A 6-month clinical investigation of custom tray application of peroxide gel with or without doxycycline as adjuncts to scaling and root planing for treatment of periodontitis

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ABSTRACT: Purpose: To evaluate the 6-month clinical effects of one scaling and root planing (SRP) procedure alone or combined with local administration of hydrogen peroxide gel (with or without inclusion of doxycycline for 2 weeks) using periodontal medicament carriers in the form of customized prescription trays for treatment of subjects with chronic periodontitis. **Methods:** Using a randomized controlled design, 61 subjects with moderate to advanced periodontitis were assigned to three parallel treatment groups: 1) SRP combined with prescription-tray (Perio Tray) application of 1.7% hydrogen peroxide gel (Perio Gel) and, for the first 2 weeks, doxycycline, 2) SRP combined with prescription-tray application of peroxide gel, and 3) SRP alone. All subjects brushed twice daily with standard dentifrice and toothbrush for a 4-week acclimation phase, and continued this regimen throughout the 6-month treatment phase. Pocket probing depth (PPD) and bleeding index (BI) were assessed on natural and restored sites at baseline and after 2, 5, 13, and 26 weeks. SRP was performed 3 weeks after baseline. Clinical variables were compared by ANCOVA and paired t-tests after each treatment interval, analyzing natural and restored sites separately. **Results:** 57 subjects completed the trial. Analysis of pockets > 5 mm at baseline showed that mean PPD for both test groups significantly decreased from baseline approximately 0.50 mm prior to SRP. Two weeks following SRP, mean PPD significantly decreased from baseline by > 0.90 mm for both test groups and 0.29 mm for the control. By 26 weeks, mean PPD decreased > 1.10 mm for both test groups compared to 0.38 mm for the SRP-only control (P< 0.001 for test versus control at all post-SRP comparisons). Analysis of pockets ≤ 5 mm at baseline showed the same relationship between groups (P< 0.001 for test versus control). Mean BI dropped significantly only for test groups before SRP, and the tray/peroxide-doxycycline group was significantly different from the control (P= 0.033). Two weeks post-SRP, mean BI reductions for test groups were significantly greater than the control, and remained so for most comparisons. For restored sites, mean PPDs of both test groups were significantly better (P< 0.05) than the control for all post-baseline comparisons. (*Am J Dent* 2014;27:273-284).

CLINICAL SIGNIFICANCE: Customized prescription-tray application of peroxide gel (with or without doxycycline) as an adjunct before and after SRP benefited patients with moderate to advanced periodontitis.

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Introduction

Progressive destruction of tooth supporting structures is the hallmark of periodontal diseases, and their management continues to present a challenge for clinicians. This is a multifactorial process induced by microorganisms that stimulate an immune response by the host, which leads to localized chronic inflammation, progressive connective tissue destruction, and ultimately alveolar bone resorption and tooth loss.[1,2] Additionally, periodontitis more recently has been associated with various systemic diseases and their progression, particularly cardiovascular diseases,[3,4] and as a chronic inflammatory condition, researchers are investigating its potentially causal relationship to systemic diseases.[5,6] Thus, treatment of periodontitis is of paramount importance, not only for controlling oral infections, but also for improving systemic health.[7,8]

Primary goals of periodontal therapy are reduction/elimination of bacterial communities (biofilm) on tooth surfaces and in periodontal pockets and management of inflammatory responses associated with these localized biofilm infections. The traditional approach has been non-surgical reduction of the periodontal bacterial load by means of professionally-administered mechanical removal of supra- and subgingival plaque and debridement, i.e. scaling and root planing (SRP),[9-11] followed

by surgery if needed.[12] This therapy results in clinical improvement and can temporarily decrease progression of the disease,[13,14] but it is not always successful in reducing all periodontal pockets.[15] Furthermore, the risk of future periodontal breakdown is positively related to residual pocket depth.[16] In fact, SRP alone has significant limitations because vision into the pocket is restricted, and it is physically impossible to eliminate subgingival bacteria from areas inaccessible to periodontal instruments,[17] as well as from reservoirs in dentin tubules and epithelial cells.[18] Moreover, viable bacteria that remain after SRP rapidly regenerate, and bacteria are continually introduced into the oral cavity, resulting in new biofilm formation,[19-22] and accordingly, it is often necessary to repeat SRP at least every 3 months for periodontal maintenance.

This recurrent pattern of mechanical debridement contributes to well-known negative secondary effects, such as gingival recession, tooth substance loss, and dentin hypersensitivity.[23] Repetitive mechanical intervention also can be problematic for patients with systemic disease or compromised immune systems who need to avoid the risk of bacteremia associated with these procedures or for patients with limited financial resources who cannot afford treatment as often as necessary.

All these patients would benefit from effective adjunctive therapeutics that reduce the progression of periodontal disease and improve oral health.[24,25] For these reasons, numerous adjunctive treatments have been proposed and investigated, mostly the use of systemic or time-release local delivery agents (LDAs) that provide antimicrobial or chemotherapeutic activity as adjuncts to SRP for deeper pockets ($\geq$ 5 mm) of chronic periodontitis patients.[26-29] Active ingredients in LDAs are bacteriostatic antibiotics, such as 10% doxycycline hyclate in Atridox gel[a] and minocycline hydrochloride in Arestin,[b] or bacteriocidal antimicrobials, like chlorhexidine gluconate in PerioChip.[c] These products are professionally inserted into periodontal pockets ($\geq$ 5 mm) as frequently as every 3 months, and remain for 7-10 days (chlorhexidine chip) and 21 days (doxycycline gel and minocycline spheres) before absorption by tissue.

Still, in spite of extensive use of these adjunctive treatments, clinical and immunological manifestations of disease often persist and sometimes progress.[30] Unfortunately, for both patients and clinical practitioners, several problems and limitations are associated with these therapies, including homecare restrictions for brushing/flossing around treated sites, biofilm resistance to antibiotics, drug allergies/sensitivities, potential overgrowth of resistant and/or commensal microorganisms, and concerns about judicious drug use in general. Furthermore, they are unsuitable for shallower pockets (< 5 mm) because they can be dislodged, and thus are not appropriate for treating earlier stages of disease progression when it is easier to control and less tissue damage has occurred.

Therefore, there is still a need for other localized treatments that can safely and effectively reduce inflammation and disease progression in patients with chronic periodontitis. Topical applications of peroxides, which are well known antimicrobials that can help reduce plaque and gingival inflammation,[31-34] can circumvent many of the limitations associated with LDAs. Currently, peroxides are most commonly used for tooth whitening, but aqueous hydrogen peroxide at low concentrations (i.e. $\leq$ 3%) has an extensive history with a long-term safety record[35-39] of topical application in mouthrinses, dentifrices, and antiseptic gels and as an oral debriding agent and wound cleanser.[40]

However, the challenge for using peroxide to treat periodontitis has been its delivery deep into periodontal pockets for sufficient time to have significant therapeutic activity.[35] A custom-fabricated, prescription dental tray (Perio Tray[d]), which was developed to overcome gingival crevicular fluid flow and deliver peroxide directly into the sulcus, has shown effectiveness for supra- and subgingival biofilm management.[41] When 1.7% hydrogen peroxide gel (Perio Gel[e]) was introduced via this prescription tray into periodontal pockets as an adjunctive chemical therapy before and after SRP, case studies indicated evidence of subgingival biofilm debridement and reductions in bleeding on probing and pocket probing depths. When prescription-tray local delivery of this peroxide gel was evaluated over a 3-month period as adjunctive therapy to SRP in chronic periodontitis patients with moderate to advanced periodontitis,[42] the results of this randomized, controlled trial demonstrated statistically significant improvements in gingival bleeding and pocket depths at sites throughout the mouth, in-cluding interproximal sites, in both shallower ($\leq$ 5 mm) and deeper (> 5 mm) pockets, when compared with SRP alone. Furthermore, when the trial was extended for another 3 months, continued significant improvements in pocket depths were maintained in subjects without additional SRP therapy.[43]

