

Photodynamic Therapy as an Adjunct to Non-Surgical Periodontal Treatment: A Randomized, Controlled Clinical Trial

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Background: Recent preclinical and clinical data have suggested a potential benefit of photodynamic therapy (PDT) in the treatment of periodontitis. However, there are very limited data from controlled clinical trials evaluating the effect of PDT in the treatment of periodontitis. The aim of this study was to evaluate the clinical and microbiologic effects of the adjunctive use of PDT to non-surgical periodontal treatment.

Methods: Twenty-four subjects with chronic periodontitis were randomly treated with scaling and root planing followed by a single episode of PDT (test) or scaling and root planing alone (control). Full-mouth plaque score (FMPS), full-mouth bleeding score (FMBS), probing depth (PD), gingival recession, and clinical attachment level (CAL) were measured at baseline and 3 and 6 months after therapy. Primary outcome variables were changes in PD and CAL. Microbiologic evaluation of *Aggregatibacter actinomycetemcomitans* (previously *Actinobacillus actinomycetemcomitans*), *Porphyromonas gingivalis*, *Prevotella intermedia*, *Tannerella forsythia* (previously *T. forsythensis*), *Treponema denticola*, *Parvimonas micra* (previously *Peptostreptococcus micros* or *Micromonas micros*), *Fusobacterium nucleatum*, *Campylobacter rectus*, *Eubacterium nodatum*, *Eikenella corrodens*, and *Capnocytophaga* spp. was performed at baseline and 3 and 6 months following therapy by using a commercially available polymerase chain reaction test.

Results: At 3 and 6 months after treatment, there were no statistically significant differences between the groups with regard to CAL, PD, FMPS, or microbiologic changes. At 3 and 6 months, a statistically significantly greater improvement in FMBS was found in the test group.

Conclusion: The additional application of a single episode of PDT to scaling and root planing failed to result in an additional improvement in terms of PD reduction and CAL gain, but it resulted in a significantly higher reduction in bleeding scores compared to scaling and root planing alone. *J Periodontol* 2008;79:1638-1644.

KEY WORDS

Clinical study; periodontitis; photodynamic therapy.

Periodontitis is a multifactorial disease that is associated with loss of the supporting tissues (i.e., periodontal ligament and alveolar bone) around the tooth.¹ A major objective of periodontal therapy is to remove soft and hard, supra- and subgingival deposits from the root surface to stop disease progression.² Numerous studies³⁻⁶ reported significant improvements in clinical and microbial parameters following non-surgical periodontal therapy. To further enhance the effectiveness of scaling and root planing (SRP), power-driven instruments, such as sonic and ultrasonic scalers, have been introduced. Studies⁵⁻⁷ demonstrated comparable clinical results following sonic or ultrasonic and manual instrumentation. Despite the fact that non-surgical periodontal treatment may result in significant clinical improvements in the great majority of cases, none of the currently available instrumentation techniques are effective in completely eliminating subgingival bacteria and calculus.⁸ These limitations could be attributed to several factors, such as the complex anatomy of teeth (i.e., furcation-involved teeth) and mechanical limitations related to the size of instruments or invasion of periodontal pathogens into the surrounding soft tissues or possible recolonization of periodontal pockets from other diseased sites or intraoral niches.⁹

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Photodynamic therapy (PDT), also called photoradiation therapy, phototherapy, or photochemotherapy, was introduced in medical therapy in 1904 as the light-induced inactivation of cells, microorganisms, or molecules.¹⁰ PDT involves the combination of visible light, usually through the use of a diode laser and a photosensitizer. The photosensitizer is a compound that is capable of absorbing light of a specific wavelength and transforming it into useful energy.¹¹ Each factor is harmless by itself, but when combined they can produce lethal cytotoxic agents that can selectively destroy cells.¹¹ Thus, PDT may represent a promising alternative for reducing the bacterial load or even for eradicating certain periodontal pathogens.^{12,13}

The action mechanism of PDT has been described.¹⁴ Briefly, upon illumination, the photosensitizer is excited from the ground state to the triplet state. The longer lifetime of the triplet state enables the interaction of the excited photosensitizer with the surrounding molecules, and it is generally accepted that the generation of the cytotoxic species produced during PDT occurs while in this state.¹⁵ The cytotoxic product, usually O₂, cannot migrate >0.02 μm after its formation, thus making it ideal for the local application of PDT without endangering distant molecules, cells, or organs.¹⁶

