

Case Series Report of 66 Refractory Maintenance Patients Evaluating the Effectiveness of Topical Oxidizing Agents

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Abstract

- **Objective:** To evaluate the clinical effects of a prescription tray application of hydrogen peroxide gel as an adjunct to frequent maintenance appointments for refractory periodontal patients.
- **Methods:** Case series data were analyzed from 66 failing periodontal maintenance patients who had exhausted treatment options before using prescription trays with a 1.7% hydrogen peroxide gel once or twice daily for two-and-a-half to five years. Data included pocket probing depths (PPD), bleeding on probing (BOP), smoking status, and compliance with tray usage. Data were collected prior to tray usage and after tray delivery at six months, one year, and annual intervals.
- **Results:** A clinical and statistical reduction in BOP was maintained over the length of the study ($p \leq 0.01$). No differences were seen in patients who used trays two times or one time a day or in patients who smoked or did not smoke. The 1.7% peroxide delivered via a prescription tray was most effective in shallow pockets. Aggregate PPD distribution did not change significantly. Of clinical relevance, only one tooth out of 1,745 teeth studied was lost due to periodontal disease during the study period.
- **Conclusion:** Prescription tray application of peroxide gel, as an adjunct to frequent periodontal maintenance appointments for refractory patients, demonstrated significant reductions in BOP for smokers and non-smokers who used tray delivery once or twice a day.

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Introduction

Periodontitis is a chronic inflammatory disease, destroying tooth supporting structures induced by specific known and unknown micro-organisms in a subgingival biofilm.¹ Controlling periodontal pathogens and localized chronic inflammation, as reflected by a reduced bleeding index (BI), has dental benefits plus potential systemic benefits as oral pathogens are implicated in a host of systemic diseases.^{2–11} Further controlling periodontal pathogens with mechanical removal of biofilm and debridement by means of scaling and root planing (SRP), followed by surgery if needed, helps arrest the disease and arrest the destruction of the periodontal ligament and alveolar bone.

Traditional periodontal therapy follows a standard protocol. After diagnosis and initial treatment, a routine prescribed schedule of SRP and maintenance therapy is instituted. This method is not universally successful over time.^{12,13} Adjunctive treatments are available to augment basic periodontal treatment, but these adjuncts vary in effectiveness and share one common trait: the effectiveness is transitory.^{1,14–19} It would be a significant improvement in the treatment of periodontal disease to find an adjunctive therapy with longer-lasting effects.²⁰

One adjunctive approach with potential longer-term benefits involves patient-administered antimicrobials via a prescription customized tray. An initial report on this approach indicated that regular delivery of non-targeted anti-biofilm agents may be an effective strategy for treating periodontal biofilms, especially if these agents include oxidative agents that dissolve the biofilm matrix.¹ In 2004, a customized prescription tray (Perio Tray[®], Perio Protect,

LLC, St. Louis, MO, USA) received 510(k) clearance to place solutions into periodontal pockets. A study to test the concept demonstrated that the prescription Perio Tray delivered medication into shallow and deep (> 6 mm) pockets with subsequent improvement in health.²¹

A 13-week study of patients with moderate to severe periodontal disease, using a 1.7 percent hydrogen peroxide gel (Perio Gel[®], QNT Anderson, LLC, Bismarck, ND, USA) in a prescription customized tray (Perio Tray) as an adjunct to SRP, demonstrated a clinically significant improvement in pocket probing depths (PPD) and bleeding indices when compared to SRP alone. It appears that the effect was not transitory since the test group reductions from baseline were maintained for three months.²⁰

This study was extended another three months to test the possibility of maintaining clinical improvements for a total of six months, without additional mechanical therapy or surgical intervention. After the initial SRP procedure, ten subjects in the test group continued to use the prescription tray delivery of 1.7% hydrogen peroxide gel for 26 weeks, but, contrary to conventional protocols, they did not receive periodontal maintenance therapy. In the follow-up article by the same authors, the initial reductions in PPD were maintained for the adjunctive treatment group as compared to the control group for the entire six-month treatment period.²²

Most recently, a second six-month clinical trial tested the effects of one SRP procedure alone or in combination with prescription tray delivery (Perio Tray) of 1.7% hydrogen peroxide gel (Perio Gel) with or without doxycycline (Vibramycin[®], Pfizer Inc. New York,

NY, USA) for patients with chronic periodontitis. The results demonstrated a clinically significant improvement in PPD and BI for subjects using prescription tray delivery compared to subjects in the control group with SRP only.²³