An advantage of the prescription-tray delivery approach is that patients can use it daily at home between office visits to deliver peroxide (and other medications) into periodontal pockets of all depths,[41] allowing for adjunctive care at the earliest stages of disease. For treating specific conditions of individual patients, this delivery method also may be used at the supervising dentist's discretion with other medications, particularly antimicrobials with anti-oxidative and anti-inflammatory activity such as doxycycline, which when delivered during an acute inflammatory period may inhibit the breakdown of collagen fibers and bone and, when delivered for an extended period of time, promote healing and bone repair.[44]

This randomized, controlled study with chronic periodontitis subjects, using a combination of mechanical scaling and debridement with prescription tray subgingival placement of medications, had the following objectives: (1) to determine if 1.7% hydrogen peroxide gel produces reductions in periodontitis when compared to traditional SRP alone over a 6-month period to corroborate the results of a previous study;[42,43] (2) to evaluate whether the combination of doxycycline and hydrogen peroxide gel in prescription trays for 2 weeks prior to SRP reduces clinical parameters of periodontitis (namely bleeding and pocket depth) relative to using peroxide gel alone; (3) to establish if 2 weeks of doxycycline treatment in combination with long-term use of hydrogen peroxide gel provides residual post-SRP improvements to periodontal health over peroxide gel alone when monitored over a 6-month period; (4) to investigate if 1.7% hydrogen peroxide gel (with or without short-term doxycycline) improves clinical parameters of periodontitis when compared to traditional SRP alone for tooth sites with restorations; and (5) to examine the effects of tray-applied 1.7% hydrogen peroxide gel on tooth whiteness during the 6-month treatment period.

Materials and Methods

Experimental design - This study used a randomized, controlled, examiner-blinded, parallel-group design which was similar to that of numerous other clinical evaluations of local antimicrobials as adjuncts to SRP.[28] The effects of subgingival placement of hydrogen peroxide gel with or without doxycycline were evaluated using a custom-fabricated, prescription tray as an adjunct to mechanical scaling and debridement (SRP) to treat existing periodontitis of both natural and restored teeth. The overall study comprised three treatment arms and was divided into three phases: (1) a 4-week pre-SRP acclimation phase, (2) a 3-week pre-SRP treatment phase, (3) a 23-week post-SRP treatment phase with clinical assessments after 2, 10, and 23 weeks.

Subject population - A study population of 61 qualifying adults was selected by screening exams from volunteers who were identified as suitable subjects with chronic periodontitis, based on the classification system of the American Academy of Periodontology.[45] Patients were referred by several local den-

tists and the Dental Hygiene Department of Indiana University-Purdue University Fort Wayne. Periodontitis was classified as Mild (pocket depth ≤ 4 mm), Moderate (pocket depth 5-7 mm), or Severe (pocket depth > 7 mm). 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 IRB, U.S. Investigational Review Board, Inc. (U.S.IRB2012UPR/02).

Inclusion and exclusion criteria - Inclusion criteria were as follows: (1) adults (18-70 years) in good general health with adequate oral hygiene; (2) 16 or more natural teeth (excluding third molars) in a good state of repair; (3) moderate to severe generalized periodontitis (i.e. one site with pocket depth > 5 mm in at least two quadrants); (4) no SRP for < 6 months prior to the study; and (5) willingness to comply with study instructions and procedures and refrain from using oral hygiene products/procedures outside the study protocol for the duration of the trial.

Exclusion criteria were as follows: (1) professional periodontal therapy before study enrollment; (2) extensive calculus deposits that may interfere with clinical assessments; (3) significant oral soft tissue pathology or tooth mobility (e.g. scores ≥ 2 on a 0-4 tooth motility scale; (4) orthodontic bands, fixed appliances, or partial dentures; (5) need for prophylactic antibiotics prior to dental treatment; (6) therapy with systemic antibiotic medications within the previous month; (7) systemic condition or disease that may interfere with trial (e.g. diabetes, immunological disorders); (8) drug allergies or adverse effects following oral hygiene product use; (9) genetic predisposition to periodontitis (e.g. IL1 Allele II Polymorphism); and (10) pregnant or lactating females.

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

• Oral soft tissue health (OST) was determined by means of a comprehensive 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, tonsillar 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 in millimeters from the gingival margin to the attached periodontal tissue. The instrument tip was held flat against the tooth near the gingival margin approximately parallel to the long axis of the tooth, and was advanced using light pressure until tactile contact was made with the attached tissue. Circumferential probing was achieved by maintaining the probe in the sulcus or pocket of each tooth and advancing the tip millimeter by millimeter along the facial and lingual surfaces into the proximal areas and taking depth measurements at the designated sites.

• Gingival bleeding (BI) was determined using the bleeding component of the Gingival Index,[46,47] in which the marginal and papillary segments of each tooth were assessed as follows. After lightly drying with compressed air, the probe was inserted into the gingival crevice to about 2 mm or until slight pressure was felt, and then run gently around the tooth at an angle of approximately 60° and gently stretching the sulcular epithelium. All teeth in one quadrant were probed/stroked in this manner (~30 seconds) before recording the number of gingival sites that bled. A site was categorized as bleeding if hemorrhage occurred instantaneously or if observed within 30 seconds of stroking.

• Tooth whiteness was visually graded using a Vita Shade Guide[f] under a full-spectrum fluorescent ceiling light after drying the labial surface of the incisors with a gauze. Each of the shade tabs was assigned a number from 1 to 16 according to the Munsell color ranking from lightest to darkest.

Clinical measurements for PPD and BI were taken at six sites (mesio-buccal, buccal, disto-buccal, mesio-lingual, lingual, disto-lingual) of all natural teeth, except third molars (168 possible sites). In addition, PPD and BI were assessed for teeth or tooth sites with restorations in contact with the gingivae (fillings, crowns, inlays, onlays, etc.), and data from these sites were analyzed separately. A per-subject mean for each clinical assessment was calculated by summing all values and dividing by the number of sites scored.

Examiner dry run/calibration/repeatability session - A dry run/calibration/repeatability session involving both examiners and auxiliary personnel was conducted 2 weeks prior to study initiation. Examiners performed clinical assessments for bleeding and PPD with five periodontitis patients, who had mild to severe disease, using the same recorders and equipment under identical conditions used during the trial. At least one other subject was examined between repeat assessments. Both examiners, who had extensive prior experience with the respective methods, demonstrated very good repeatability with weighted kappa values > 0.8.

Study schedule - At Visit 1 a screening exam was performed to identify adults with chronic, generalized periodontitis, and subjects were randomly assigned to one of three treatment arms. Subjects assigned to the two test tray/peroxide groups had dental impressions taken and sent to a certified laboratory for preparation of custom-fabricated trays. Following enrollment all subjects began an acclimation phase to standardize home oral care and oral conditions for all groups after receiving an adult, flat-trim bristle profile toothbrush[g] and a marketed dentifrice (Crest Cavity Protection Toothpaste[h]), which were replenished as needed. Trays were fabricated for subjects in the two test groups during this phase. All subjects were instructed to brush twice daily (morning and evening) for the study duration.