Experimental examinations revealed that light from a helium/neon (He/Ne) laser or a gallium-aluminum-arsenide laser, in combination with appropriate photosensitizers, resulted in a significant reduction in the viability of aerobic and anaerobic bacteria in a solution of subgingival plaque from subjects with chronic periodontitis.^{17,18} It was also demonstrated that bacteria associated with periodontal disease can be killed through photosensitization with toluidine blue O and irradiation with an He/Ne soft laser.¹⁹ Moreover, data from an in vitro study²⁰ indicated that PDT could also kill bacteria organized in a biofilm. In an animal study,²¹ PDT was distinctly advantageous in reducing the periodontal signs of redness and bleeding on probing, and *Porphyromonas gingivalis* (*Pg*) was significantly suppressed. A very recent controlled clinical study²² compared the effects of PDT treatment alone (i.e., without subgingival SRP) to subgingival SRP in subjects with aggressive periodontitis. At 3 months following therapy, both treatments yielded comparable outcomes in terms of reduction of bleeding on probing and probing depths (PDs) and gains in clinical attachment level (CAL), thus suggesting a potential clinical effect of PDT.

However, the data from controlled clinical studies evaluating the effects of an adjunctive use of PDT to SRP are limited. Therefore, the aim of the present prospective, controlled clinical study was to clinically and microbiologically evaluate the effectiveness of the ad-

adjunctive use of PDT to non-surgical periodontal treatment in chronic periodontitis patients receiving initial periodontal therapy.

MATERIALS AND METHODS

Subject Selection

Twenty-four subjects (age range, 36 to 56 years; mean age, 45 ± 8.11 years) with chronic periodontitis, who were referred for periodontal treatment at the Department of Periodontology, Radboud University Medical Center, were included in the study after having signed an informed consent.²³ The study was performed between February 2005 and November 2006 in accordance with the Helsinki Declaration of 1975, as revised in 2002. Criteria for subject selection were no treatment of periodontitis for the last 2 years, no systemic diseases that could influence the outcome of the therapy, no pregnancy, and no use of antibiotics for the 12 months prior to treatment.

The following clinical parameters were assessed at baseline and at 3 and 6 months after active periodontal therapy using the same type of periodontal probe:[§] full-mouth plaque score (FMPS),²⁴ full-mouth bleeding score (FMBS) assessed dichotomously, probing depth (PD), gingival recession, and CAL.

All clinical measurements were made at six sites per tooth: mesio-facial, mid-facial, disto-facial, mesio-lingual, mid-lingual, and disto-lingual by the same calibrated investigator (DN). The examiner was not aware of the type of treatment rendered. The cemento-enamel junction (CEJ) was used as the reference point. In cases in which the CEJ was not visible, a restoration margin was used for these measurements.

Study Design

The study was performed according to a parallel design. Treatment allocation was performed by a toss of a coin. All subjects were treated within 24 hours with SRP using hand instruments^{||} and sonic instrumentation[¶] followed by a single episode of PDT[#] (test) or SRP using hand instruments and sonic instrumentation (control). Oral hygiene instruction individualized for every subject was given at the first appointment followed by initial periodontal treatment. Following local anesthesia, subgingival instrumentation for test and control groups was performed until the operator believed that the root surfaces were adequately debrided and planed. Randomization was performed immediately following the completion of instrumentation. In the test group, the photosensitizer liquid** was applied with a blunt needle to the instrumented sites, starting from the apical

§ UNC 15, Hu-Friedy, Chicago, IL.

|| Gracey curets, Hu-Friedy.

¶ Sonicflex, KaVo Dental, Biberach, Germany.

HELBO Photodynamic Systems, Grieskirchen, Austria.

** HELBO Blue Photosensitizer, HELBO Photodynamic Systems.

end of the pocket and moving coronally to avoid entrapment of air bubbles. Three minutes later all pockets were thoroughly rinsed with sterile saline to remove the excess photosensitizer. Immediately after rinsing, the diode laser, with 670 nm wavelength and 75 mW of power output,^{††} equipped with a probe tip, was placed at the depth of the pocket and moved circumferentially around the tooth for 1 minute, according to the manufacturer's instructions. In all cases, treatment was performed under local anesthesia by the same experienced operator (NC) in a single session. The subjects returned at 3 months for evaluation. After microbiologic testing and clinical measurements were performed, the subjects received one session of prophylaxis, including reinforcement of oral hygiene, supragingival debridement, and tooth polishing. The study was completed at 6 months. After microbiologic and clinical evaluation, the subjects received a session of periodontal maintenance therapy, whereas subjects with multiple deep sites were scheduled for surgical therapy. If a site lost >2 mm CAL from baseline it was excluded from the study, and subgingival instrumentation would be performed.