This case series report diverges from studies discussed above primarily in the patient population examined and the duration of data collection. Not only did all subjects in this investigation have prior long-term, comprehensive periodontal care, including ongoing maintenance therapy every 2–4 months, but they were also all failing to respond and at high risk for continual destruction of the periodontal ligament and alveolar bone. For these refractory patients, traditional periodontal therapies had been exhausted. In an attempt to arrest further disease destruction and to save teeth, the patients used prescription custom trays (Perio Trays) with 1.7% hydrogen peroxide gel (Perio Gel) twice daily for 10 minutes. Tray treatment continued in long-term maintenance therapy over a period of 2.5–5 years. The patients in the case series thus serve as their own historical control group.

IRB approval to analyze patient data was sought following years of standard-of-care treatment to determine if the addition of the tray delivery significantly improved bleeding scores and PPD. Consent was obtained by the treating periodontist to analyze the data retrospectively using an IRB-approved consent form signed by each patient.

Materials and Methods

Subject Population Inclusion and Exclusion Criteria

The study population in this case series consisted of 66 qualifying adult patients from the office of a periodontist with more than 35 years of experience. All patients were classified with chronic periodontitis, based on the current classifications of the American Academy of Periodontology.²⁴ These patients had been originally treated with either SRP alone or SRP augmented by either Doxycycline, Amoxicillin and Flagyl, or Z-pack. Surgical intervention included isolated areas or full-mouth pocket elimination surgery, Widman flaps, or regenerative techniques depending on the treating periodontist's clinical experience. All patients were considered to be failing refractory maintenance patients and were selected for the study when they elected to follow the tested adjunctive treatment protocol.

The criteria for failure included at least one of the following conditions:

1. 50 percent or more of available bleeding points exhibited both extensive and heavy bleeding;
2. An increase in PPD of 2 mm or more during maintenance therapy;
3. Uncontrolled bleeding furcation involvement; or
4. Exhibited 70 to 80% bone loss (severe Class IV) with either solid teeth or minimal mobility.

Patients exhibiting any of these conditions were not candidates for additional surgical improvement due to the atrophic nature of their disease, or the patients faced additional surgical procedures which they declined. The treating periodontist then discussed prescription tray therapy with each patient and prescribed trays for those who consented. The key rationale for recommending usage of prescription trays was that additional teeth were expected to be lost.

After years of tray treatment in long-term periodontal maintenance therapy, the lead author obtained written patient consent to

include patient records in this study, which has IRB approval through Ohio University. All patients who had used trays for 2.5 years or more were considered for this study.

The clinical records of patients contained medical and dental histories, an extensive periodontal exam, long-term treatment records with consistent periodontal maintenance therapy every two to four months, and complete PPD and BI data collected at baseline and recall appointments.

Clinical Assessments

Records from 37 women (aged 43–78, average 63) and 29 men (aged 35–78, average 57) fit the inclusion criteria; 16 smoked (24%). At baseline all patients were charted for BI and PPD data.

Using a modification of Caton's BI (the mesial, distal, and interproximal surfaces), there were 34 possible bleeding points from the distal of 1 to the distal of 16, and from the distal of 17 to the distal of 32.²⁵ As a predictor of periodontal disease, BOP to the depth of the pocket has a low sensitivity due to a high incidence of false positive responses, but has a high specificity in that failure to bleed indicates health.²⁶ Since the overall purpose of this study was to investigate whether the use of prescription customized trays leads to gingival health, a recording system which utilized deep probing BOP was appropriate.

Pockets were probed and stimulated to their depths. Any surface which bled within 15 seconds was a positive. The data are reported as a percentage of the number of surfaces available and the number of surfaces that bled. This study includes only PPD of Caton's BI sites for the statistical analysis.

There were six examiners in this study: one periodontist with 37 years of clinical practice and five hygienists with 3 to > 20 years of experience. Prior to the study, all hygiene examiners were trained and supervised by the treating periodontist, observing pocket probing and bleeding induction probing techniques to standardize exam scores. Repeatability sessions confirmed standardized exams. Specifically for BI, probing was done to the base of the pocket, gently stroked, and observed over a 15-second period. Any bleeding (heavy, medium, or light) was considered positive.

