Custom tray application of peroxide gel as an adjunct to scaling and root planing in the treatment of periodontitis: A randomized, controlled three-month clinical trial

Article *in* The Journal of clinical dentistry · July 2012

Source: PubMed

2 authors, including:

Mark S Putt

Indiana University-Purdue University Fort Wa…

79 PUBLICATIONS **392** CITATIONS

SEE PROFILE

Custom Tray Application of Peroxide Gel as an Adjunct to Scaling and Root Planing in the Treatment of Periodontitis: A Randomized, Controlled Three-Month Clinical Trial

Mark S. Putt, MSD, PhD

University Park Research Center
Health Science Research Center
Indiana University-Purdue University
Fort Wayne, IN, USA

Howard M. Proskin, PhD

Howard M. Proskin & Associates
Rochester, NY, USA

Abstract

- **Objective:** Periodontitis is an inflammatory condition of the supporting dental tissues that is normally treated by mechanical removal of the subgingival biofilm. This mechanical treatment, generally known as scaling and root planing (SRP), is not entirely effective, and various adjunctive therapies have been investigated to improve the clinical outcome. This study evaluated the clinical effects of SRP alone or combined with local administration of hydrogen peroxide gel using customized trays in the treatment of subjects with chronic periodontitis.
- **Methods:** An examiner-blind clinical trial was conducted among 30 subjects with moderate to advanced periodontitis, who were randomized to SRP alone or SRP combined with a prescription custom-tray application (Perio Tray®) of 1.7% hydrogen peroxide gel (Perio Gel®) for a period of three months. Following impressions for the test group, all subjects brushed twice daily with a regular dentifrice and toothbrush for a four-week acclimation phase to standardize oral conditions (while trays were fabricated) prior to initiating the treatment phase. Clinical assessments, *i.e.*, pocket probing depth (PPD) and bleeding index (BI), were conducted at baseline and after two, five, and 13 weeks of peroxide applications; SRP was performed three weeks after baseline. Clinical variables were compared by ANOVA and paired t-tests after each treatment interval.
- **Results:** A total of 13 test and 15 control subjects completed the study. After two weeks of peroxide gel use prior to SRP, mean whole-mouth PPD was unchanged for the control group, but significantly decreased 0.21 mm in the test group. Two weeks following SRP, mean PPD decreased from baseline by 0.17 mm for the control group and 0.65 mm for the test group. Ten weeks following SRP, mean PPD decreases were 0.13 mm for the control group and 0.77 mm for the test group. After two weeks of peroxide use prior to SRP, mean whole-mouth BI decreased 0.03 (from 15% to 12%) for the control and 0.14 (from 23% to 9%) for the test group. Two weeks after SRP, the mean whole-mouth BI score decreased 0.05 from baseline (15% to 10%) for the control and 0.17 (23% to 6%) for the test group. Ten weeks after SRP, there was no change from baseline for the control group, but BI was 0.14 lower (23% to 9%) for the test group. Further analysis showed the same statistical relationship between groups for PPD assessments of deeper pockets. For pockets ≥ 6 mm at baseline, mean PPD decreased by 0.04 mm for the control compared to 0.48 mm for the test group after two weeks of peroxide gel use and prior to SRP. Two weeks after SRP, mean PPD decreased from baseline by 0.60 mm for the control and 1.40 mm for the test group, and 10 weeks after SRP by 0.58 mm for the control and 1.57 mm for the test group. All reductions cited above for the test group were statistically significantly different from the control group for both PPD and BI.
- **Conclusion:** The adjunctive use over three months of 1.7% hydrogen peroxide gel, locally administered using prescription customized trays in the treatment of subjects with moderate to advanced periodontitis, demonstrated statistically significant clinical improvements in pocket depths and bleeding when compared with SRP alone.

(J Clin Dent 2012;23:48–56)

Introduction

Periodontitis is a localized inflammatory disease of the tooth-supporting structures caused by specific micro-organisms residing in subgingival biofilm.[1] The consequence of this infection is chronic inflammation that leads to progressive destruction of the periodontal ligament and alveolar bone, resulting in gingival recession and pocket formation.[2] While the etiology of periodontitis is multi-factorial, bacteria are the primary agents. Many bacterial species are present in the subgingival biofilm, but only a few anaerobic species have been definitely associated with periodontal pathology.[3]

The traditional primary treatment for decades has been mechanical removal of supra- and subgingival biofilm and debridement by means of scaling and root planing (SRP), followed by surgery, if needed,[4,5] but this approach is not always successful in reducing all periodontal pockets.[6] SRP has significant limitations since it is performed with restricted vision into the pocket, and it is mechanically impossible to remove all bacteria from grooves, furcations, dentinal tubules, and soft tissues. Viable bacteria that remain after SRP regenerate, and bacteria constantly introduced into the oral cavity result in new biofilm formation.[7-9] Moreover,

the risk of future periodontal breakdown is positively related to residual pocket depth.[10]

For these reasons, mechanical procedures are necessary as frequently as every three months.[11] Also, the recurrent pattern of mechanical debridement is problematic for patients with systemic disease or compromised immune systems who want to avoid the risks of bacteremia associated with surgical or non-surgical debridement procedures,[12,13] and for patients who experience root sensitivity or cannot financially afford treatment as often as needed.

All these patients would benefit from an effective adjunctive chemotherapeutic approach to help stop the progression of disease and improve oral health.[14,15] One popular approach is the use of sustained or controlled-release local delivery agents that provide antimicrobial or chemotherapeutic activity as adjuncts to SRP. In 2006, the American Academy of Periodontology proclaimed that local delivery agents should be considered for chronic periodontitis patients as an adjunct to SRP when inflamed pockets with depths ≥ 5 mm are still present following conventional therapies.[16]

The active ingredients in local delivery agents are bacteriostatic antibiotics such as 10% doxycycline hyclate in Atridox® gel (Tolmar, Fort Collins, CO, USA) and minocycline hydrochloride in Arestin® (OraPharma Inc., Warminster, PA, USA), or bactericidal antimicrobials like chlorhexidine gluconate in Periochip® (Dexcel Pharma Technologies, Ltd., Edison, NJ, USA). These time-released products are used site-specifically, professionally inserted into periodontal pockets ≥ 5 mm as frequently as once every three months. Controlled release local delivery agents remain between one week to 10 days (chlorhexidine chip) and 21 days (doxycycline hyclate gel and minocycline spheres) before they are absorbed by the tissue.

Unfortunately, for both patients and clinical practitioners there are several problems and limitations associated with the use of local delivery agents. These include home care restrictions for brushing and/or flossing around local delivery agent sites, biofilm resistance to antibiotics, drug allergies and sensitivities, potential overgrowth of resistant microorganisms or commensal organisms, and concerns about judicious drug use in general. Additionally, local delivery agents are recommended only for deeper pockets (≥ 5 mm) where they will not be easily dislodged, and thus are not appropriate for treating earlier stages of disease progression when the disease is easier to control.

