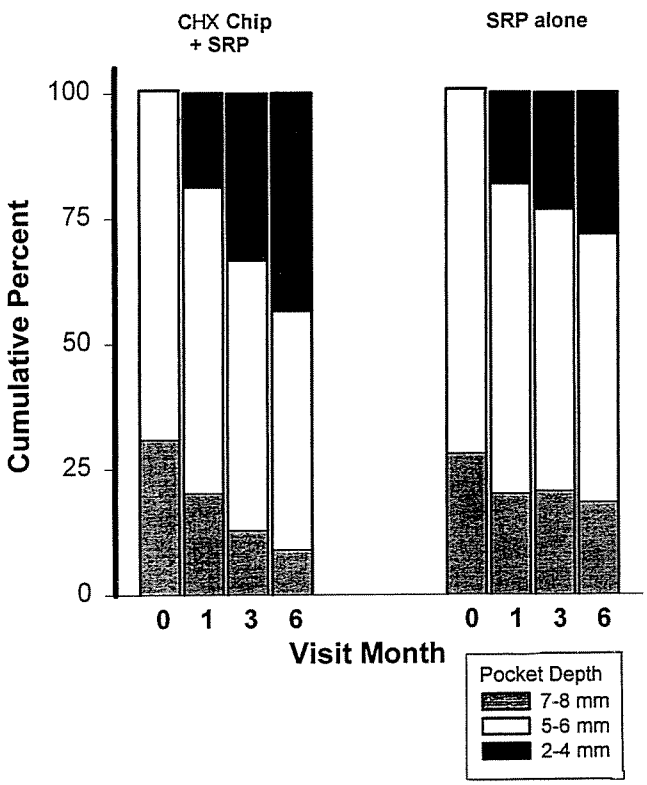

Figure 3. Distribution of probing depth at 1, 3, and 6 month examinations for all pockets.

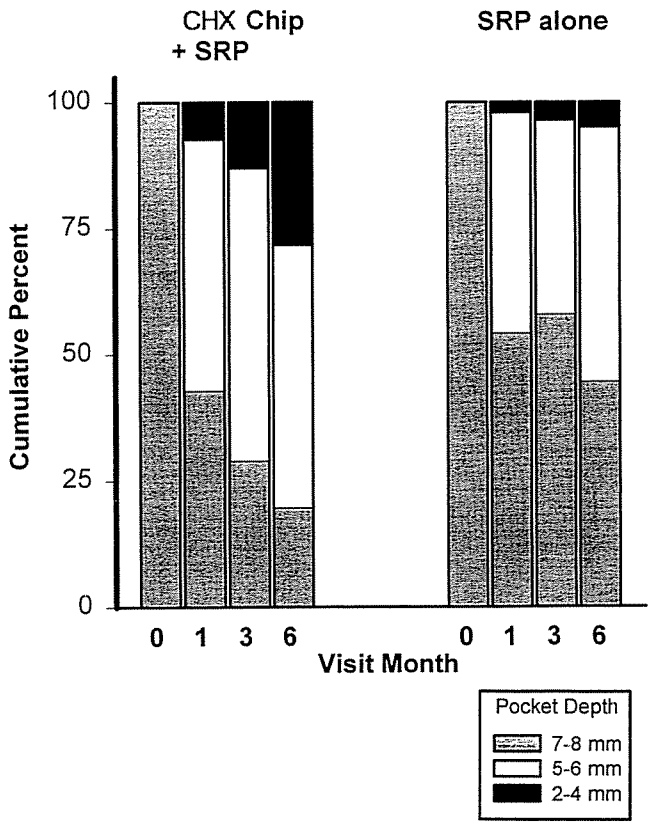

Figure 4. Distribution of probing depth at 1, 3, and 6 month examinations for pockets ≥ 7 mm.

greater than that obtained by SRP alone at 3 months (0.31 mm ± 0.057 vs. 0.23 mm ± 0.055) and 6 months (0.47 mm ± 0.062 vs. 0.31 mm ± 0.06). The differences reached significance at the 6-month visit only ($P < 0.05$).

Examination of the subset of pockets with PD ≥ 7 mm showed a similar but more marked decrease in the mean PD and CAL per patient over the treatment period with the CHX providing significantly better results than SRP alone (Fig. 2). At 3 months the mean improvement in PD was 1.36 mm ± 0.125 for the CHX versus 0.75 mm ± 0.127 for SRP alone ($P \leq 0.0003$) and at 6 months 1.77 ± 0.128 for the CHX versus 1.05 ± 0.130 for SRP alone ($P \leq 0.0001$). The mean improvement in CAL was 0.69 mm ± 0.143 for the CHX versus 0.18 mm ± 0.145 for SRP ($P \leq 0.008$) at 3 months and 0.98 mm ± 0.146 for the CHX versus 0.33 mm ± 0.149 for SRP ($P \leq 0.001$) at 6 months.