Treatment Schedule and Procedures

At the beginning of maintenance therapy, all patients had been taught and demonstrated multiple times the techniques of subgingival brushing and the subgingival use of Perio-Aid® (Marquis Dental Mfg. Co., Aurora, CO, USA) and Stim-U-Dent® (Revive Personal Products, Madison, NJ, USA). All patients were informed of the study's purpose as well as the potential risks (bleaching and sensitivity), and verbally consented to use the prescription trays with 1.7% hydrogen peroxide gel.

At the visit prior to prescription tray delivery, PPD and BI were recorded and maxillary and mandibular impressions were taken. The impressions, a tray prescription, and periodontal chart were sent to a dental laboratory (Ohlendorf Appliance Laboratory, St. Louis, MO, USA) trained by Perio Protect, LLC and registered with the FDA for fabrication of the prescription tray.

Trays were delivered three weeks after impressions. BI was recorded at baseline (at tray impression visit), at three months, six months, one year, and then yearly as clinical demand indicated. PPDs were charted at impressions, at one year, and then every two years as

clinical demands indicated. Data were collected from December 2007 through December 2012. The number of years data were collected for each patient equaled the number of years that each patient used the trays during this five-year period.

At delivery, trays were confirmed for good fit and a sufficient peripheral seal. Patients were instructed to place three or four pea-sized drops of gel in the tray and to evenly distribute those drops throughout tooth indentations.

Patients were instructed to use the trays twice a day for ten minutes each time. LIVE/DEAD® studies indicate that 1.7% hydrogen peroxide gel debrides the cell walls of bacteria on the exposed layers of a biofilm within 10 minutes.²² Compliance data with tray usage were collected from patient self-reports to the treating dentist.

Patients used trays after their normal hygiene procedures. Patients also maintained two- to four-month recall visits for maintenance therapy.

Statistical Analyses

Overall, the data to be analyzed did not meet the assumption of normality. This is not surprising given the nature of the data. BI data provided is count data that has a lower bound of zero. To have zero bleeds across the PPDs was one treatment goal, so if treatment was successful a high number of zero bleeds would be expected. Since the data set was a count, a transformation would not solve the underlying kurtosis and skew issues. Therefore, all of the tests completed were non-parametric, with significance level set at $p = 0.05$. Group comparisons were completed to determine if there was an effect of smoking status and/or if the number of times trays were worn per day had any effect on BI. Repeated measure comparisons were then completed to compare BI across measurement occasions and to compare changes in BI across pocket depth. Bonferonni adjustments were made to ensure that the family-wise error rate across the reported tests was $p = 0.05$.

This data set is not underpowered. Significant effects were found across a range of analyses, indicating that the study is sufficiently powered. The statistical analyses examined the following conditions:

1. Comparisons across groups
 - a. Subject-wise analysis of BI differences in smokers and non-smokers.
 - b. Subject-wise analysis of BI differences for prescription tray usage compliance.
2. Repeated measures within-group comparisons
 - a. Subject and site-wise analysis of changes from baseline in whole mouth presence/absence BI at six months, one year, and final year for patients using trays 2.5–5 years.
 - b. Differences in reduction in bleeding over time in shallow and deep pockets.
 - c. Subject-wise analysis of PPD changes from baseline and final scores.

Results

Smoking Status and Compliance

The first analyses determined if smoking status and the frequency of tray usage affected whole mouth BI scores. If group differences exist, then further statistical analyses would be needed to account for a patient's smoking status and/or the number of times trays were worn per day. Self-reported data indicated patients used trays once

(50%) or twice (50%) a day for 10 minutes each time.

Difference scores in whole mouth BI between the baseline measurement and the last measurements were then calculated considering the impact of smoking and tray usage. No significant effect of smoking status on the change in BI (Mann-Whitney U test: $U_{(65)} = 326.5$, $p = 0.271$) was observed (Figure 1). There was also no significant effect of the number of treatments per day on the change in BI ($U_{(65)} = 467.5$, $p = 0.323$). Therefore, these variables were not segmented out for additional analyses.