Other agents that also have been explored as antimicrobials for controlling supra- and subgingival biofilms are peroxides.[17,18] Currently, they are used most commonly for tooth whitening, but hydrogen peroxide at low concentrations (*i.e.*, ≤ 3%) also has an extensive history of topical application in mouthrinses, dentifrices, and antiseptic gels, with a long-term safety record.[19,20] Aqueous hydrogen peroxide (≤ 3%) also has long been known as an oral debriding agent and wound cleanser.[21] Topical peroxide application can reduce plaque and gingival inflammation,[22-24] and tray delivery of a carbamide peroxide gel appears to be effective for supragingival biofilm management.[16] However, the challenge for peroxide use in treating periodontitis has been to identify a method for delivering peroxide deep into periodontal pockets for sufficient time to have a significant therapeutic effect.[20]

The development of a prescription custom-fabricated dental tray (Perio Tray®, Perio Protect LLC, St. Louis, MO, USA) appears to have overcome the problem of gingival crevicular fluid flow to deliver peroxide directly into the sulcus.[25] In case studies where 1.7% hydrogen peroxide gel (Perio Gel®, Dakota Pharmacy, Bismarck, ND, USA) was introduced via a prescription tray into the periodontal pocket as an adjunctive chemical therapy before and after SRP, there was evidence of subgingival biofilm debridement and reductions in bleeding on probing and pocket probing depths.[26,27] Since the prescription tray-delivered oral debriding agents reduced symptoms of inflammation before and after SRP, the scope and extent of the mechanical procedures were reduced, as were, by definition, the risks of bacteremia. Potential advantages of the prescription tray-delivery approach are that patients can use the system at home between office visits, and medication can be placed into periodontal pockets, theoretically allowing for adjunctive care at the earliest stages of disease.

The objectives of this randomized, controlled clinical study with chronic periodontitis patients were: 1) to determine if prescription tray delivery of a 1.7% hydrogen peroxide gel adjunctive to SRP results in greater clinical improvements than SRP alone over a three-month period; 2) to evaluate whether two-week use of tray delivery of peroxide gel prior to SRP affects gingival bleeding and pocket depth; 3) to investigate prescription tray delivery of peroxide as adjunctive debridement care in shallow (≤ 5 mm) and deep (> 5 mm) pockets with SRP alone on disease severity; and 4) to examine the effects of the treatments at various sites throughout the mouth.

Materials and Methods

Subject Population

A study population of 31 qualifying adults was selected from a pool of volunteers who were identified previously by general screening examinations as suitable subjects with chronic periodontitis, based on the current classification system of the American Academy of Periodontology.[2] Detailed medical and dental histories were obtained by questionnaire and interview, and subjects who fulfilled the inclusion criteria were invited to participate.

All eligible subjects were fully informed of the purpose and timeline of the study, as well as potential risks and benefits of participation, and signed a Research Study Information and Consent Form. Prior to initiation of clinical procedures, the protocol and all study documents were approved by an independent institutional review board.

Inclusion and Exclusion Criteria

Subjects had to fulfill the following inclusion criteria: 1) 30–70 years of age, in good general health with adequate oral hygiene; 2) 12 or more natural teeth (excluding third molars) in a good state of repair; 3) moderate to severe generalized periodontitis (one site with pocket depth ≥ 6 mm in at least two quadrants); 4) no mechanical debridement for > 6 months prior to study; and 5) willingness to use assigned products according to instructions, and refrain from using oral hygiene products/procedures outside the study protocol for the duration of the study.

The exclusion criteria were as follows: 1) professional periodontal therapy before study enrollment; 2) calculus deposits that

may interfere with assessments; 3) significant oral soft tissue pathology or tooth mobility associated with advanced periodontitis (*e.g.*, scores of ≥ 2 on a 0–4 scale of tooth mobility); 4) orthodontic bands, fixed appliances, or partial dentures; 5) need for prophylactic antibiotics prior to dental treatment; 6) therapy with systemic medications in the previous month that might interfere with study outcome; 7) systemic condition or disease that may interfere with study results (*e.g.*, diabetes, immunological disorders); 8) drug allergies or adverse effects following use of oral hygiene products; 9) a history of IL1 Allele II Polymorphism or other genetic predisposition to periodontitis; or 10) pregnant or lactating females.

Clinical Assessments

The following clinical assessments were performed throughout the study by the same examiners who were blinded to the treatment.

- Oral soft tissue health was determined by means of a visual inspection of the oral cavity using a dental light, mirror, and gauze. Structures examined included the gingival mucosa, hard and soft palatal regions, buccal and labial mucosa, mucogingival folds, tongue, sublingual and submandibular regions, tonsilar and pharyngeal areas, salivary glands, and lips.
- Pocket probing depth (PPD) was measured using a manual calibrated periodontal probe (WHO Periodontal Probe) as the distance from the gingival margin to the attached periodontal tissue; the instrument tip was held flat against the tooth near the gingival margin with the probe approximately parallel to the long axis of the tooth. Depths were determined by counting the millimeters that show above the gingival margin on the calibrated probe and subtracting the number from the total number of millimeters, rounding off to the nearest millimeter.
- Bleeding index (BI) was determined after lightly drying with compressed air by stroking with a probe along the inner wall of the gingival crevice.[28] The probe was inserted into the gingival crevice to a depth of about 2 mm or until slight pressure was felt, and then run gently around the tooth at an angle of approximately 60 degrees and in contact with the sulcular epithelium. Minimum axial force was used to avoid undue penetration into the tissue as the probe moved around the crevice, gently stretching the epithelium.

Clinical measurements were taken at six sites (mesio-buccal, buccal, disto-buccal, mesio-lingual, lingual, disto-lingual) of each tooth (168 possible sites).

Experimental Design and Study Schedule

The experimental design was a randomized, controlled, examiner-blinded, parallel-group study to evaluate the effects of subgingival placement of hydrogen peroxide gel with a custom-fabricated prescription tray as an adjunct to mechanical debridement (SRP) to treat existing periodontitis. Periodontitis was classified as mild (pocket depth ≤ 4 mm), moderate (pocket depth 5–7 mm), or severe (pocket depth > 7 mm). The overall study was divided into two phases: 1) a pre-SRP phase consisting of a four-week acclimation period and a three-week treatment period prior to SRP; and 2) a 10-week post-SRP treatment phase with clinical assessments after two and 10 weeks.

At Visit 1 prior to the treatment phase, a screening examination, including PPD measurements, was performed to identify 30 adults of both sexes with chronic generalized periodontitis, and these subjects were randomly assigned to one of two treatment arms. Subjects assigned to the peroxide/tray group had a dental impression taken that was then sent to a laboratory for preparation of custom-fabricated trays. Following enrollment, all subjects were provided with a regular dentifrice and a standard adult toothbrush to use for the duration of the study. They began the acclimation phase by brushing their teeth twice daily to standardize home oral care and oral conditions for both groups. The trays were fabricated for subjects in the test group during this phase.

Approximately four weeks later at the baseline (Visit 2), clinical assessments were performed for oral soft tissue health status and BI. Subjects assigned to the test group received their trays which they began using with 1.7% hydrogen peroxide gel at home four times a day for 15 minutes. After two weeks (during which subjects in the test group performed the peroxide/tray treatments), clinical assessments were performed for oral soft tissue health, BI, and PPD (Visit 3). A week later (Week 3, Visit 4) all subjects received full-mouth SRP. Subjects in both groups continued to brush twice daily with the assigned dentifrice and toothbrush throughout the pre-SRP phase.

Following SRP, subjects began a 10-week treatment period during which they continued their home treatment regimens. After two weeks (Week 5, Visit 5), all subjects returned to the clinic, and oral soft tissue health status, BI, and PPD were performed, and impressions for new trays were taken for subjects in the test group; the trays were delivered approximately one week later. Subjects in the test group were instructed to reduce prescription tray peroxide gel usage to two times a day for 15 minutes until the final visit. They returned to the clinic 10 weeks after SRP (Week 13, Visit 6) to have the same clinical assessments performed.