Approximately 4 weeks later at baseline (Visit 2), assessments for OST, BI, and PPD were performed. Subjects assigned to the test groups began using their trays with peroxide gel (and doxycycline if so issued) at home for 15 minutes four times per day. After 2 weeks (during which subjects in test groups performed tray/peroxide treatments), assessments were performed for OST, BI, and PPD (Visit 3) and tray usage was decreased to 15 minutes two times per day for the study duration. A week later (Week 3, Visit 4) all subjects received full-mouth SRP.

Following SRP, subjects began a 23-week treatment period during which they continued their home treatment regimens. OST, BI, and PPD were performed for all subjects 2, 10, and 23 weeks after SRP. Impressions for new trays were taken for subjects in the test groups at Visit 5, and new trays were delivered approximately 1 week later.

A study schedule summary follows:

Visit 1. Screening: Assess PPD; inclusion and exclusion criteria
Visit 2. Baseline: Assess OST, shade, BI, PPD; begin tray and peroxide (and doxycycline if assigned) use for test groups
Visit 3. Week 2: Assess OST, BI, PPD; collect doxycycline (if assigned)
Visit 4. Week 3: Full-mouth debridement and scaling for all subjects
Visit 5. Week 5: Assess OST, shade, BI, PPD
Visit 6. Week 13: Assess OST, shade, BI, PPD
Visit 7. Week 26: Assess OST, shade, BI, PPD

Randomization and allocation to treatment - Subjects were sequentially assigned consecutive identification numbers during enrollment (Visit 1). Allocation to treatment was accomplished by an investigator who was not directly involved with examination or treatment procedures, by stratifying subjects according to pocket depth and number of pockets with a depth ≥ 6 mm, and percentage of bleeding sites. Within each stratum, subjects were randomly assigned according to tobacco use and gender to a treatment group, resulting in distribution into three groups with similar periodontal conditions and demographic factors. The treatment identification code was concealed from all individuals directly involved in assessments until all examinations were concluded and data submitted to the statistician.

Treatment procedures - All subjects received full-mouth SRP using ultrasonic and hand instruments by four licensed dental hygienists, who had extensive experience with periodontal pocket debridement and were under no time restriction. A licensed dentist, experienced with periodontal debridement, administered local anesthetic only if needed. Subjects were randomly assigned in approximately equal numbers from each group to each hygienist, who was unaware of the treatment assignment.

The three adjunctive treatment regimens to which subjects were assigned were as follows:

Group 1. Tray delivery of 1.7% hydrogen peroxide gel (thin ribbon applied throughout tooth indentations to provide a dosage of ~0.75 gram in each tray) and 3 drops per tray of Vibramycin[i] syrup (50 mg doxycycline per 5 mL) for the first 2 weeks of treatment prior to SRP followed by peroxide delivery only for the remaining 24 weeks.

Group 2. Tray delivery of 1.7% hydrogen peroxide gel (same frequency and dosage as Group 1) for 26 weeks.

Group 3. Control, no adjunctive therapy.

For subjects assigned to the test groups, impressions of maxillary and mandibular arches were taken with irreversible hydrocolloid material, and yellow stone models were poured and sent with a prescription of the patient's presenting conditions at screening to an FDA-registered dental laboratory for fabrication of custom, ethylene-vinyl copolymer trays (Perio Trays). Thickness of the prescription-tray seal, and length and thickness of extensions were determined by precise measurements on the models provided in conjunction with the subject's periodontal probing depth measurements.

First use of trays and 1.7% hydrogen peroxide gel (Perio Gel) was supervised by an instructor, and if needed, adjustments were made to trays so that they would seat completely and comfortably in the subject's mouth while maintaining an adequate seal. The trays and written instructions were provided to each subject during the instructor's explanation and initial placement in the mouth.

Table 1. Demographic characteristics for randomized subjects by treatment group.

Characteristic	Group 1 (Peroxide+Doxycycline)	Group 2 (Peroxide)	Group 3 (Control)
Number of subjects (n)	20	20	21
Age			
Mean (SD)	53.8 (10.4)	54.6 (10.8)	53.5 (9.6)
Range	25 - 66	31 - 70	31 - 68
Gender			
Female (n, %)	12 (60%)	12 (60%)	15 (71%)
Male (n, %)	8 (40%)	8 (40%)	6 (29%)
Race			
White (n, %)	19 (95%)	17 (85%)	18 (86%)
Black (n, %)	1 (5%)	3 (15%)	3 (14%)
Other ethnicities (n, %)	0 (0%)	0 (0%)	0 (0%)
Tobacco users (n, %)	6 (30%)	7 (35%)	7 (33%)

Tray treatment frequency varied depending on the stage of the study as follows:

- Baseline Exam (Visit 2) to Week 2 (Visit 3): four treatments per day, 15 minutes each (~14 total contact hours)
- Week 2, Visit 3) to Final Exam (Week 26, Visit 7): two treatments per day, 15 minutes each (~83 total contact hours)

Thus, for the 2-week period following baseline, subjects used ~6.0 grams of gel per day, and for the final 24 weeks subjects used ~3.0 grams of gel per day. Doxycycline use was discontinued after 2 weeks, and the bottles were collected at Visit 3.

Subjects documented toothbrushing and peroxide/tray applications on a diary for the entire treatment phase. Compliance was estimated throughout the treatment phase by reviewing diaries, and by weighing tubes of peroxide gel (for subjects in the test groups) before dispensing and after collecting. At the 2-week exam (Visit 3) an instructor thoroughly reviewed peroxide gel (and doxycycline) usage with subjects and corrected any deviations regarding technique or dosage.

Data analysis - Analyses were performed on data from all subjects who received full-mouth scaling and debridement (SRP) during the treatment phase of the study. Subject mean scores for PPD and BI were calculated based on all measured sites with natural tooth surfaces, or on subsets of all measured sites as indicated. Similarly, subject mean scores for PPD and BI were calculated separately on all measured sites with restored surfaces.

Efficacy data analysis consisted of between-treatment and within-treatment (longitudinal) comparisons of PPD and BI at all exam time points using parametric procedures. Between-treatment comparisons employed ANOVA for baseline data and ANCOVA for follow-up data in order to adjust for baseline scores. In addition, within-treatment comparisons of baseline versus follow-up mean scores were performed using paired t-tests. All comparisons were performed using two-sided hypothesis tests, and employed a 0.05 level of significance.

Results

Demographics and subject retention - The demographic characteristics of all randomized subjects at baseline are shown in Table 1. The average age for each group was approximately 54 years, and the majority of subjects were white. Approximately a third of subjects in each group were tobacco users.
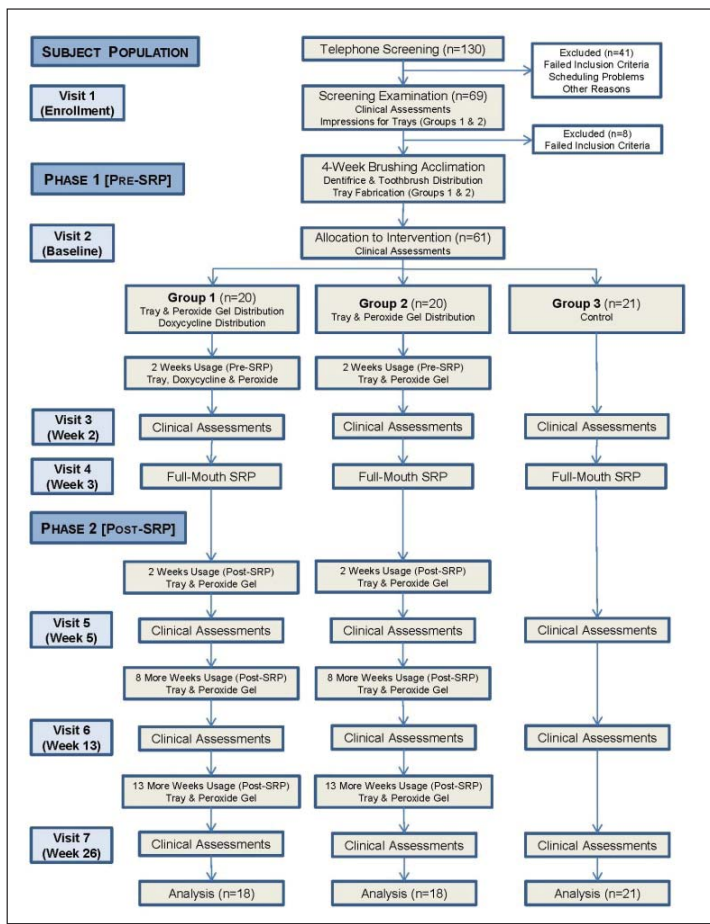
Fig. 1. Flow diagram showing recruitment and all stages of the study design for the 6-month trial. Prior to the 2-week exam, two subjects in Group 2 withdrew. Following the 13-week exam (Visit 6), in Group 1 one subject stopped product use and was disqualified, and another subject was unable to attend the final exam (Visit 7).