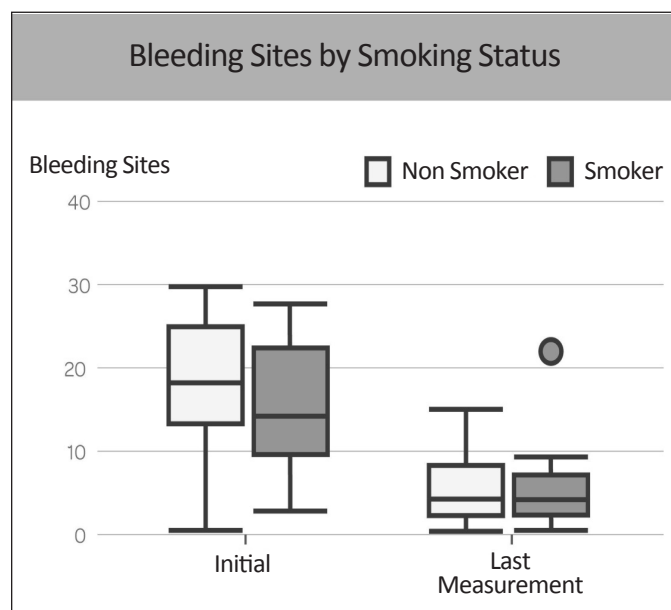


Figure 1. Interquartile ranges of the number of bleeding sites for smokers and non-smokers. The dot represents a single outlier among smokers at the last measurement.

BI Data

Subject and site-wise data analysis of changes from baseline in whole mouth BI exhibited a significant decreased in the number of sites bleeding (compared to baseline scores) at six months of use, at one year, and at the last measurement (2.5–5 five years). A significant decrease in whole mouth BI across measurement occasions was found (Friedman's test: $F_{(3,62)} = 115.1$, $p < 0.0001$).

Post hoc comparisons (Dunn's multiple comparison tests: $p = 0.01$) indicated that the initial whole mouth BI scores were significantly higher than the BI from all subsequent measurements. The *post hoc* comparisons also indicated no significant change in whole mouth BI after the 6-month assessment, indicating that BI reductions were maintained over time (Figure 2).

BI Data Relative to PPD

To determine the difference in BI between the initial and end measurement across different PPDs, data were summarized into three groups: PPDs of 3 mm, PPDs 4–6 mm inclusive, and PPDs ≥ 7 mm. A significant decrease in BI was found at all PPD levels (Figure 3): shallow 3 mm (Wilcoxon: $W_{(64)} = -1003$, $p < 0.0001$), moderate 4–6 mm. ($W_{(64)} = -2074$, $p < 0.0001$) and severe ≥ 7 mm ($W_{(64)} = -464$, $p = 0.0003$).

Examination of individual PPD levels from initial to last BI score show that all bleeding reductions were not uniform across levels but were greater in the lower PPD levels. Values greater than 9 mm

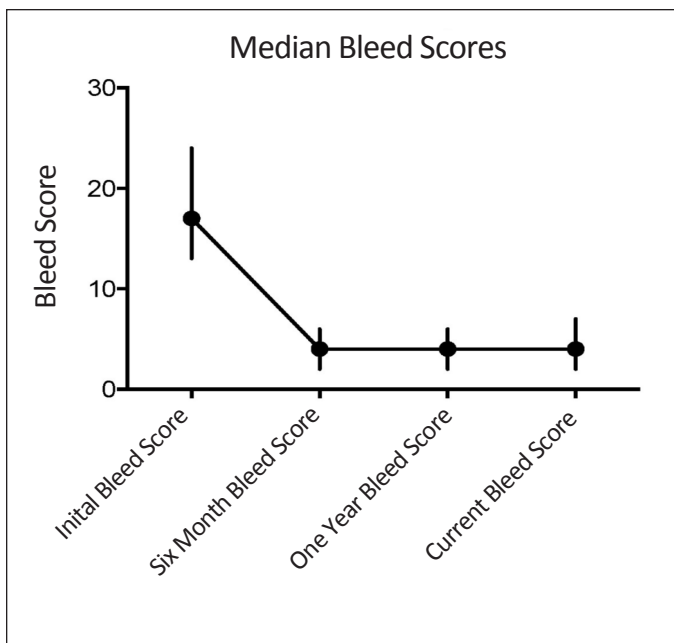


Figure 2. Median BI scores over time with the interquartile range for each measurement occasion. Initial measurement is significantly different from all other times ($p \leq 0.01$). The last measurement varied from 2.5–5 years, indicating that the adjunctive treatment sustained bleeding reduction over time.