Trial Design Summary

Visit 1, Screening.
Visit 2, Baseline. Tray and peroxide use begins for test group.
Visit 3, Week 2. Evaluate oral health status, BI, PPD.
Visit 4, Week 3. Whole-mouth debridement and scaling for all subjects.
Visit 5, Week 5. Evaluate oral health status, BI, PPD.
Visit 6, Week 13. Evaluate oral health status, BI, PPD.

Randomization and Allocation to Treatment

Each subject was given a sequential identification number during enrollment (Visit 1). Assignment to treatment was accomplished by the study coordinator, who did not participate in the clinical assessments, by stratifying subjects on site according to the number of pockets (≤ 4 or > 4) and pocket depth (≤ 6 mm or > 6 mm). Within each stratum, they were randomly assigned to a treatment group, resulting in distribution into two groups with similar periodontal conditions. Examiners and recorders did not know which treatments were administered to subjects, nor did they have access to the treatment code.

Treatment Procedures

Both groups of subjects brushed twice daily (morning and evening) with a marketed dentifrice (Crest® Cavity Protection Toothpaste, Procter & Gamble Co., Cincinnati, OH, USA) and an adult flat-trim bristle profile toothbrush (American Dental Association, Chicago, IL, USA).

All subjects received whole-mouth SRP using ultrasonic and hand instruments by two licensed dental hygienists who had extensive experience with periodontal pocket debridement. No time restriction was imposed for the procedure. The hygienists were supervised by a licensed dentist who was experienced with periodontal debridement, and administered local anesthetic only if needed. Subjects were randomly assigned to each hygienist in equal numbers from each treatment group by the study coordinator, but the hygienists were unaware of group assignment.

For subjects assigned to the test group, impressions of maxillary and mandibular arches were taken with irreversible hydrocolloid material (Accu-Dent System 2, Ivoclar Vivadent, Amherst, NY, USA), and yellow stone models were poured and sent with a prescription of the patient's presenting conditions at the time of the screening examination to an FDA-registered dental laboratory for tray fabrication of custom-fabricated, ethylene-vinyl copolymer trays (Perio Trays). The thickness of the prescription tray seal, and the length and thickness of the extensions were determined by precise measurements on the models, provided in conjunction with the subject's bleeding indices and/or periodontal probing depth measurements.

First use of the trays and 1.7% hydrogen peroxide gel (Perio Gel) was supervised. The trays and written instructions were available to each subject during the instructor's explanation and initial placement in the mouth. If needed, adjustments were made to the trays for divergent/convergent areas to seat completely and comfortably in the subject's mouth while maintaining an adequate seal. Each subject applied a thin ribbon of gel throughout tooth indentations to provide a dosage of ~ 0.75 gram in each tray. After completing treatment, the subject removed the trays and brushed and rinsed them with cold water before blotting dry for the next use.

Treatment frequency varied depending on the stage of the study as follows:

Baseline exam (Visit 2) to SRP (Week 3, Visit 4): four treatments per day, 15 minutes each (21 contact hours).

SRP (Visit 4) to final exam (Week 13, Visit 6): two treatments per day, 15 minutes each (35 contact hours).

Thus, for the three-week period following the baseline, subjects used ~ 6.0 grams of gel per day, and for the 10-week period following SRP, subjects used ~ 3.0 grams of gel per day for a total of 56 contact hours.

Subjects documented tooth brushing and peroxide/tray applications in a diary for the entire treatment phase. Subject compliance was estimated throughout the treatment phase by reviewing the diaries and by weighing the toothpaste tubes and the tubes of peroxide gel (for subjects in the test group) before dispensing and after collecting.

Data Analysis

The modified intent to treat (mITT) population consisted of all subjects who were administered a whole-mouth scaling and debridement (SMD) during the treatment phase of the study. The per-protocol (PP) population consisted of all subjects in the mITT population who completed all study visits and procedures, and for whom no major protocol violations (*e.g.*, use of certain medications not permitted by the exclusion criteria, or failure to comply with instructions) were noted by the investigators. The determination of subject inclusion in the study populations was completed prior to the unmasking of the study database.

The efficacy data analyses were performed on the mITT and PP study populations. The primary analysis was that performed on the mITT population. The primary efficacy variables were PPD and BI. Probing depth data were computed to provide a mean score per mouth, and also analyzed to yield frequency distributions that showed shifts resulting from treatment. The BI scores were computed to provide a mean score per mouth for each clinical assessment. Thus, the efficacy parameters were subject-wise mean scores (measured both before and at various intervals after treatment) based on all sites or surfaces measured. In addition, these efficacy parameters encompassed corresponding subject-wise mean scores based on evaluations made on various subsets of the mouth, including those consisting of proximal, facial, lingual, anterior, and posterior measurement sites.

The efficacy data analysis consisted of between-treatment and within-treatment (longitudinal) comparisons of PPD and BI at all examination time points using parametric procedures on a subject basis. Parametric analyses for baseline data were performed using analysis of variance (ANOVA), and after each treatment interval by ANOVA or analysis of covariance (ANCOVA). In addition, the within-treatment analysis of the clinical index data compared baseline mean scores and post-treatment mean scores, as well as calculated percentage changes from baseline for PPD and BI using Student's t-test for paired data. All comparisons were tested at a 0.05 level of significance using two-sided tests.

Results

Subject Retention

A total of 63 adult volunteers were assessed for eligibility; 28 were excluded because they failed inclusion/exclusion criteria or had scheduling problems or other reasons for not participating. At the screening exam (Visit 1), 35 subjects were examined and four were disqualified for failing the pocket inclusion criterion; thus, 31 subjects were enrolled. Prior to SRP, in the test group one subject stopped product use and another relocated, while in the control group one subject was disqualified for antibiotic use. Thus, 28 completed all visits during the study, 17 females and 11 males with a mean age of 54.8 ± 9.2 years (range 33–69 years). Twenty subjects were non-smokers and eight were smokers.

Compliance and Adverse Effects

For subjects who completed the study, the tray/peroxide treatment generally was well received. The diary entries and amounts used (based on weights) for both the dentifrice and peroxide gel indicated that the subjects followed the treatment instructions.

Three subjects in the test group reported sensitivity that they associated with peroxide/tray use. One subject had mild, intermittent sensitivity to cold that was localized to one tooth with recession, and also experienced occasional discomfort when

positioning the trays due to a TMJ problem. Two subjects had mild, generalized, intermittent sensitivity immediately after treatment. The only other treatment condition associated with peroxide/tray use that was reported by subjects was an improvement (*i.e.*, whitening) in the color of their teeth.

Pocket Probing Depth Clinical Findings

Tables I–III present summaries of subject-wise average pocket probing depths (measured in mm) across sites for the baseline visit and for changes from baseline at each subsequent visit. For every follow-up visit, a negative mean change from baseline indicates an improvement (reduction) in pocket depths, while a positive change from baseline indicates a worsening (increase) in pocket depths.