There were no significant differences between groups for any baseline demographic variables.

A flow chart of the experimental study design and subject participation is provided in Fig. 1. Initially, 130 adults were interviewed by telephone, and 89 were considered acceptable for screening examination; 41 were excluded because they failed inclusion/exclusion criteria or had scheduling problems or other reasons for not participating. At screening (Visit 1) 69 subjects were examined, and eight were disqualified for failing the pocket inclusion criterion. A total of 61 subjects were enrolled, and all were examined at baseline (Visit 2). Prior to the 2-week exam (Visit 3), two subjects in Group 2 withdrew. Following the 3-month exam (Visit 6), one subject in Group 1 stopped product use and was disqualified. Another subject in Group 1 was unable to attend the final exam (Visit 7) due to work assignment. Thus, 57 completed the final clinical assessments at Visit 7.

Compliance and adverse effects - For subjects in the two tray/peroxide groups, the treatment generally was well received although a few subjects indicated that it was sometimes a challenge to incorporate four treatments per day into their work schedules during the first 2 weeks of the trial. Diary entries and amounts used (based on tube weights) for both dentifrice and peroxide gel indicated that subjects satisfactorily followed treatment instructions for daily usage.
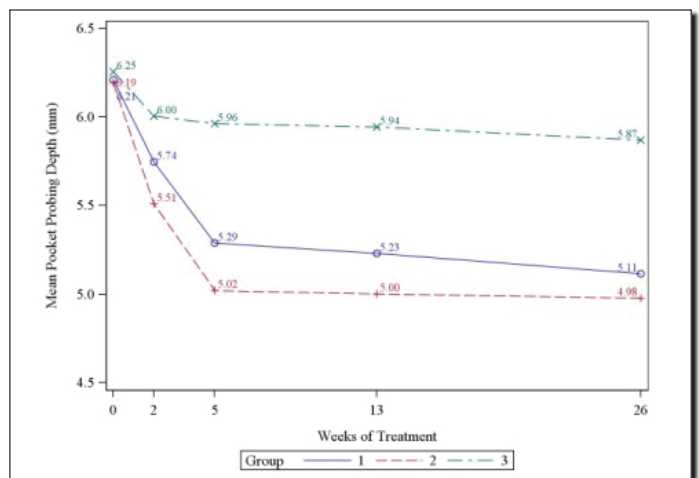

Fig. 2. Pocket probing depth measurements. Subjectwise analysis of whole-mouth data from baseline to 6 months for deep pockets (i.e. PPD sites > 5 mm) at baseline. Between-group comparisons for change from baseline at 26 weeks: Grp 1 vs. Grp 3, P< 0.0001; Grp 2 vs. Grp 3, P< 0.0001.

No subjects in the tray/peroxide groups reported sensitivity that they associated with treatment. The OST examiner observed occasional isolated cases of inflammation, petechiae, desquamation, and other lesions on various oral tissues in a few subjects from all three groups throughout the trial. However, none of these conditions were directly attributable to study treatments. The only other treatment condition associated with peroxide/tray use reported by subjects was an improvement (i.e. whitening) in the color of their teeth.

Pocket probing depth - Mean pocket probing depth data (in mm) for all natural tooth sites are provided in Table 2 for the baseline assessments (Visit 2). The data are summarized according to three categories: whole-mouth PPD scores, PPD scores ≤ 5, and PPD scores > 5. For all categories there were no statistically significant differences between treatment groups at baseline.

Figure 2 provides whole-mouth PPD data for all natural tooth sites examined at baseline with deep pockets (i.e. > 5 mm) of all treatment groups after 2 weeks of test product use prior to SRP, and after 5, 13, and 26 weeks (i.e. 2, 10, and 23 weeks post SRP). Following 2 weeks of treatment prior to SRP, both tray/peroxide groups exhibited significant decreases (P< 0.0001) in PPD from baseline that also were significantly different (P= 0.04 for Group 1 and P= 0.002 for Group 2) from the control (Group 3). Two weeks after SRP (5 weeks from baseline), both tray/peroxide groups showed further significant decreases in pocket depth, but the control group showed no further improvement. The two test groups had statistically lower PPD values (P< 0.0001) than the control group. This same pattern continued 10 weeks and 23 weeks after SRP (i.e. 13 and 26 weeks, respectively, from baseline). Highly significant PPD reductions (P< 0.0001) from baseline of 1.10 and 1.20 mm were observed for both tray/peroxide treatments (Groups 1 and 2, respectively) compared to 0.38 mm for the control group at the final exam after 26 weeks of treatment (Visit 7). For all comparisons, the reductions for both test groups (tray/peroxide + SRP) were statistically greater (P< 0.001) than the control (SRP only), reflecting an average improvement in deep pocket depth over SRP of nearly 1 mm that persisted for 6 months. The small differences in mean PPD scores between the adjunctive therapy treatments of Group 1 (tray/peroxide + doxycycline) and Group 2 (tray/peroxide) were

Table 2. Baseline clinical data for natural tooth sites by treatment group (randomized subjects).