The probing depth distribution per patient at the different examinations is given in Figure 3. At baseline the probing depth distribution was similar for both treatments. As the study progressed there was a shift in the PD distribution per patient toward shallower pockets. This shift was significantly greater in the CHX-treated sites at 3 and 6 months ($P \leq 0.0001$). The subset of pockets having PD ≥ 7 mm (Fig. 4) showed a similar shift toward

Table 2. Distribution of All the Pockets in the Study

Time/Treatment	N(n)*	Changes in PD from Baseline		
		≥2 mm ± SE	1 mm ± SE	≤0 mm ± SE
1 month				
CHX + SRP	118 (474)	13.4% ± 1.8	30.7% ± 2.3	55.9% ± 2.4
SRP	118 (485)	11.2% ± 1.8	34.3% ± 2.2	54.5% ± 2.3
3 months				
CHX + SRP	111 (457)	26.1% ± 1.9	34.1% ± 2.4	39.8% ± 2.5
SRP	111 (468)	15.4% ± 1.8	32.7% ± 2.3	51.9% ± 2.4
6 months				
CHX + SRP	94 (401)	35.4% ± 2.1	34.4% ± 2.6	30.2% ± 2.7
SRP	94 (412)	21.3% ± 2.0	32.8% ± 2.5	45.9% ± 2.6

*N = number of patients; (n) = number of pockets.

Table 3. Distribution of the Subgroup of Pockets With an Initial PD of 7 to 8 mm

Time/Treatment	N(n)*	Changes in PD from Baseline		
		≥2 mm ± SE	1 mm ± SE	≤0 mm ± SE
1 month				
CHX + SRP	56 (131)	27.2% ± 4.8	31.5% ± 5.0	41.3% ± 4.8
SRP	56 (111)	20.5% ± 4.9	40.7% ± 5.1	38.8% ± 4.9
3 months				
CHX + SRP	53 (125)	44.7% ± 5.0	26.6% ± 5.3	28.7% ± 5.0
SRP	53 (107)	23.2% ± 5.1	31.1% ± 5.3	45.7% ± 5.1
6 months				
CHX + SRP	49(116)	49.5% ± 5.1	33.7% ± 5.4	16.8% ± 5.1
SRP	49(99)	32.1% ± 5.2	32.8% ± 5.5	35.1% ± 5.2

*N = number of patients; (n) = number of pockets.

shallower pockets with the difference between the two treatment groups being more dramatic.

In Table 2 the mean percent of pockets per patient showing a decrease in PD of ≥ 2 mm, 1 mm, no change or an increase in PD (≤ 0) is given. The percent of pockets per patient showing a change of ≥ 2 mm is greater in the CHX-treated pockets than in the pockets treated by SRP alone. These differences are significant at both the 3-month (26% vs. 15%) and 6-month (35% vs. 21%) visits ($P \leq 0.0001$). Table 3 shows similar changes for the subgroup of patients with initial PD ≥ 7 mm.

When the pockets showing increasing PD were separated from the group showing no PD changes, a higher percent of test pockets showed an increase in probing depth (17%) than control pockets (10%) at 1 month. At 3 months the situation was reversed with a reduction in the percent of test pockets showing deterioration (7%) while the controls remained at a constant 10%. At 6 months there was a further reduction in the percent of CHX-treated pockets showing deterioration to 4% while the controls remained at approximately the same level (9%). Again in the subset of patients with PD ≥ 7 mm a similar but more marked trend was seen with 5% of the CHX-treated pockets showing an increase in PD at 1 month, increasing to 6% at 3 months, and then decreasing to 2% at 6 months. Seven percent of the pockets that were treated by SRP only showed an increase in PD at one month, 9% at 3 months, and 6% at 6 months.

There was a small but consistent drop in the proportion of sites per patient with detectable supragingival plaque throughout the study in both the treatment groups, with no significant differences detectable between them. The mean score for bleeding on probing to the base of the pocket showed a similar small but consistent drop throughout the study for both treatment groups. The CHX group showed consistently less BOP with a significant difference between the treatment groups occurring at the 3-month examination only. The test quadrants showed a significant decrease in GI when compared to control quadrants at 3 and 6 months (Fig. 5). No changes in the SI were noted over the study period.