Table I provides whole-mouth PPD data of both treatment groups for all examined sites at baseline, and changes in PPD after two weeks of test product use prior to SRP, and five and 13 weeks after baseline (*i.e.*, two and 10 weeks post-SRP). In addition, Table I shows the data for all examined sites when calculated according to assessment sites (*i.e.*, interproximal and marginal) and mouth locations (*i.e.*, facial, lingual, anterior, posterior, maxilla, and mandible). For all comparisons, no statistically significant differences were found between the test and control groups at baseline (Visit 2). However, following two weeks of tray/peroxide treatment prior to SRP, the test group exhibited a significant decrease ($p < 0.0001$) from baseline in PPD that was significantly different ($p < 0.0001$) from the control group, which had a slight decrease that was not statistically different ($p = 0.053$) from baseline. Two weeks after SRP (five weeks from baseline) and 10 weeks after SRP (13 weeks from baseline), the same relationship between treatment modalities occurred, in which the test group had statistically larger decreases ($p < 0.0001$) in PPD than the control group. When the site and mouth PPD data subsets were examined, the same pattern emerged and all differences between groups for all sites and locations were highly significant.

Table II, which is laid out the same way as Table I, provides the same comparisons for shallow pockets (*i.e.*, ≤ 5 mm) at baseline. Again, the test group yielded statistically significant reductions in PPD ($p < 0.0001$) relative to the control group at all assessments for whole-mouth, as well as for all site and mouth data subsets. The whole-mouth data for shallow pockets at baseline and all other assessment visits are presented graphically in Figure 1.

Table III provides the same PPD comparisons for deep pockets (*i.e.*, > 5 mm) at baseline. It follows the same format as the other tables, except that the data subsets are limited to interproximal and posterior categories due to the fact that not all subjects had deep sites for the other site and mouth location categories. The number of baseline deep pockets per subject in all

Table I
Summary of Changes from Baseline in Pocket Probing Depth Data for All Examined Sites

	PPD (mm)					PPD Change from Baseline (mm)														
	Baseline					2-Week					5-Week					13-Week				
	Test n = 13		Control n = 15			Test n = 13		Control n = 15			Test n = 13		Control n = 15			Test n = 13		Control n = 15		
Measurement Sites	Mean	SD	Mean	SD	p-value	Mean	SD	Mean	SD	p-value	Mean	SD	Mean	SD	p-value	Mean	SD	Mean	SD	p-value
Whole-mouth	3.26	0.74	2.97	0.45	0.2202	−0.21	0.11	0.03	0.06	< 0.0001	−0.65	0.14	−0.17	0.11	< 0.0001	−0.77	0.22	−0.13	0.13	< 0.0001
Interproximal	3.65	0.72	3.35	0.47	0.2020	−0.20	0.12	0.04	0.08	< 0.0001	−0.68	0.16	−0.19	0.12	< 0.0001	−0.81	0.22	−0.13	0.14	< 0.0001
Marginal	2.49	0.83	2.22	0.44	0.2845	−0.24	0.14	0.01	0.03	< 0.0001	−0.59	0.20	−0.13	0.11	< 0.0001	−0.70	0.30	−0.14	0.14	< 0.0001
Facial	3.25	0.75	3.00	0.50	0.2915	−0.24	0.14	0.03	0.06	< 0.0001	−0.68	0.12	−0.17	0.11	< 0.0001	−0.79	0.20	−0.14	0.12	< 0.0001
Lingual	3.27	0.75	2.95	0.43	0.1728	−0.18	0.11	0.04	0.07	< 0.0001	−0.63	0.18	−0.18	0.14	< 0.0001	−0.76	0.26	−0.13	0.18	< 0.0001
Anterior	2.75	0.85	2.36	0.47	0.1353	−0.22	0.14	0.01	0.05	< 0.0001	−0.65	0.22	−0.18	0.13	< 0.0001	−0.77	0.30	−0.15	0.16	< 0.0001
Posterior	3.67	0.71	3.50	0.47	0.4598	−0.20	0.11	0.05	0.07	< 0.0001	−0.65	0.12	−0.17	0.11	< 0.0001	−0.76	0.21	−0.12	0.13	< 0.0001
Maxilla	3.35	0.79	3.09	0.44	0.2734	−0.23	0.14	0.03	0.07	< 0.0001	−0.67	0.18	−0.19	0.14	< 0.0001	−0.79	0.23	−0.15	0.16	< 0.0001
Mandible	3.16	0.74	2.85	0.52	0.2095	−0.20	0.16	0.04	0.05	< 0.0001	−0.63	0.17	−0.15	0.12	< 0.0001	−0.75	0.27	−0.12	0.13	< 0.0001

Table II
Summary of Changes from Baseline in Pocket Probing Depth Data for All Examined Sites with Baseline PPD ≤ 5 mm

	PPD (mm)					PPD Change from Baseline (mm)														
	Baseline					2-Week					5-Week					13-Week				
	Test n = 13		Control n = 15			Test n = 13		Control n = 15			Test n = 13		Control n = 15			Test n = 13		Control n = 15		
Measurement Sites	Mean	SD	Mean	SD	p-value	Mean	SD	Mean	SD	p-value	Mean	SD	Mean	SD	p-value	Mean	SD	Mean	SD	p-value
Whole-mouth	3.03	0.57	2.76	0.36	0.1380	−0.19	0.12	0.03	0.06	< 0.0001	−0.61	0.14	−0.16	0.11	< 0.0001	−0.71	0.18	−0.12	0.13	< 0.0001
Interproximal	3.37	0.54	3.10	0.36	0.1304	−0.17	0.13	0.04	0.08	< 0.0001	−0.62	0.17	−0.17	0.12	< 0.0001	−0.73	0.18	−0.11	0.14	< 0.0001
Marginal	2.41	0.71	2.11	0.41	0.1693	−0.23	0.14	0.01	0.03	< 0.0001	−0.57	0.18	−0.12	0.11	< 0.0001	−0.67	0.25	−0.14	0.14	< 0.0001
Facial	3.02	0.59	2.81	0.40	0.2782	−0.22	0.14	0.03	0.05	< 0.0001	−0.62	0.14	−0.16	0.11	< 0.0001	−0.71	0.16	−0.13	0.12	< 0.0001
Lingual	3.04	0.57	2.70	0.36	0.0663	−0.16	0.11	0.04	0.07	< 0.0001	−0.59	0.18	−0.16	0.14	< 0.0001	−0.71	0.22	−0.10	0.18	< 0.0001
Anterior	2.67	0.73	2.34	0.46	0.1596	−0.21	0.14	0.01	0.05	< 0.0001	−0.64	0.21	−0.18	0.13	< 0.0001	−0.75	0.27	−0.15	0.16	< 0.0001
Posterior	3.36	0.48	3.16	0.27	0.1822	−0.17	0.11	0.05	0.07	< 0.0001	−0.57	0.12	−0.14	0.11	< 0.0001	−0.65	0.16	−0.08	0.13	< 0.0001
Maxilla	3.12	0.61	2.88	0.35	0.1924	−0.20	0.15	0.03	0.07	< 0.0001	−0.62	0.20	−0.17	0.15	< 0.0001	−0.73	0.20	−0.13	0.17	< 0.0001
Mandible	2.94	0.58	2.64	0.41	0.1220	−0.18	0.16	0.04	0.04	0.0001	−0.59	0.17	−0.14	0.13	< 0.0001	−0.69	0.24	−0.10	0.14	< 0.0001