| Clinical parameters	Group 1 Peroxide+Doxycycline	Group 2 Peroxide	Group 3 Control	Between-group P-values 1 vs 2	1 vs 3	2 vs 3
Number of subjects (n)	20	20	21			
Baseline pocket probing depth - All sites						
Mean (SD)	3.42 (0.45)	3.37 (0.50)	3.44 (0.45)	0.700	0.892	0.599
Median	3.32	3.22	3.38			
Min - Max	2.8 - 4.5	2.7 - 4.9	2.9 - 4.7			
Baseline pocket probing depth - PPD≤ 5						
Mean (SD)	3.10 (0.34)	3.06 (0.32)	3.12 (0.26)	0.661	0.800	0.487
Median	3.01	3.05	3.06			
Min - Max	2.7 - 4.0	2.6 - 3.7	2.6 - 3.7			
Baseline pocket probing depth - PPD> 5						
Mean (SD)	6.21 (0.23)	6.19 (0.31)	6.25 (0.37)	0.877	0.638	0.531
Median	6.15	6.13	6.15			
Min - Max	6.0 - 6.8	6.0 - 7.3	6.0 - 7.3			
Baseline Bleeding Index - All sites						
Mean (SD)	0.46 (0.24)	0.45 (0.20)	0.44 (0.20)	0.897	0.713	0.813
Median	0.41	0.41	0.40			
Min - Max	0.1 - 1.0	0.2 - 0.9	0.1 - 0.8			
Baseline Bleeding Index - PPD≤ 5						
Mean (SD)	0.44 (0.24)	0.43 (0.20)	0.42 (0.21)	0.834	0.759	0.924
Median	0.36	0.37	0.38			
Min - Max	0.1 - 1.0	0.2 - 0.9	0.1 - 0.8			
Baseline Bleeding Index - PPD> 5						
Mean (SD)	0.67 (0.26)	0.73 (0.21)	0.67 (0.24)	0.424	0.938	0.464
Median	0.61	0.79	0.63			
Min - Max	0.1 - 1.0	0.3 - 1.0	0.3 - 1.0			
Baseline Vita Shade Munsell values						
Mean (SD)	8.02 (3.62)	7.19 (3.60)	6.25 (3.75)	0.478	0.126	0.411
Median	7.75	7.00	5.50			
Min - Max	1.9 - 14.0	2.0 - 13.5	1.0 - 13.5			
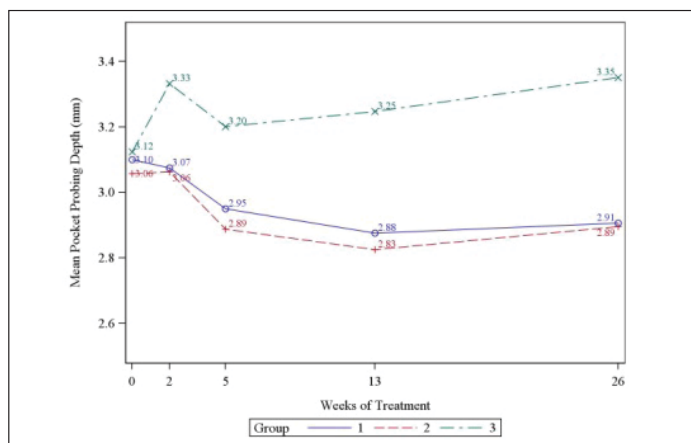
Fig. 3. Pocket probing depth measurements. Subjectwise analysis of whole-mouth data from baseline to 6 months for shallow pockets (i.e. PPD sites ≤ 5 mm) at baseline. Between-group comparisons for change from baseline at 26 weeks: Grp 1 vs. Grp 3, P< 0.0001; Grp 2 vs. Grp 3, P< 0.0001.
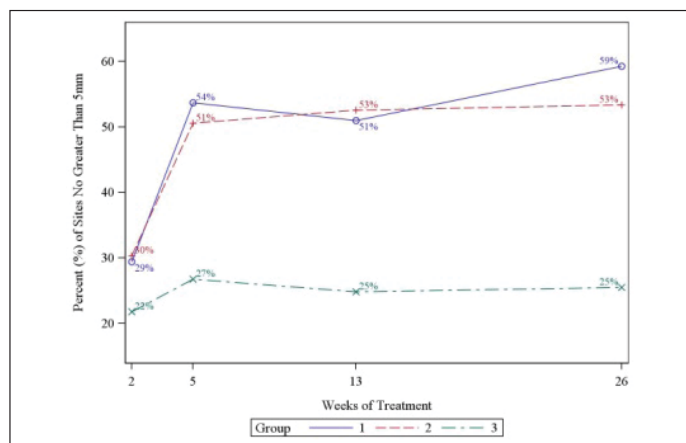

Fig. 4. Pocket probing depth improvement. Subjectwise evaluation measuring changes from baseline in percentage of sites with deep pockets (i.e. PPD sites > 5 mm) at baseline that dropped below the surgical threshold (i.e. PPD ≤ 5 mm) at subsequent time periods. Between-group comparisons for change from baseline at 26 weeks: Grp 1 vs. Grp 3, P< 0.0001; Grp 2 vs. Grp 3, P< 0.0001.

not significantly different at any assessment. The PPD data for deep pockets also were 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 the same statistical relationships between treatment groups persisted for the data subsets. For brevity these data are not included in this report.

Figure 3 provides the same whole-mouth PPD comparisons for all examined natural tooth sites with shallow pockets (i.e. ≤ 5 mm) at baseline. The adjunctive treatments (Groups 1 and 2) produced significant PPD reductions from baseline, whereas the control group PPD actually increased at all subsequent visits. Differences in PPD data between both test groups (tray/

peroxide + SRP) and the control (SRP only) were highly significant (P< 0.0001) for all post-baseline comparisons, indicating on average that shallow pocket depths improved relative to the control by ~0.25 mm 2 weeks after SRP, and then improved further to ~0.4 mm after 3 months where they remained until completion of the study after 6 months. The small differences in mean PPD scores between the two tray/ peroxide treatments (Groups 1 and 2) were not significantly different for any comparison of the shallow pocket data.

Figure 4 is a 5 mm-pocket threshold evaluation for all groups, indicating the percentage of deep pockets (i.e. > 5 mm)
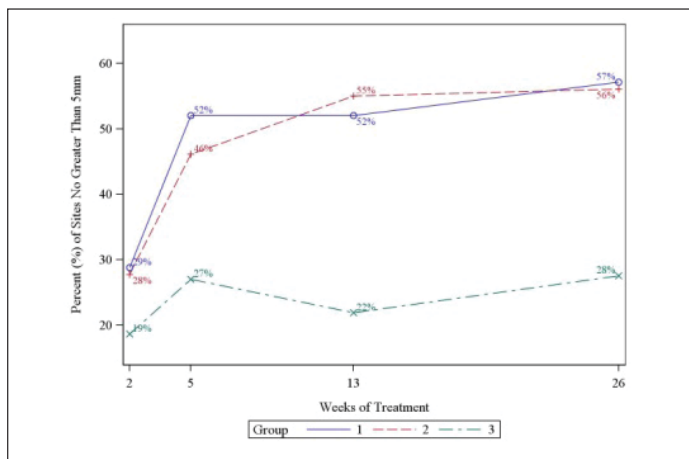
Fig. 5. Pocket probing depth improvement. Subjectwise evaluation measuring changes from baseline in percentage of sites with bleeding and deep pockets (i.e. PPD > 5 mm) at baseline that dropped below the surgical threshold of PPD ≤ 5 mm at subsequent time periods. Between-group comparisons for change from baseline at 26 weeks: Grp 1 vs. Grp 3, P< 0.0001; Grp 2 vs. Grp 3, P< 0.0001.

at baseline that dropped below the surgical threshold by changing to shallow pockets (i.e. ≤ 5 mm) after 2, 5, 13, and 26 weeks (i.e. 1 week before SRP and 2, 10, and 23 weeks after SRP). After 2 weeks of treatment (i.e. 1 week before SRP), both tray/peroxide groups had approximately 30% of sites with pockets that changed from > 5 mm to ≤ 5 mm, whereas the control group had 22% of sites that changed. After 5 weeks of tray use (i.e. 2 weeks after SRP), both test groups increased dramatically to more than 50% of sites that converted versus just 27% for the control group. This relationship continued until study completion after 26 weeks of tray use (i.e. 23 weeks after SRP) where the number of conversion sites for test and control groups were 59% and 53%, for Groups 1 and 2, respectively, and 26% for control Group 3.

Figure 5 shows a similar presentation to Fig. 4 with the addition that the sites also were classified as bleeding at baseline. Thus, it is a surgical threshold evaluation for all groups, indicating the percentage of deep, bleeding pockets (i.e. > 5 mm) at baseline that changed to shallow pockets (i.e. ≤ 5 mm) after 2, 5, 13, and 26 weeks. The percentages and relationships between groups were nearly identical to those in Fig. 4.