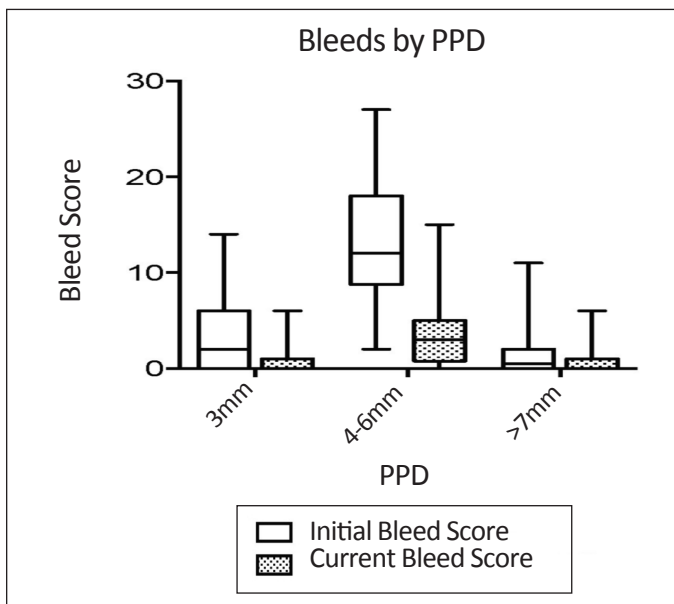


Figure 3. BI scores by PPD category: shallow, moderate, and severe. All categories demonstrated significant reductions from initial to last measurement. Bottom half of some plots are missing reflecting the zero bleed scores of multiple subjects.

PPD were eliminated from this analysis because the sample size was so low. This reduction trend can be seen in the percent reduction (Figure 4), as well as in the absolute BOP numbers (Figure 5).

To help sort out the data, a chi-square test on the condensed data for shallow (3–4 mm), moderate (5–6 mm), and deep (≥ 7 mm) pockets was completed to measure how much a distribution deviates from what is expected. There were significant differences in the distribution of bleeding PPD for the pre- and post-treatment scores ($X^2 = 23.88$, $df = 8$, $p < 0.0001$, effect size: $V = 0.13$). If the prescription tray delivery was equally effective across all PPD measurements, it would be expected that the relative decrease in BOP

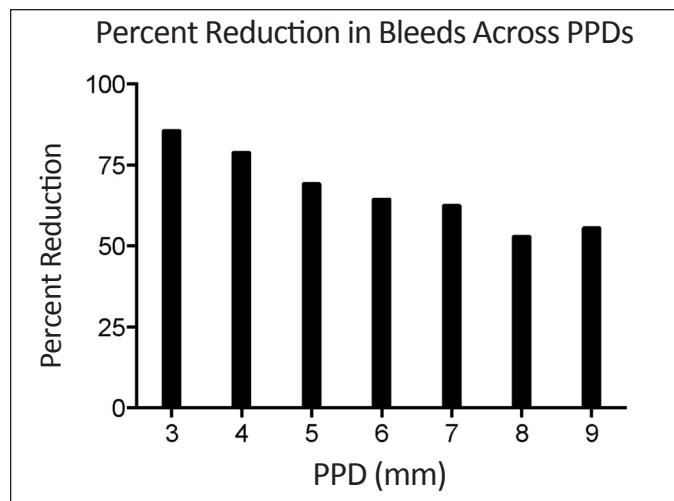


Figure 4. Percent reduction in bleeding points at each PPD. There are fewer bleeds across all PPDs, but those bleeds are particularly reduced at the shallower PPDs.

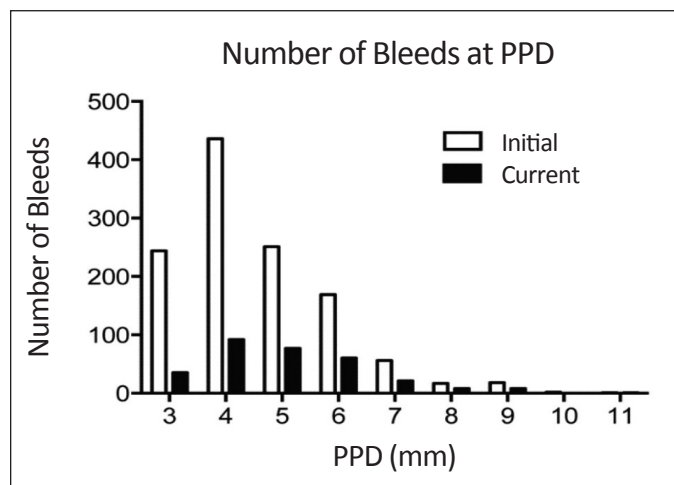


Figure 5. Absolute BOP numbers at each PPD pre- and post-treatment.

would be equal across all PPDs. The results, however, show that there is not a uniform decrease in bleeding points across the shallow, moderate, and deep PPDs. Prescription tray delivery was most effective reducing bleeding in shallower pockets; 3–4 mm pockets exhibited an 85% reduction in bleeding and pockets ≥ 7 mm had a 60% reduction in BOP.