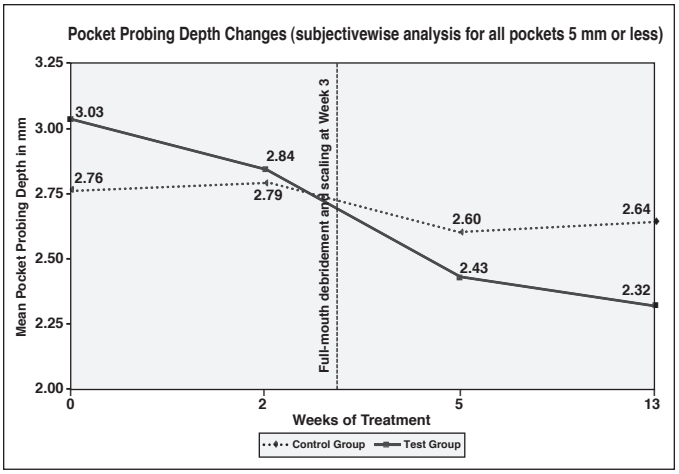

Figure 1. *Pocket probing depth changes measured in mm for whole-mouth data for shallow pockets. Between-treatment p-values (reflecting changes from baseline) were < 0.0001 at weeks 2, 5, and 13.*

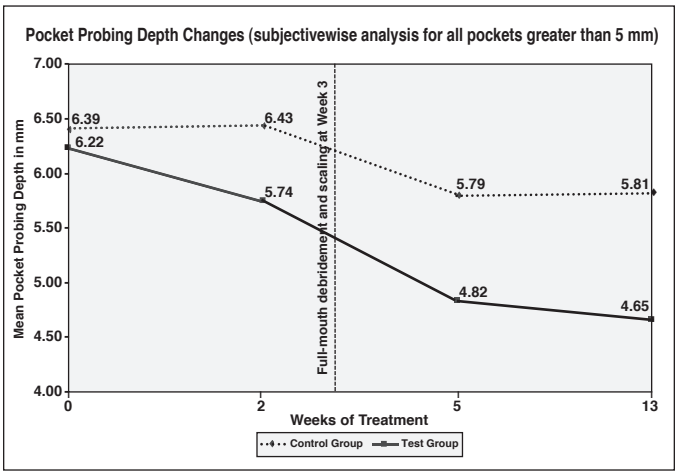

Figure 2. *Pocket probing depth changes measured in mm for whole-mouth data for deep pockets. Between-treatment p-values (reflecting changes from baseline) were ≤ 0.0015 at weeks 2, 5, and 13.*

Table III
Summary of Changes from Baseline in Pocket Probing Depth Data for All Examined Sites with Baseline PPD > 5 mm

	PPD (mm)					PPD Change from Baseline (mm)														
	Baseline					2-Week					5-Week					13-Week				
Measurement	Test n = 13		Control n = 15			Test n = 13		Control n = 15			Test n = 13		Control n = 15			Test n = 13		Control n = 15		
Sites	Mean	SD	Mean	SD	p-value	Mean	SD	Mean	SD	p-value	Mean	SD	Mean	SD	p-value	Mean	SD	Mean	SD	p-value
Whole-mouth	6.22	0.27	6.39	0.52	0.2832	−0.48	0.42	0.04	0.17	0.0003	−1.40	0.54	−0.60	0.55	0.0015	−1.57	0.31	−0.58	0.55	< 0.0001
Interproximal	6.22	0.26	6.41	0.53	0.2436	−0.47	0.42	0.05	0.19	0.0003	−1.36	0.57	−0.59	0.56	0.0032	−1.52	0.34	−0.57	0.56	< 0.0001
Posterior	6.19	0.24	6.41	0.55	0.1936	−0.47	0.42	0.04	0.19	0.0004	−1.40	0.53	−0.61	0.55	0.0020	−1.55	0.31	−0.59	0.54	< 0.0001

Table IV
Summary of Changes from Baseline in Bleeding Index Data for All Examined Sites

	BI					BI Change from Baseline														
	Baseline					2-Week					5-Week					13-Week				
Measurement	Test n = 13		Control n = 15			Test n = 13		Control n = 15			Test n = 13		Control n = 15			Test n = 13		Control n = 15		
Sites	Mean	SD	Mean	SD	p-value	Mean	SD	Mean	SD	p-value	Mean	SD	Mean	SD	p-value	Mean	SD	Mean	SD	p-value
Whole-mouth	0.23	0.18	0.15	0.09	0.1366	−0.14	0.12	−0.03	0.06	0.0140	−0.17	0.14	−0.05	0.07	0.0004	−0.14	0.13	0.00	0.08	0.0014
Interproximal	0.24	0.19	0.15	0.09	0.1120	−0.16	0.16	−0.04	0.08	0.0835	−0.19	0.16	−0.06	0.08	0.0037	−0.17	0.16	0.00	0.09	0.0067
Marginal	0.22	0.17	0.15	0.10	0.1997	−0.12	0.11	−0.03	0.07	0.0150	−0.15	0.13	−0.05	0.08	0.0014	−0.12	0.12	0.01	0.09	0.0039
Facial	0.19	0.17	0.10	0.09	0.0979	−0.14	0.12	−0.03	0.05	0.0101	−0.15	0.14	−0.05	0.07	0.0150	−0.12	0.10	0.00	0.09	0.0081
Lingual	0.26	0.20	0.19	0.11	0.2489	−0.14	0.13	−0.03	0.09	0.0294	−0.19	0.16	−0.06	0.09	0.0008	−0.16	0.16	0.00	0.10	0.0018
Anterior	0.22	0.16	0.15	0.11	0.1468	−0.15	0.10	−0.04	0.07	0.0077	−0.17	0.12	−0.08	0.09	0.0186	−0.14	0.13	−0.04	0.07	0.0645
Posterior	0.23	0.23	0.14	0.10	0.1878	−0.13	0.15	−0.03	0.08	0.0415	−0.17	0.19	−0.03	0.09	0.0002	−0.15	0.16	0.04	0.11	0.0009
Maxilla	0.18	0.20	0.11	0.07	0.2501	−0.10	0.13	−0.04	0.05	0.1058	−0.14	0.18	−0.05	0.08	0.1860	−0.12	0.16	0.01	0.07	0.0009
Mandible	0.28	0.19	0.18	0.13	0.1359	−0.17	0.12	−0.03	0.09	0.0040	−0.20	0.13	−0.05	0.10	0.0001	−0.16	0.15	−0.01	0.12	0.0188

subsets reported in Table III ranged from 7.7–8.9 deep pockets/subject in the control group, and 10.5–12.6 deep pockets/subject in the test group. The whole-mouth, as well as the interproximal and posterior subsets, produced highly significant PPD reductions ($p = 0.001$) of more than 1.5 mm from baseline, compared to less than 0.6 mm for the control group at the final exam after 13 weeks of treatment (Visit 6). The reductions for the test group (tray/peroxide + SRP) were statistically greater ($p < 0.004$) than the control (SRP only) for all comparisons. The whole-mouth data for deep pockets at baseline and all other assessment visits are presented graphically in Figure 2.

Bleeding Index Clinical Findings

Tables IV–VI present a summary of subject-wise bleeding index scores for the baseline visit and their changes from baseline. Each subject was characterized at each visit by the proportion of pockets that bled on probing at that visit. For every follow-up visit, a negative change from baseline indicates an improvement in bleeding scores, while a positive change from baseline indicates a worsening condition.