Figure 6 provides a more detailed presentation of the changes in PPD over the course of the trial, showing the distribution of PPD scores as percentages for sites with deep pockets (i.e. > 5 mm) at baseline. All groups began with similar deep pocket distributions of approximately 80% 6 mm sites and 20% ≥ 7 mm sites. After 2 weeks of treatment in both tray/peroxide groups prior to SRP, there was a decrease in the percentage of 6 mm and ≥ 7 mm sites and an increase in 4- and 5 mm sites, but no noticeable difference between Group 1, which had doxycycline, and Group 2, which did not. On the other hand, the control group's percentage of ≥ 7 mm sites remained unchanged, but there was a decrease in 6 mm and an increase in 5 mm sites. Two weeks following SRP (i.e. at the 5-week visit), both tray/peroxide groups had pronounced decreases in deep pocket sites (i.e. 6 mm and ≥ 7 mm) and similar increases in the percentages of 4 mm and 5 mm sites. However, the control group's ≥ 7 mm sites remained constant, but its percentage of 6 mm sites decreased modestly and was accompanied by a proportional increase primarily in 5 mm
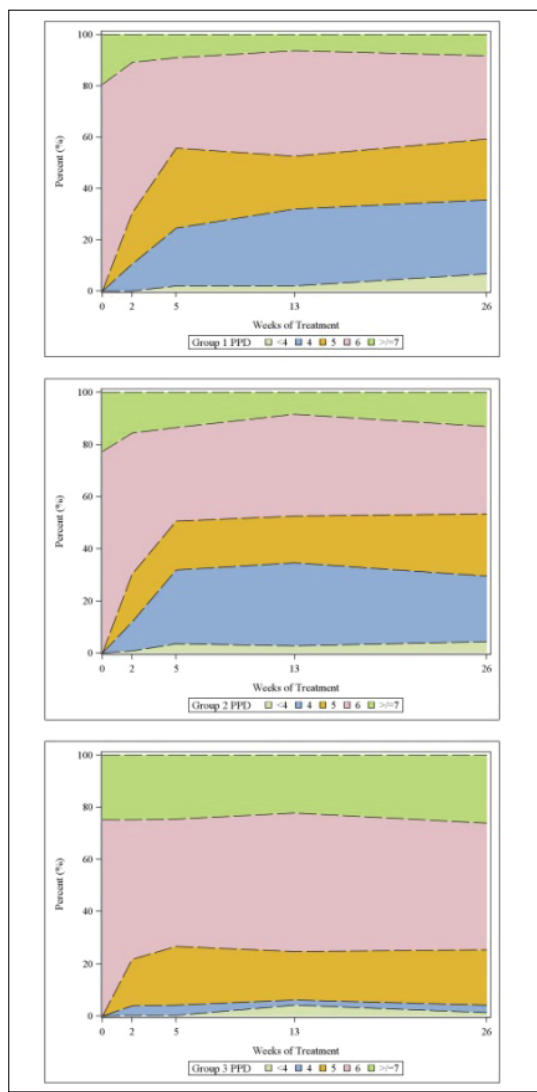

Fig. 6. Pocket probing depth changes for each group. Sitewise category transitions (as percentages) on all examined sites from baseline to subsequent time periods for subjects completing the 26-Week Visit.

sites. For the remainder of the trial (i.e. at both the 13- and 26-week visits), the two test groups maintained these decreases in the percentage of deep pockets and continued modest shifts toward shallower pockets, particularly 4 mm and 5 mm sites, but also some < 4 mm sites. In contrast, the control group's distribution between deep and shallow pockets remained relatively constant during the final 26 weeks.

Restored tooth sites - Mean pocket probing depth whole-mouth data for baseline assessments (Visit 2) are summarized in Table 3 for sites around restored teeth or surfaces. Because all sub-jects did not have restored tooth sites, the population for this analysis was reduced by about a third. Nevertheless, there were no statistically significant differences between groups at baseline.

Figure 7 provides whole-mouth PPD data for all restored tooth sites examined at baseline of all groups after 2 weeks of treatment prior to SRP, and after 5, 13, and 26 weeks (i.e. 2, 10, and 23 weeks post SRP). The two tray/peroxide groups showed decreases in PPD from baseline that were significant for most assessments, but the control group actually showed increases in PPD at all subsequent visits, including a significant increase at the final visit. The differences in PPD data between both test groups (tray/peroxide + SRP) and the control (SRP only) were

Table 3. Baseline clinical data for restored tooth sites by treatment group (randomized subjects).

Clinical parameters	Group 1 Peroxide+Doxycycline	Group 2 Peroxide	Group 3 Control	Between-group P-values 1 vs 2	1 vs 3	2 vs 3
Number of subjects (n)	13	11	14			
Baseline pocket probing depth - Restored sites						
Mean (SD)	3.91 (0.57)	3.74 (0.73)	4.02 (1.29)	0.657	0.756	0.456
Median	3.87	3.67	4.12			
Min - Max	3.0 - 5.0	2.4 - 4.8	1.0 - 6.0			
Baseline Bleeding Index - Restored sites						
Mean (SD)	0.55 (0.31)	0.46 (0.32)	0.38 (0.26)	0.493	0.158	0.506
Median	0.50	0.39	0.33			
Min - Max	0.0 - 1.0	0.1 - 1.0	0.0 - 0.9			
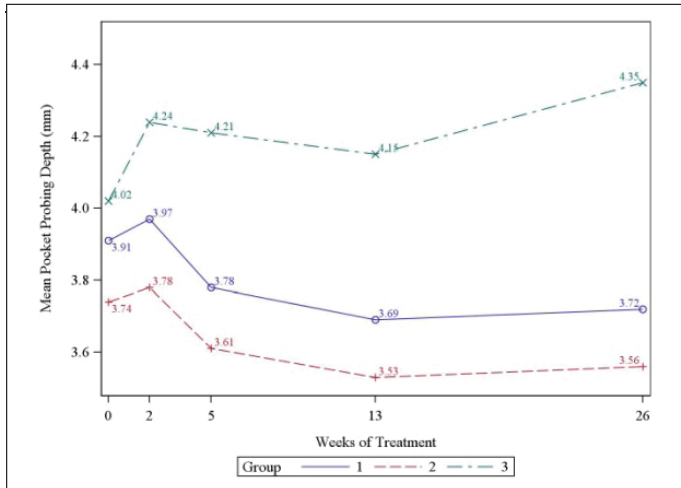
Fig. 7. Pocket probing depth measurements. Subjectwise analysis of whole-mouth data from baseline to 6 months for all pockets at restored sites. Between-group comparisons for change from baseline at 26 weeks: Grp 1 vs. Grp 3, P= 0.003; Grp 2 vs. Grp 3, P= 0.002.
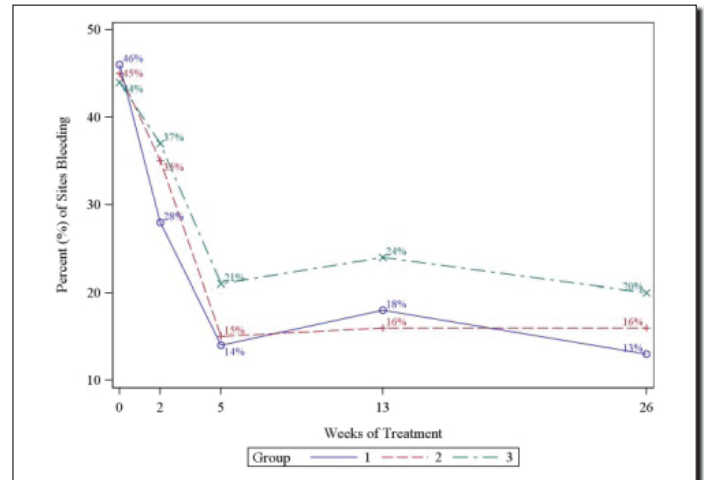