DISCUSSION

The results of this study show that the treatment of periodontal pockets with CHX as an adjunct to SRP provides a significantly greater improvement in PD compared to the improvement obtained with SRP alone. This adjunctive effect of the CHX is apparent at the 3-month visit and becomes even more pronounced at the 6-month visit. This indicates that the additive effect of the CHX is due to a long-term effect beyond that obtained by scaling and root planing alone. The continuing improved efficacy of the CHX compared to SRP alone through the 6-month visit must be due, at least in part, to the fact that the majority of pockets received a second application of CHX at 3 months while the controls only received a supragin-

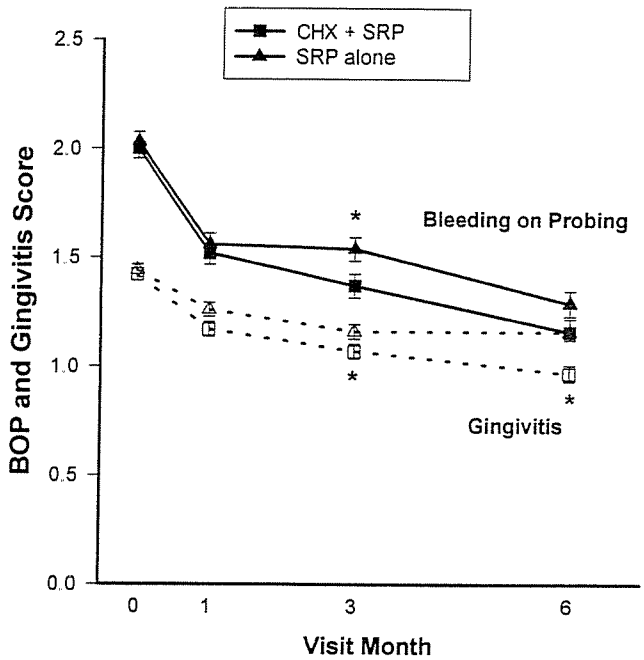

*Figure 5. BOP score and gingivitis score at each visit. *Statistically significant difference between the two treatments (P ≤ 0.05).*

gival prophylaxis. Overall the CAL measurements followed a trend similar to PD; however, they did not reach levels that could be considered clinically significant. In the deep pockets the CAL changes were statistically and clinically better in the CHX-treated pockets.

The clinical results obtained by SRP alone at the 6-month visit fall into the range of results obtained in other reports.[4,26–28] However Egelberg and Claffey,[29] summarizing studies carried out by Badersten and collaborators in which SRP was carried out with no time limit by skilled operators and under local anesthesia, showed improvements in PD and CAL greater than those obtained in the control pockets in the present study. It is well accepted that the thoroughness of the SRP, which is at least in part dependent on the anatomy of the defect and the skill of the operator, affects the resolution of pockets. In this study an attempt was made to standardize the SRP performed by the different therapists by having a calibration meeting prior to commencing the trial and by limiting the therapy time to 1 hour. It was felt that this reflected the time that is likely to be given to such therapy in an average general dental practice. When the PD and CAL changes obtained in this study are examined it is seen that the changes achieved by SRP alone (PD = 0.7 mm; CAL = 0.31 mm at 6 months for the overall group) are improved by the adjunctive use of the CHX (PD = 1.16 mm; CAL = 0.47 mm at 6 months for the overall group). The changes are comparable to those obtained by a skilled operator using local anesthesia and with unlimited time to perform the SRP.[3,29]

Studies using intrapocket delivery systems to deliver other antibacterial agents such as tetracycline, minocycline, and metronidazole[9–16] resulted in clinical changes similar to those obtained in this study. Therefore, it would seem 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 strains.[19,20]

The length of time that the pocket is exposed to the drug is probably the most critical factor in determining the efficacy of treatment. Pocket irrigation with antibacterial agents, which in most studies has been episodic and short term, have shown minimal if any response.[7,8] There is some evidence, however, that suggests that more frequent, daily, subgingival irrigation with chlorhexidine does have a more lasting effect.[30] The sustained exposure of the pocket environment to chlorhexidine for 3 days showed a short-lived antibacterial effect.[31] However a continuous 6 to 9 day exposure gave long-lasting antibacterial and clinical results.[32] Tetracycline has also been shown to need a similar time of exposure.[33] Delivery systems which release their active ingredient over short periods of time, therefore, require repeated applications.[13,16] The CHX used in this study has been shown to maintain chlorhexidine levels of ≥ 100 ppm in the gingival fluid for at least 7 days (article in preparation).

The results of this study therefore show the CHX used in this study to be an effective adjunct to scaling and root planing in the treatment of periodontal disease. It provides a safe, easily applied single dose means of achieving significantly better clinical results than SRP alone.

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