Table IV provides whole-mouth BI data of both groups for all examined sites at baseline, and changes in BI after two weeks of test product use prior to SRP, and five and 13 weeks after baseline

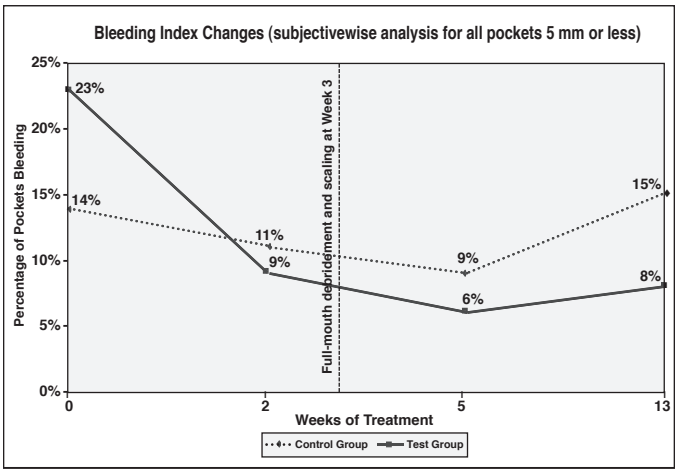

Figure 3. *Bleeding index changes (percentage of sites bleeding) for whole-mouth data for shallow pockets. Between-treatment p-values (reflecting changes from baseline) were ≤ 0.015 at weeks 2, 5, and 13.*

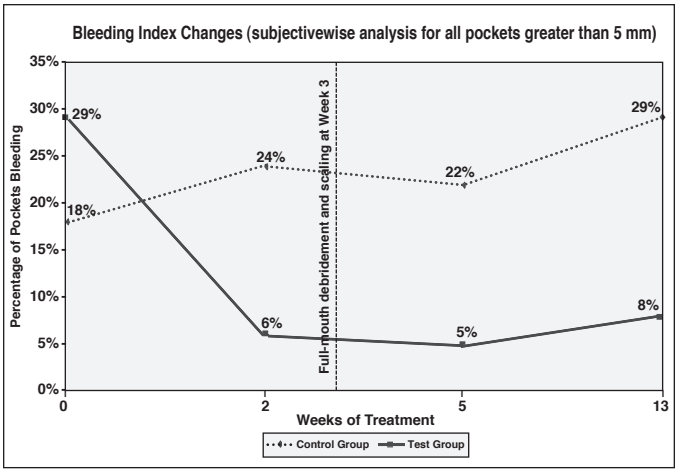

Figure 4. *Bleeding index changes (percentage of sites bleeding) for whole-mouth data for deep pockets. Between-treatment p-values (reflecting changes from baseline) at 2, 5, and, 13 weeks are 0.67, 0.013, and 0.035, respectively; p-values within the test group were < 0.05 at 2, 5, and 13 weeks.*

Table V
Summary of Changes from Baseline in Bleeding Index Data for All Examined Sites with Baseline PPD ≤ 5 mm

	BI					BI Change from Baseline														
	Baseline					2-Week					5-Week					13-Week				
	Test n = 13		Control n = 15			Test n = 13		Control n = 15			Test n = 13		Control n = 15			Test n = 13		Control n = 15		
Measurement Sites	Mean	SD	Mean	SD	p-value	Mean	SD	Mean	SD	p-value	Mean	SD	Mean	SD	p-value	Mean	SD	Mean	SD	p-value
Whole-mouth	0.23	0.18	0.14	0.08	0.1005	−0.15	0.13	−0.03	0.06	0.0148	−0.18	0.15	−0.05	0.06	0.0009	−0.15	0.13	0.00	0.08	0.0013
Interproximal	0.24	0.20	0.14	0.09	0.0895	−0.16	0.16	−0.04	0.06	0.0472	−0.19	0.16	−0.06	0.08	0.0076	−0.17	0.16	0.00	0.09	0.0048
Marginal	0.22	0.17	0.14	0.10	0.1697	−0.12	0.11	−0.03	0.07	0.0195	−0.15	0.13	−0.04	0.07	0.0008	−0.12	0.12	0.01	0.09	0.0022
Facial	0.19	0.17	0.11	0.10	0.1184	–0.13	0.11	−0.04	0.06	0.0288	−0.16	0.15	−0.06	0.08	0.0595	−0.12	0.10	0.00	0.11	0.0182
Lingual	0.27	0.21	0.18	0.11	0.1324	−0.16	0.15	−0.02	0.08	0.0168	−0.20	0.17	−0.05	0.07	0.0010	−0.18	0.17	0.01	0.08	0.0009
Anterior	0.22	0.16	0.14	0.11	0.1178	−0.15	0.11	−0.03	0.07	0.0115	−0.18	0.14	−0.07	0.08	0.0179	−0.14	0.13	−0.03	0.07	0.0229
Posterior	0.24	0.25	0.14	0.09	0.1438	−0.14	0.16	−0.03	0.07	0.0327	−0.18	0.20	−0.03	0.08	0.0020	−0.16	0.17	0.04	0.11	0.0008
Maxilla	0.19	0.21	0.11	0.08	0.2131	−0.12	0.15	−0.04	0.05	0.1805	−0.14	0.20	−0.06	0.09	0.4115	−0.13	0.18	0.02	0.08	0.0017
Mandible	0.27	0.19	0.17	0.12	0.1072	−0.18	0.13	−0.03	0.08	0.0022	−0.21	0.13	−0.05	0.09	0.0002	−0.17	0.15	−0.01	0.11	0.0215

Table VI
Summary of Changes from Baseline in Bleeding Index Data for All Examined Sites with Baseline PPD > 5 mm

	BI					BI Change from Baseline														
	Baseline					2-Week					5-Week					13-Week				
	Test n = 13		Control n = 15			Test n = 13		Control n = 15			Test n = 13		Control n = 15			Test n = 13		Control n = 15		
Measurement Sites	Mean	SD	Mean	SD	p-value	Mean	SD	Mean	SD	p-value	Mean	SD	Mean	SD	p-value	Mean	SD	Mean	SD	p-value
Whole-mouth	0.29	0.34	0.18	0.27	0.3344	−0.24	0.37	0.06	0.35	0.0668	−0.25	0.36	0.04	0.27	0.0133	−0.22	0.36	0.11	0.39	0.0348
Interproximal	0.29	0.34	0.17	0.25	0.2660	−0.23	0.38	0.07	0.36	0.0941	−0.25	0.36	0.06	0.23	0.0099	−0.21	0.36	0.14	0.37	0.0236
Posterior	0.31	0.36	0.18	0.28	0.3243	−0.24	0.40	0.06	0.35	0.0795	−0.30	0.36	0.04	0.27	0.0012	−0.21	0.40	0.11	0.39	0.0568

(*i.e.*, two and 10 weeks post-SRP). As presented for the PPD data, Table IV also includes BI data for all examined sites, subgrouped according to assessment sites and mouth locations. For all comparisons, no statistically significant differences were observed between the test and control groups at baseline (Visit 2), but after two weeks of tray/peroxide treatment prior to SRP, the test group exhibited significant reductions ($p < 0.010$) in bleeding that were statistically different ($p < 0.040$) from the control group for whole-mouth and all data subsets, except interproximal sites and the maxilla. Two weeks and 10 weeks after SRP (*i.e.*, five and 13 weeks from baseline), the same relationship was present in which the test group had statistically larger reductions ($p < 0.001$) in BI than the control group. When the site and mouth BI data subsets were examined, the same pattern emerged, and all differences between groups were statistically significant with only two exceptions.

Table V, which is in the same format as Table IV, provides the same BI data comparisons for shallow pockets (*i.e.*, ≤ 5 mm) at baseline. The test group yielded statistically significant reductions in BI relative to the control group at all assessments for whole-mouth, as well as for all site and mouth data subsets, except the maxilla at two and five weeks after baseline. The whole-mouth

data for shallow pockets at baseline and all other assessment visits are presented graphically in Figure 3, where the percentages of pockets bleeding differ slightly from the subtraction figures provided in Table V due to rounding.