Fig. 8. Gingival bleeding measurements. Subjectwise analysis of whole-mouth data from baseline to 6 months for all pockets.
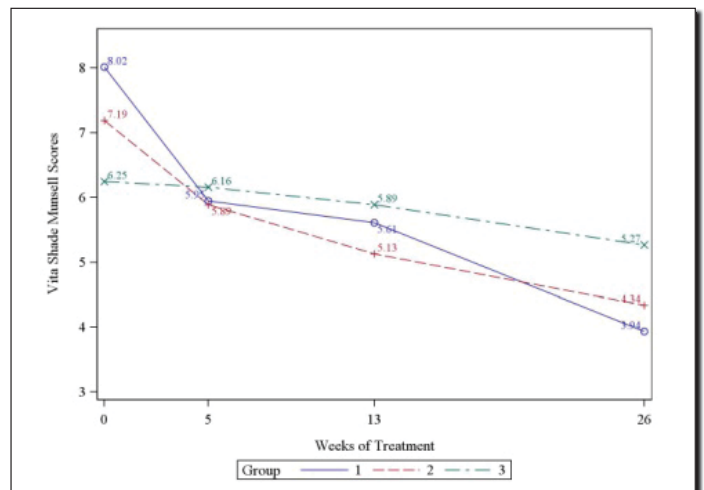

Fig. 9. Tooth whitening measurements. Subjectwise analysis of Vita Shade Munsell data from baseline to 6 months. Between-group comparisons for change from baseline at 26 weeks: Grp 1 vs. Grp 3, P< 0.005; Grp 2 vs Grp 3, P< 0.032.

significant (P< 0.05) for all post-baseline comparisons, indicating on average that pocket depths improved as a result of adjunctive treatment by more than 0.4 mm 2 weeks after SRP, and remained constant after 3 months, then improved further to more than 0.6 mm by study completion. The minor differences in mean PPD scores of restored sites between the two tray/ peroxide treatments were not significantly different for any comparison.

Bleeding assessments also were performed throughout the trial for restored tooth sites, but data are not included here. Although differences between groups were not significant, the relationship between the test groups and control group for the data followed that of the BI findings for natural teeth (Fig. 8).

Bleeding index - Mean pocket bleeding index (BI) data for all examined tooth sites are provided in Table 2 for the baseline assessments (Visit 2). The baseline mean BI data for all groups were quite similar and not significantly different.

Figure 8 presents whole-mouth BI data for all groups 2 weeks after baseline (1 week prior to SRP) and 5, 13 and 26 weeks after baseline (i.e. 2, 10 and 23 weeks post SRP). The two tray/peroxide groups produced significant BI reductions (P< 0.02) from baseline after 2 weeks of treatment prior to SRP. The reductions increased further after SRP and were highly significant (P< 0.0001) after 5, 13, and 26 weeks. The control group did not attain a significant reduction after 2 weeks, but also produced significant decreases in BI at all post-SRP assessments. After 2 weeks of treatment prior to SRP, the tray/peroxide test group with doxycycline exhibited a reduction in bleeding that was statistically lower (P = 0.033) than the control group. In addition, reductions for both test groups were statistically better (P< 0.04) than the control (SRP only) 2 weeks after SRP, but did not quite attain significance for comparisons at subsequent exams (13 and 26 weeks), except for Group 2 at 13 weeks (P< 0.018).

Tooth whiteness- Baseline mean Vita Shade Munsell scores are provided in Table 2. Although numerically disparate, the mean scores for the three groups were not statistically different. Figure 9 shows the scores at the three post-SRP exams (Visits 5, 6, and 7). Measurements were not taken at the pre-SRP exam (Visit 3). Both tray/peroxide regimens increased tooth white-

ness after 5 weeks of treatment (Visit 5), but only Group 1 was significantly (P< 0.05) better than the control. However, by the final visit both tray/peroxide treatment groups resulted in significantly (P≤ 0.04) whiter tooth scores than the control.

Discussion

The effectiveness of daily treatment with 1.7% hydrogen peroxide gel using prescription, custom-fabricated dental trays was evaluated in subjects with chronic periodontitis as an adjunct to a single scaling and root planing (SRP) procedure in a randomized, examiner-blind, parallel-design clinical trial over a period of 6 months. The results demonstrated that the prescription tray/peroxide gel treatment regimen in combination with SRP was statistically significantly more effective than traditional SRP therapy alone in reducing pocket depths at all post-SRP assessments (i.e. after 2, 10, and 23 weeks), corroborating the findings of an earlier trial[42,43] with a different subject population and different clinical examiners. Similarly, improvements in bleeding were observed at all visits relative to SRP alone, and some comparisons were statistically significant. In addition, as observed in the earlier trial, the effectiveness of the tray/peroxide regimen was manifested at all sites throughout the mouth, encompassing both initially deep (> 5 mm) and shallow (≤ 5 mm) periodontal pockets (data not included in this report for brevity). As in many evaluations of local antimicrobials as adjuncts, clinical attachment loss and bone loss were not measured in this study because these are generally considered a measure of accumulated past disease at a site rather than current activity conditions,[48] and thus are more reflective of epidemiological analyses outside the scope of this study.

Use of the tray/peroxide regimen for 2 weeks prior to SRP in this clinical trial also demonstrated significantly decreased pocket depths and bleeding prior to mechanical intervention. This finding supports the results of a previous trial,[42] as well as published case studies, and it indicates that use of the tray/peroxide regimen may reduce the scope and frequency of more invasive procedures, e.g. full-mouth SRP, which increase risk, especially to medically compromised patients, of introducing pathogenic bacteria into the bloodstream.[50,51] Based on the results of this investigation and a similar earlier 6-month trial,[42,43] prescription-tray delivery of 1.7% hydrogen peroxide is an adjunctive debridement therapy that was effective before and after full-mouth mechanical procedures in reducing PPD and BI and in maintaining significant PPD improvements over SRP alone for up to 6 months.

The addition of doxycycline to the tray/peroxide gel treatment regimen (Group 1) for the first 2 weeks after baseline did not reduce pocket depths further, indicating that doxycycline did not result in residual post-SRP improvements to periodontal health over peroxide gel alone. However, it did provide a significant improvement in bleeding scores after 2 weeks of use, suggesting that its inclusion may help patients reduce gingival inflammation prior to SRP. This may be explained in part by the anti-inflammatory, immune-modulating and neuroprotective properties of doxycycline.[52] Overall, the two prescription tray treatments (Groups 1 and 2) provided comparable PPD and BI data for all post-SRP assessments (i.e. Visits 5-7), which provides further support for the validity of this trial's

findings, thus demonstrating the effectiveness of the tray/peroxide treatment regimen as adjunct therapy to SRP for improving periodontal health in subjects with moderate to severe periodontal disease.

Improvements in probing depths after SRP are related to pre-treatment pocket depths. For initially deeper pockets, greater reductions in probing depths can be expected as compared to shallower pockets.[53] In this study, mean PPD reductions of 1.10 and 1.21 mm were observed in tray/peroxide Groups 1 and 2, respectively, after 23 weeks of treatment for initial pocket depths > 5 mm, as compared to 0.38 mm for the SRP control (Group 3). 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.[54,55] These reductions in PPD compare favorably with the weighted mean average of 0.5 mm reported in a systematic review[28] for other well-known adjunctive LDA treatments involving subgingival application of tetracycline fibers and sustained-release doxycycline and minocycline.