Sample-Size Calculation

The sample-size calculation determined that 10 subjects per treatment group would provide 80% power to detect a true difference of 1 mm between test and control using PD reduction in pockets as the primary outcome variable, assuming that the common standard deviation was 0.8 mm. Accordingly, a sample of 12 subjects per group (24 total) was recruited to compensate for possible dropout during the study period.

Intraexaminer Reproducibility

Five subjects, not related to the study and each showing two pairs of contralateral teeth (single- and multi-rooted) with PD >6 mm on at least one aspect of each tooth, were used to calibrate the examiner (DN). The examiner evaluated the subjects on two occasions 48 hours apart. Calibration was accepted if 90% of the recordings could be reproduced within a 1.0-mm difference.

Microbiologic Assessment

Subgingival plaque samples were taken at baseline from the deepest pocket per quadrant. The same sites were resampled at 3 and 6 months. Following meticulous removal of supragingival calculus and plaque using sterile standard periodontal scalers and sterile cotton pellets, each selected site was dried and isolated from water and saliva using cotton rolls. Subsequently, a sterile paper point was inserted and left in place for 20 seconds. The four samples from each subject were collected in a sterile vial (pooled sample) and sent to the laboratory for analysis.

DNA analysis was performed using a commercially available kit.^{‡‡} The analysis was performed to identify the following microorganisms: *Aggregatibacter actinomycetemcomitans* (previously *Actinobacillus actinomycetemcomitans*; Aa), *Pg*, *Prevotella intermedia* (Pi), *Tannerella forsythia* (previously *T. forsythensis*; Tf), *Treponema denticola* (Td), *Parvimonas micra* (previously *Peptostreptococcus micros* or *Micromonas micros*; Pm), *Fusobacterium nucleatum* (Fn), *Campylobacter rectus* (Cr), *Eubacterium nodatum* (En), *Eikenella corrodens* (Ec), and *Capnocytophaga* spp. (Cs).

Bacterial levels were expressed as genome equivalents ($<10^3 = 0$; 10^3 to $10^4 = 1$; 10^4 to $10^5 = 2$; and 10^5 to $10^6 = 3$). The test had a detection threshold of 10^3 genome equivalents.

Statistical Analysis

The statistical analysis was performed using commercially available software.^{§§} A subject-level analysis was performed for each of the parameters. All teeth were included in the statistical evaluation. Primary clinical outcome variables were changes in CAL and PD. Secondary clinical outcome variables were changes in FMBS and FMPS. Mean \pm SD for the clinical variables were calculated for each treatment. The Student *t* test was used for continuous variables after confirming normality of the data distribution. The method of Kolmogorov and Smirnov was used to confirm that the data were sampled from a Gaussian distribution. Likewise, the significance of the difference within each group before and after treatment was evaluated with the paired samples *t* test. Ordinal data (microbiologic values) were analyzed with the Mann-Whitney U test. Finally, the χ^2 test was used for categorical data. Differences were considered statistically significant when the *P* value was <0.05.

RESULTS

All subjects completed the 6-month evaluation period. Healing was uneventful in all cases. No adverse effects, such as discomfort, burning sensation, or pain related to the laser irradiation, were reported by any of the subjects.

The baseline characteristics of the 24 participants are displayed in Table 1. The mean age was 43.7 ± 7.3 years for the test group and 47.3 ± 8.8 years for the control group. There were seven females and five males in the test group and six females and six males in the control group. Two subjects in the test group and one subject in the control group were smokers (≥ 10 cigarettes per day). None of these demographic parameters showed a statistically significant difference between the groups.

†† HELBO TheraLite Laser, HELBO Photodynamic Systems.

‡‡ Micro-IDent, Hain Lifescience, Nehren, Germany.

§§ Instat 2000, version 3.05, GraphPad Software, San Diego, CA.