Table VI provides the same BI comparisons for sites with deep pockets (*i.e.*, > 5 mm) at baseline. It follows the same format as Table III in which data subsets are limited to interproximal and posterior categories. The number of baseline deep pockets per subject in all subsets reported in Table VI ranged from 7.7–8.9 deep pockets/subject in the control group and 10.5–12.6 deep pockets/subject in the test group. The whole-mouth data produced significant BI reductions ($p < 0.05$) from baseline for every visit (two, five, and 13 weeks) compared to the control group which did not produce a significant reduction for any visit ($p > 0.29$). The reductions for the test group (tray/peroxide + SRP) were statistically greater ($p < 0.04$) than the control (SRP only) for whole-mouth and interproximal comparisons at the five-week and 13-week exams. The whole-mouth data for deep pockets at baseline and all other assessment visits are presented graphically in Figure 4, where the percentages of pockets bleeding differ slightly from the subtraction figures provided in Table VI due to rounding.

Discussion

This randomized, examiner-blind, parallel-design, clinical trial compared the effectiveness of SRP to daily treatment with 1.7% hydrogen peroxide gel using prescription, custom-fabricated dental trays as an adjunct to SRP. The results of this study demonstrated that the peroxide/prescription tray treatment regimen in combination with SRP was statistically significantly more effective than traditional SRP therapy alone in reducing pocket depths and bleeding both two weeks and 10 weeks after SRP. Moreover, the effectiveness of the peroxide/prescription tray system was manifested at all sites throughout the mouth, and encompassed both initial shallow (≤ 5 mm) and deep (> 5 mm) periodontal pockets.

This study also showed that use of the peroxide/prescription tray regimen for two weeks prior to SRP significantly decreased pocket depths and bleeding without mechanical intervention. This finding supports the case studies[25-27,29] predicating this clinical trial that emphasized minimally invasive dentistry without whole-mouth debridement or SRP, and suggests that the peroxide/prescription tray regimen potentially may reduce the scope of more invasive procedures, *e.g.*, whole-mouth SRP, or the necessary subsequent frequency of those procedures, which increase the risk of introducing pathogenic bacteria into the blood stream. However, additional research is necessary to establish when patients may need full-mouth treatment instead of site-specific procedures. At this time, based on the results of this study, it can be stated that prescription tray delivery of hydrogen peroxide is an adjunctive debridement therapy that was shown to be effective before and after whole-mouth mechanical procedures in reducing PPD and BI.

Clinical attachment loss and bone loss were not measured in this 13-week study because these are generally considered an indicator of long-term disease conditions[30] outside the scope of this study. Improvements in probing depths and clinical attachment levels after SRP are related to the pre-treatment depths of the pockets. In this study, a mean reduction in PPD of 0.77 mm was observed in the test group after 13 weeks of treatment for all sites examined, as compared to a mean PPD reduction of 0.13 in the control group. For initially deeper pockets, greater reductions in probing depths and gains in clinical attachment levels can be expected as compared to shallower pockets.[31] Thus, in this study a mean reduction in PPD of 1.57 mm was observed in the test group after 13 weeks of treatment for initial pocket depths > 5 mm, as opposed to a mean PPD reduction of 0.58 mm for the control group. General consensus in the periodontal literature is that a difference of 1 mm between treatments for pocket depth at initially deep sites is clinically relevant.[32,33] These reductions compare favorably with those reported for other well-known adjunctive local delivery agent treatments, such as Atridox, Arestin, and Periochip.

Another important observation of the present study was the lower percentage of sites with probing depths > 5 mm after treatment in the test group as compared to the control group. The presence of deep residual pockets after treatment was associated with further disease progression.[34] Residual sites with probing depths > 5 mm represent a risk factor for additional attachment or tooth loss, and may be useful as a measure of need for further treatment.[35] Bleeding scores also were reduced in this study, but comparisons of these reductions to those obtained in other studies cited are limited by the fact that different methods of assessing bleeding were used.

In this study, the SRP control group after 13 weeks of treatment resulted in a mean PPD reduction from baseline of 0.58 mm for initial pocket depths > 5 mm. This change falls within the range of improvements (0.2 mm to 1.0 mm) for SRP three months post-treatment in other recently reported studies.[36,37] Obviously, the reductions produced by SRP are dependent on initial PPD values and other study variables. Generally, subgingival debridement combined with oral hygiene instruction, the standard approach to non-surgical periodontal therapy, results in improved clinical outcomes, which may make it difficult to show any adjunctive effect in addition to the original treatment, as has been the case with other interventions.[36,38] Therefore, it is noteworthy that highly significant reductions in both PPD and BI were observed at all time points for treatment with 1.7% hydrogen peroxide gel in prescription, custom-fabricated dental trays as an adjunct to SRP.

A potential problem with the prescription tray delivery approach is that it requires daily use to be effective. However, in this study the subjects generally were receptive to using properly fitted trays, especially after observing rapid improvements in their oral condition. There are several limitations associated with the use of local delivery agents, such as home care restrictions around the sites, microbial overgrowth, bacterial resistance to antibiotics, patient drug allergies and sensitivities, and retention problems. This prescription tray (Perio Tray) delivery overcomes most of these problems and offers some potential advantages: 1) patients can use the system at home between office visits; 2) it is non-invasive; 3) there are no restrictions on brushing or flossing around treatment sites; 4) full arch treatment is beneficial for patients with significant numbers of deep and/or bleeding pockets; 5) adjunctive intervention is possible earlier

than with other time-released local delivery agents; 6) it can place medication into periodontal pockets of all depths, theoretically allowing for adjunctive care at the earliest stages of disease progression when the disease is easier to control; and 7) it can deliver low-concentration hydrogen peroxide gel, which is a safe, well-known oral debriding agent and wound cleanser.[25]

Conclusions

The adjunctive use over three months of 1.7% hydrogen peroxide gel, locally administered using prescription, customized trays for the treatment of subjects with moderate to advanced periodontitis, demonstrated statistically significant clinical improvements in pocket depths and bleeding when compared with SRP alone. Application of the peroxide/tray system for two weeks prior to SRP significantly decreased gingival bleeding and pocket depth from baseline and when compared to the untreated control. Use of the prescription tray delivery of peroxide as adjunctive debridement care, compared with SRP alone, exhibited significant activity at all sites examined throughout the mouth, and was effective in reducing disease severity in both shallow (≤ 5 mm) and deep (> 5 mm) pockets, significantly decreasing PPD in the latter by 1.57 mm versus 0.58 mm for SRP alone after 10 weeks.

Acknowledgments: *The authors are grateful to T. Van Dyke, DDS, PhD and M. Marshall, PhD for input and suggestions during the design of this study, and acknowledge D.S. Kuebler for coordinating the study and J.L. Milleman, DDS and K.R. Milleman, RDH for performing the clinical assessments. This study was supported by Perio Protect, LLC.*

For correspondence with the authors of this paper, contact Dr. Mark Putt—putt@ipfw.edu.