Another important observation for this study was the lower percentage of sites with probing depths > 5 mm after treatment for subjects using tray/peroxide adjunctive therapy as compared to SRP alone, which corroborates the findings of an earlier trial.[42,43] The presence of deep residual pockets after treatment was associated with further disease progression in a systematic review.[56] Also, residual sites with PPD > 5 mm represent a risk factor for additional attachment and tooth loss, and may be useful as an indicator for further treatment.[57] The percentage of sites exhibiting PPD > 5 mm at baseline and improving to ≤ 5 mm at subsequent visits (Fig. 4) followed the same trend for all groups at visits just before and after SRP, indicating a similar effect of SRP on all subjects. However, a noteworthy difference is that the two test groups, which used the trays and peroxide gel from baseline, had a substantial improvement before SRP was performed 3 weeks after baseline, and this improvement (over and above that from SRP) continued after SRP, whereas the relatively modest improvement for the control group due to SRP alone was maintained for the duration of the trial. The same pattern for the treatment groups was observed for the percentage of sites that exhibited bleeding as well as PPD > 5 mm at baseline and PPD ≤ 5 mm at follow-up (Fig. 5). Since surgery is generally considered necessary for sites with persistent PPD > 5 mm, these data suggest that surgical intervention may be needed less frequently for patients who daily administer 1.7% hydrogen peroxide gel in prescription trays as an adjunct to SRP.

Similar to earlier studies,[42,43] bleeding scores were reduced, significantly in several cases, by adjunctive use of the tray/peroxide regimen relative to SRP alone during this trial. However, comparisons of reductions in bleeding scores to those obtained in other studies with other adjunctive LDAs are limited by the fact that bleeding is not always reported and a standard method for assessment of bleeding is not universally used. Also, a systematic review on the effects of subgingival application of antimicrobial LDAs as adjuncts to SRP found that no significant differences occurred for changes in bleeding on probing.[28] Variability associated with changes in bleeding that result from LDA adjunctive therapies during long-term trials may also be due to other factors, such as SRP frequency

and biofilm re-colonization of deeper pockets, due either to inherent limitations of SRP or through seeding from nearby tissues by infected epithelial cells. Thus, patients with extensive disease that is less responsive to therapy may benefit by additional SRP or by surgical intervention while using the adjunctive treatment regimen. Other instances in which adjunctive therapy may be less effective for controlling bleeding include sites where subgingival calculus remains or reforms, presence of endo-periodontal lesions or granulomatous tissue, cracked teeth, and occlusion trauma.

In this clinical trial, the control group, 23 weeks after SRP, resulted in a mean PPD reduction from baseline of 0.38 mm for initial pocket depths > 5 mm. This change falls within the range of improvements (0.2-1.0 mm) for 6 months post-SRP in other recently reported studies.[43,58-61] While reductions produced by SRP are dependent on initial PPD values and other study variables, subgingival debridement combined with oral hygiene instruction, which is the standard approach to non-surgical periodontal therapy, is considered an effective treatment modality. Consequently, this may make it difficult to show any adjunctive effect over and above the original treatment, as has been the case with other interventions.[55,56] Thus, it is noteworthy that highly significant reductions in PPD were observed at all time points for subjects in both groups treated with 1.7% hydrogen peroxide gel in prescription, custom-fabricated dental trays as an adjunct to SRP, coupled with the observation that the PPD improvements were maintained for 6 months.

A unique aspect of this trial was the evaluation of periodontal tissue associated with restored teeth and tooth surfaces. Typically, only tissues adjacent to natural teeth are considered in gingivitis and periodontitis clinical trials, and sites around restored teeth or surfaces are rarely, if ever, evaluated. In this trial any sites in which the gingivae were in contact with restorations, such as crowns, restorations, inlays, onlays, etc., were assessed at the same time as the natural tooth sites, but tallied and analyzed separately. There were substantial differences in the number of restored sites between individual subjects, with some having no restorations to others with nearly as many restored sites as natural tooth sites. Consequently, it was considered likely that inter-subject variability would mask potential treatment effects. Nevertheless, although only about two-thirds of the subjects had relevant restorations, a similar pattern for probing depth changes to that for natural teeth was apparent (Fig. 7). Furthermore, the differences in PPD between the two tray/peroxide adjunct treatment groups and the control (SRP only) group were statistically significant for all follow-up assessments, resulting in mean improvements in PPD of 0.6-0.8 mm versus the control by study end. For practicing dentists, analysis of restored sites merits attention in future periodontal studies to help identify and evaluate effective treatment options for tissues adjacent to restorations that are difficult to restore to and maintain in healthy condition.

Anecdotal evidence from patients using prescription-tray delivery of 1.7% hydrogen peroxide gel indicated that tooth whitening occurs when following a normal treatment regimen. Thus, supplemental tooth shade assessments were performed during this trial following the initial 4-week acclimation brushing period for all subjects prior to baseline clinical assessments. Because this was done on an exploratory basis, no effort was made to assign subjects to groups according to tooth shade. Still, despite substantial numerical differences between groups at baseline, both tray/peroxide treatment groups exhibited increasing tooth whiteness throughout the trial (Fig. 9) that resulted in significant improvements relative to the control group after 26 weeks of treatment, thus providing support for the anecdotal observations. Peroxide concentrations in marketed tooth whitening products are much higher than the 1.7% level used in the gel of this trial, so the significant whitening effect observed was most likely attributable to the treatment frequency and cumulative exposure time.

Prescription-tray delivery of 1.7% hydrogen peroxide gel overcomes most of the limitations and problems associated with the use of LDAs, such as homecare restrictions around LDA sites, microbial overgrowth, bacterial resistance to antibiotics, patient drug allergies and sensitivities, and retention problems, and offers some potential advantages to patients in that it: (1) can be used at home between office visits; (2) is non-invasive; (3) puts no restrictions on brushing or flossing around treatment sites; (4) is beneficial as full-arch treatment for numerous deep and/or bleeding pockets; (5) is possible for earlier adjunctive intervention than with time-released LDAs; (6) can place medication into periodontal pockets of all depths, theoretically allowing for adjunctive care at the earliest stages of disease; (7) delivers low-concentration hydrogen peroxide gel, which is a safe, well-known, oral-debriding agent and wound cleanser.[41] Furthermore, while the prescription-tray delivery method requires daily use to be effective, subjects in this trial, as well as a previous study, overall were receptive to performing treatments using properly fitted trays, especially after observing rapid improvements in their oral condition.

One of the most important implications of this trial, which deserves additional research, is the decrease in BI for the test groups prior to SRP. Currently, the overuse of systemic antibiotics taken orally contributes to a public health crisis documented with the Centers for Disease Control. If prescription tray delivery of peroxides can help decrease bleeding before mechanical intervention, the cases requiring pre-medication before dental treatment may potentially be addressed without reliance on systemic antibiotics. As bacterial resistances increase, this kind of treatment will have significant clinical application.

In conclusion, compared with SRP alone, the adjunctive use over 6 months of 1.7% hydrogen peroxide gel (with or without inclusion of doxycycline for 2 weeks) when locally administered using prescription, customized trays, for the treatment of subjects with moderate to advanced periodontitis, demonstrated significant clinical improvements in pocket depths and bleeding. Application of the tray/peroxide regimen for 2 weeks prior to SRP decreased gingival bleeding and pocket depth from baseline and when compared to the control group. Use of prescription-tray delivery of peroxide as adjunctive debridement care, compared with SRP alone, exhibited 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, decreasing PPD in the latter by 1.10-1.20 mm versus 0.38 mm for SRP after 23 weeks. Inclusion of doxycycline in the trays for 2 weeks prior to SRP modestly reduced bleeding, but had no post-SRP residual benefits on BI

or PPD. Significant clinical improvements in PPD also were observed for restored tooth sites at all post-baseline assessments. Relative to the control, tooth whiteness improved progressively at each visit for both tray/peroxide treatment groups.

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