Table 1.
Subject and Clinical Characteristics at Baseline

Parameter	Test Group (SRP+PDT) (n = 12)	Control Group (SRP) (n = 12)	P Value
Age (years; mean \pm SD)	43.7 \pm 7.3	47.3 \pm 8.8	0.289
Females (n [%])	7 (58)	6 (50)	0.682
Smokers (n [%])	2 (16)	1 (8)	0.538
CAL (mm; mean \pm SD)	4.1 \pm 0.5	4.5 \pm 1.0	0.219
PD (mm; mean \pm SD)	3.7 \pm 0.5	3.6 \pm 0.6	0.577
REC (mm; mean \pm SD)	0.5 \pm 0.4	1.0 \pm 0.8	0.051
FMPS (%; mean \pm SD)	58 \pm 24	62 \pm 14	0.631
FMBS (%; mean \pm SD)	54 \pm 16	59 \pm 21	0.501
Teeth per subject (n; mean \pm SD)	24 \pm 4	26 \pm 2	0.238
Sites with PD 4 to 6 mm (n; mean \pm SD)	47 \pm 14	49 \pm 25	0.812
Sites with PD \geq 7 mm (n; mean \pm SD)	9 \pm 9	8 \pm 7	0.740

REC = gingival recession.

Table 2.
Differences in CAL, PD, and Recession (mean \pm SD)

Parameter	Baseline	3 Months	Difference (0 to 3 months)	P Value	6 Months	Difference (0 to 6 months)	P Value
CAL (mm)							
Test	4.1 \pm 0.5	3.6 \pm 0.5	0.5 \pm 0.3	<0.001	3.4 \pm 0.6	0.7 \pm 0.3	<0.001
Control	4.5 \pm 1.0	4.1 \pm 1.1	0.4 \pm 0.4	0.007	4.0 \pm 1.0	0.5 \pm 0.5	0.001
P value			0.328			0.542	
PD (mm)							
Test	3.7 \pm 0.5	3.0 \pm 0.5	0.7 \pm 0.3	<0.001	2.8 \pm 0.4	0.9 \pm 0.3	<0.001
Control	3.6 \pm 0.6	2.9 \pm 0.3	0.7 \pm 0.5	0.001	2.9 \pm 0.3	0.7 \pm 0.7	0.003
P value			0.601			0.484	
REC (mm)							
Test	0.5 \pm 0.4	0.7 \pm 0.3	0.2 \pm 0.2	0.003	0.7 \pm 0.3	0.2 \pm 0.3	0.016
Control	1.0 \pm 0.8	1.3 \pm 1.0	0.3 \pm 0.3	0.008	1.2 \pm 1.0	0.2 \pm 0.4	0.233
P value			0.674			0.725	

REC = gingival recession.

Clinical Assessments

The baseline examination revealed that the two study groups showed similar characteristics for CAL, PD, and plaque and bleeding scores, with no significant differences between the groups (Table 1).

Clinical measurements (mean \pm SD) and the differences between baseline and 3 months and baseline and 6 months are displayed in Table 2. There was no significant difference between test and control at baseline. All parameters showed a statistically significant difference between baseline and 3 months. This was also true between baseline and 6 months. No statisti-

cally significant difference was observed between the groups at any time point. Furthermore, CAL and PD changes were analyzed for initially moderate (4 to 6 mm) and deep (\geq 7 mm) pockets, and no statistically significant difference was observed between the groups at any time point (data not shown). Additionally, no site showed CAL loss $>$ 2 mm in either treatment group.

FMPS and FMBS at baseline and 3 and 6 months for test and control groups are displayed in Table 3. Plaque scores decreased with both treatments from baseline to 3 and to 6 months, and the difference was statistically significant for both groups. No

difference was observed between the groups at any evaluation period. Bleeding scores decreased with both treatments from baseline to 3 and to 6 months, and the difference was statistically significant for both groups. Furthermore, there was a statistically significant difference between test and control for the improvement in the percentage of bleeding sites at 3 and 6 months favoring the test group ($P < 0.001$).

Microbiologic Assessments

Mean \pm SD for each analyzed bacterial species and the differences between the groups are presented in Figures 1 through 3. No statistically significant difference was observed between the two treatment groups at the baseline and post-treatment examinations.