References

1. Schaudinn C, Gorur A, Keller D, Sedghizadeh P, Costerton W. Periodontitis: an archetypical biofilm disease. *J Am Dent Assoc* 2009;140:978-86.
2. Armitage GC. Development of a classification system for periodontal diseases and conditions. *Ann Periodontol* 1999;4:1-6.
3. Socransky SS, Haffajee AD, Cugini MA, Smith C, Kent RL Jr. Microbial complexes in subgingival plaque. *J Clin Periodontol* 1998;25:134-44.
4. Ramfjord SP, Caffesse RG, Morrison EC, Hill RW, Kerry GJ, Appleberry EA, Nissle RR, Stults DL. 4 modalities of periodontal treatment compared over 5 years. *J Clin Periodontol* 1987;14:445-52.
5. American Academy of Periodontology statement on the efficacy of laser in the non-surgical treatment of inflammatory periodontal disease. *J Periodontol* 2011;82;513-4.
6. Kaldahl WB, Kalkwarf KL, Patil KD, Molvar MP, Dyer JK. Long-term evaluation of periodontal therapy: I. Response to 4 therapeutic modalities. *J Periodontol* 1996;67:93-102.
7. Adriaens P, Adriaens L. Effects of nonsurgical periodontal therapy on hard and soft tissues. *Periodontol 2000* 2004;36:121-45.
8 Resposo S, Tobler J, Alfant B, Gollwitzer J, Walker C, Shaddox L. Poster presentation: Differences between Biofilm Growth Before and After Periodontal Therapy. AADR 37th Annual Meeting. April 3, 2008. Abstract available online
9. Zijnge V, Meijer HF, Lie MA, Tromp JA, Degener JE, Harmsen HJ, Abbas F. The recolonization hypothesis in a full-mouth or multiple-session treatment protocol: a blinded, randomized clinical trial. *J Clin Periodontol* 2010; 37:518-25.
10 Badersten A, Nilveus R, Egelberg J. Scores of plaque, bleeding, suppuration and probing depth to predict probing attachment loss. 5 years of observation following non-surgical periodontal therapy. *J Clin Periodontol* 1990;17:102-7.
11. Schara R, Medvescek M, Skaleric U. Periodontal disease and diabetes metabolic control: a full-mouth disinfection approach. *J Int Acad Periodontol* 2006;8:61-6.
12. Lafaurie GI, Mayorga-Fayad I, Torres MF, Castillo DM, Aya MR, Baron A, Hurtado PA. Periodontopathic microorganisms in peripheric blood after scaling and root planing. *J Clin Periodontol* 2007;34:873-9.
13. Morozumi T, Kubota T, Abe D, Shimizu T, Komatsu Y, Yoshie H. Effects of irrigation with an antiseptic and oral administration of azithromycin on bacteremia caused by scaling and root planing. *J Periodontol* 2010;81:1555-63.
14. Darby I. Non-surgical management of periodontal disease. *Aust Dent J* 2009;54(Suppl):S86-95.
15. Apatzidou DA, Kinane DF. Nonsurgical mechanical treatment strategies for periodontal disease. *Dent Clin North Am* 2010;54:1-12.
16. American Academy of Periodontology statement on the local delivery of sustained or controlled release antimicrobials as adjunctive therapy in the treatment of periodontitis. *J Periodontol* 2006;77:1458.
17. Lazarchik DA, Haywood VB. Use of tray-applied 10 percent carbamide peroxide gels for improving oral health in patients with special-care needs. *J Am Dent Assoc* 2010;141:639-46.
18. Ikai H, Nakamura K, Shirato M, Kanno T, Iwasawa A, Sasaki K, Niwano Y, Kohno M. Photolysis of hydrogen peroxide, an effective disinfection system via hydroxyl radical formation. *Antimicrob Agents Chemother* 2010; 54:5086-91.
19. Gerlach RW, Barker ML, Sagel PA, Ralsont CS, McMillan DA. In-use peroxide kinetics of 10% hydrogen peroxide whitening strips. *J Clin Dent* 2008;19:59-63.
20. Marshall MV, Cancro LP, Fischman SL. Hydrogen peroxide. A review of its uses in dentistry. *J Periodontol* 1995;66:786-96.
21. 21 CFR Parts 201, 356, and 369. *Federal Register* Jan 27, 1988;53(17).
22. Gusberti FA, Sampathkumar P, Siegrist BE, Lang NP. Microbiological and clinical effects of chlorhexidine digluconate and hydrogen peroxide mouthrinses on developing plaque and gingivitis. *J Clin Periodontol* 1988;15:60-7.
23. Gomes DC, Shakun ML, Ripa LW. Effect of rinsing with 1.5% hydrogen peroxide solution (Peroxyl) on gingivitis and plaque in handicapped and non-handicapped subjects. *Clin Prev Dent* 1984;6:21-5.
24. Boyd RL. Effects on gingivitis of daily rinsing with 1.5% H_2O_2. *J Clin Periodontol* 1989;16:557-62.
25. Dunlap T, Keller DC, Marshall MV, Costerton JW, Schaudinn C, Sindelar B, Cotton JR. Subgingival delivery of oral debriding agents: A proof of concept. *J Clin Dent* 2011;22:149-58.
26. Keller DC. Managing periodontal disease in a patient suffering from renal failure. *Dent Today* 2008;27:144-7.
27. Keller DC. Management of periodontitis for HIV-AIDS patients. *Dent Today* 2006;25:110, 112-3.
28. Saxton CA, van der Ouderaa FJ. The effect of a dentifrice containing zinc citrate and triclosan on developing gingivitis. *J Periodont Res* 1989;24:75-80.
29. Keller D. How to manage oral biofilm using Perio Protect as a minimally invasive method for lasting oral health. *DPR* 2010;44:54-5.
30. American Academy of Periodontology position paper, epidemiology of periodontal diseases. *J Periodontol* 2005;76:1406-19.
31. Cobb CM. Non-surgical pocket therapy: Mechanical. *Ann Periodontol* 1996; 1:443-90.
32. Greenstein G. Clinical versus statistical significance as they relate to the efficacy of periodontal therapy. *J Am Dent Assoc* 2003;134:583-91.
33. Feres M, Gursky LC, Faveri M, Tsuzuki CO, Figueiredo LC. Clinical and microbiological benefits of strict supragingival plaque control as part of the active phase of periodontal therapy. *J Clin Periodontol* 2009;36:857-67.
34. Renvert S, Persson GR. A systematic review on the use of residual probing depth, bleeding on probing and furcation status following initial periodontal therapy to predict further attachment and tooth loss. *J Clin Periodontol* 2002; 29(Suppl 3):82-9.
35. Matuliene G, Pjetursson BE, Salvi GE, Schmidlin K, Brägger U, Zwahlen M, Lang NP. Influence of residual pockets on progression of periodontitis and tooth loss: results after 11 years of maintenance. *J Clin Periodontol* 2008; 35:685-95.
36. Carvalho J, Novak MJ, Mota LF. Evaluation of the effect of subgingival placement of chlorhexidine chips as an adjunct to scaling and root planing. *J Periodontol* 2007;78:997-1001.
37. Oteo A, Herrera D, Figuero E, O'Connor A, Gonzalez I, Sanz M. Azithromycin as an adjunct to scaling and root planing in the treatment of Porphyromonas gingivalis-associated periodontitis: a pilot study. *J Clin Periodontol* 2010:37:1005-15.
38. Slot DE, Kranendonk AA, Van der Reijden WA, Van Winkelhoff AJ, Rosema NAM, Schulein WH, Van der Velden U, Van der Weijden FA. Adjunctive effect of a water-cooled Nd:YAG laser in the treatment of chronic periodontitis. *J Clin Periodontol* 2011;38:470-8.