PPD Data Analysis

For this analysis, PPD values were considered in aggregate form at each measurement time. No statistically significant difference in the distribution of PPDs was noted ($X^2 = 10.87$, $DF = 8$, $p = 0.2095$).

Other

From a clinical perspective, it is important to note that over the time frame of the study (2.5–5 years), out of the total number of teeth investigated (1,745), ten teeth were lost; nine for restorative reasons and one for periodontal reasons.

Discussion

Prescription tray delivery of 1.7% hydrogen peroxide gel was effective at substantially reducing BOP at six months of use. Significantly, the BI reduction was not transitory, but lasted through-

out the duration of this study. For clinicians, this reflects a meaningful improvement in the treatment of periodontal disease for refractory patients.

Consistent BI reductions for smokers and non-smokers are also clinically significant. Smoking status has long been recognized as one of, if not the, primary indicator of impending periodontal failure despite all standard periodontal treatments.^{19,27-29} Although long-term studies are rare, available publications unanimously agree that treatment failure and relapse of treatment are seen in smokers. This contention is valid irrespective of treatment modality, suggesting that smoking will interfere with an expected normal outcome following conventional periodontal therapies. Furthermore, long-term studies indicate that smoking was associated with recurrence of periodontitis during periodontal maintenance. In this light, the beneficial effects of this tested adjunctive therapy over a reasonable time period for these failing maintenance patients are encouraging.

Most surprising to the authors was that the frequency of prescription tray delivery (one a day vs. twice a day) did not significantly affect BI reductions. Tray delivery for ten minutes once a day was statistically as effective as twice a day. The treating periodontist reported, however, that anecdotally several of these patients did not do well at once a day, and upon advice returned to twice a day with subsequent improvement. In addition, if a patient dropped to once a day usage and continued to do well, no effort or advice was given to return to twice a day. It would be clinically important to have future studies more closely examine the frequency of usage since the results of this study cannot be generalized.

It was clear that the prescription tray delivery had more varied BI reductions as PPDs increased and that deeper pockets were more likely to continue to bleed. While investigators believe the practice of probing to the depths of the pocket to evaluate for bleeding more accurately reflects the presence of periodontitis rather than gingivitis, the apparent efficacy in reducing BI in deep pockets merits re-testing for verification by other examiners. Furthermore, experienced clinical judgment as to when to use traditional pocket reduction or pocket elimination surgical therapies to maximize the effectiveness of this adjunctive technique will be required.

The lack of change in PPD distribution contradicts previous studies. However, significant improvements in PPD were not expected for these refractory patients who had all received comprehensive periodontal therapy followed by routine periodontal maintenance, and had failed to respond. The goal was to arrest the disease process and reduce the risks for further damage and tooth loss.

The loss of only one tooth to periodontal disease over the time frame of this study is clinically relevant. This loss represents an annual 0.0055 loss of teeth per year for restorative reasons and 0.00061 loss of teeth per year for periodontal reasons, assuming an average of three years for this study. There are several studies of 6.7 to 11.7 years recording the long-term effect of routine periodontal treatment. These studies report tooth loss in the range of 0.03 to 0.09 teeth per year.³⁰⁻³³ This observation deserves additional study, but the substantial difference is noteworthy, especially because the failing periodontal maintenance patients in this report risked tooth loss for periodontal reasons before the start of the adjunctive therapy.

Although the results from this case study are encouraging, this adjunctive treatment method needs additional research. Among areas that need to be explored are the effectiveness of this treatment in the root flutes of maxillary first bicuspids and with furcation involvements. Future studies may benefit from an arm using an inert control substance in a tray appliance. It would also be useful to know why this adjunctive therapy is not universally effective in all pockets and if additional or alternative medications would further improve results.

Conclusions

The use of prescription tray delivery of 1.7% hydrogen peroxide gel demonstrated a clinical and significant decrease in BOP at six months of treatment and at all following assessments for 66 refractory periodontal maintenance patients. There were no significant differences across time for smoking status or frequency of tray usage.

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