DISCUSSION

The results of this study showed that both treatment modalities may lead to statistically significant improvements in all investigated clinical parameters at 3 and 6 months following therapy. No statistically sig-

Table 3.
FMPS and FMBS (mean \pm SD) at 3 and 6 Months

Parameter	Test Group (SRP+PDT) (n = 12)	Control Group (SRP) (n = 12)	P Value
FMPS (%)			
Baseline	58 \pm 24	62 \pm 14	0.631
3 months	12 \pm 6	16 \pm 10	0.155
6 months	14 \pm 4	15 \pm 6	0.867
FMBS (%)			
Baseline	54 \pm 16	59 \pm 21	0.501
3 months	13 \pm 7	22 \pm 5	<0.001
6 months	10 \pm 5	20 \pm 4	<0.001

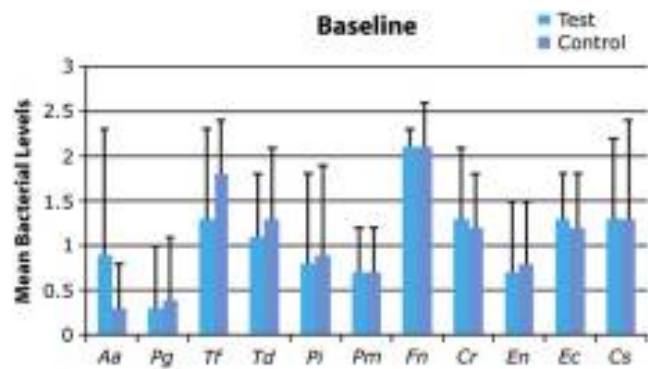


Figure 1.
Levels (mean \pm SD) of tested bacteria at baseline.

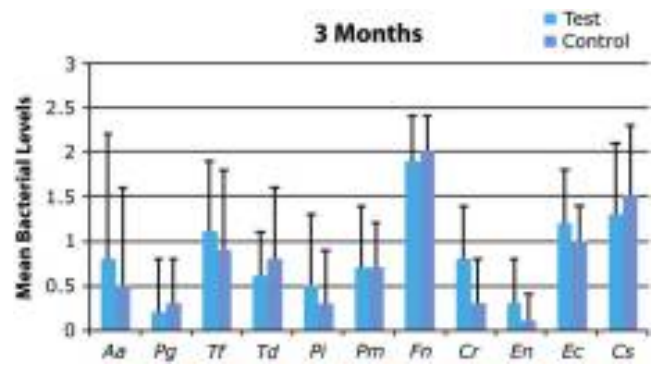


Figure 2.
Levels (mean \pm SD) of tested bacteria at 3 months.

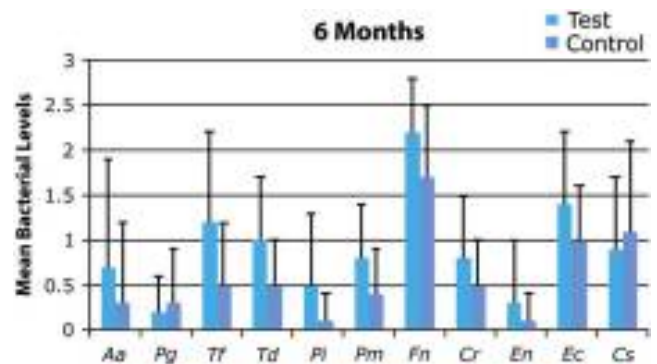


Figure 3.
Levels (mean \pm SD) of tested bacteria at 6 months.

nificant difference in terms of CAL and PD changes was found between the two groups. The positive clinical outcomes obtained in the control group are in agreement with the previously reported findings on the clinical efficacy of subgingival debridement in the treatment of chronic periodontitis that showed that in subjects with chronic periodontitis, subgingival debridement in conjunction with supragingival plaque control was effective in reducing PD and improving CAL.^{2-7,25} A systematic review²⁵ analyzing the data from 18 randomized, controlled clinical studies found a weighted mean of a 0.74-mm gain of CAL in pockets initially ≥ 4 mm following subgingival debridement.

Another aspect that should be kept in mind when interpreting the present findings is that subgingival debridement was performed in all 24 subjects within a period of 24 hours, which might have influenced the clinical outcomes. However, the results of a very recent Cochrane systematic review²⁶ comparing the effects of full-mouth subgingival debridement (i.e., within 24 hours) to conventional subgingival debridement (i.e., weekly per quadrant) in subjects with chronic periodontitis failed to demonstrate significant

differences between the two approaches. Thus, the data indicate that in this particular subject population, subgingival debridement may be performed in either way, with the expected clinical outcomes being comparable.

At 3 and 6 months, the test treatment resulted in a statistically significant improvement in FMBS compared to the control treatment. These findings are in agreement with a recent controlled clinical trial²⁷ that showed that treatment with low-level laser irradiation as an adjunct to conventional SRP in periodontal subjects significantly reduced periodontal gingival inflammation. In that study, gingival inflammation was evaluated through a sampled volume of gingival crevicular fluid (GCF) that was analyzed for elastase activity, interleukin-1 β , and metalloproteinase-8 (MMP-8). The decrease in the total volume of GCF was significantly greater in the laser group, and the difference in measured MMP-8 approached significance. A meta-analysis²⁸ of medical literature regarding animal and human studies concluded that low-level laser therapy is an effective tool for promoting wound repair. These findings seem to indicate that the positive effects upon wound healing following low-level laser therapy may also be attributed to the acceleration of collagen synthesis, reduction of inflammation, and increase in wound tensile strength.²⁸ In another review, it was suggested that PDT may also bear some possible benefits, such as an additional effect at sites with difficult access (e.g., furcations, deep invaginations, and concavities), influencing the biofilm in residual deep pockets, decreasing the risk for bacteremia which routinely occurs after periodontal treatment, or as an alternative for diminishing the danger of an increase in antibiotic resistance.²⁹

However, in a very recent controlled clinical study²² in subjects with aggressive periodontitis, treatment with PDT alone (i.e., without subgingival SRP) was compared to subgingival SRP. At 3 months following therapy, the mean PD decreased from 4.92 ± 1.61 mm to 3.49 ± 0.98 mm in the PDT group and from 4.92 ± 1.14 mm at baseline to 3.98 ± 1.76 mm in the SRP group. The mean relative CAL decreased from 9.93 ± 2.10 mm at baseline to 8.74 ± 2.12 mm in the PDT group and from 10.53 ± 2.30 mm at baseline to 9.01 ± 3.05 mm in the SRP group. There were no statistically significant differences in any of the investigated clinical parameters, thus indicating similar results for the two treatments in the non-surgical treatment of aggressive periodontitis.

In the present study, the mean microbial levels decreased significantly in both groups. These results were very difficult to interpret because there are no similar clinical studies to compare them to. Conversely, an *in vitro* study¹² evaluating the use of PDT on oral bacteria showed that the combination of a photosensitizer

with low-power laser irradiation was effective in killing *Aa*, *Pg*, and *Fn*. In a similar *in vitro* study,¹⁹ complete elimination of *Aa*, *Pg*, and *Fn* was also possible if PDT was used against bacteria organized in biofilms.

However, a direct comparison of the mentioned microbiologic findings to those from the present study is difficult. It is well known that the results of *in vitro* studies cannot always be directly extrapolated to the human situation; therefore, they need to be interpreted with caution.^{29,30} Furthermore, different types of sensitizers, light-application devices, and wavelengths were used in the studies mentioned, which makes direct comparisons between the techniques used very difficult.

When interpreting the clinical and microbiologic effects obtained with PDT, the possible effects due to the application of the photosensitizer itself should be considered. Moreover, it should be kept in mind that there are very limited data from controlled clinical studies comparing PDT used in conjunction with non-surgical periodontal therapy to PDT alone, SRP alone, or the photosensitizer alone (i.e., used without light activation). Thus, further studies are warranted before any definitive conclusions can be drawn about the possible clinical benefit of PDT used in conjunction with non-surgical therapy.

The frequency of the PDT application is another possible explanation for the absence of clinical or microbiologic differences between the groups. The manufacturer suggests that PDT treatment should be performed repeatedly during the first weeks of healing to enhance the antimicrobial effect. However, in this study, a single episode of PDT was performed to avoid an additional confounding factor (i.e., frequency of applied treatment), which could influence the clinical outcome. Future studies are needed to definitively elucidate to what extent multiple applications of PDT might enhance the outcome of therapy.

CONCLUSION

Within its limits, the present study showed that the addition of a single episode of PDT to SRP failed to result in an improvement in terms of PD reduction and CAL gain, but it resulted in a significantly greater reduction in bleeding scores compared to SRP alone.

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