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Combined photodynamic and low-level laser therapies as an adjunct to nonsurgical treatment of chronic periodontitis

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Background and Objective: In recent years, there has been a growing interest in the use of dental lasers for treatment of periodontal diseases. The purpose of this short-term clinical trial was to evaluate the effects of a combination of photodynamic therapy with low-level laser therapy as an adjunct to nonsurgical treatment of chronic periodontitis.

Material and Methods: Twenty-four nonsmoking adults with untreated chronic periodontitis were randomly assigned in a split-mouth design to receive scaling and root debridement with or without one course of adjunctive photodynamic therapy and low-level laser therapy within 5 d. Plaque, bleeding on probing, probing depth and gingival recession were recorded at baseline, 1 and 3 mo after the treatment. Gingival crevicular fluid was collected for assay of interleukin-1β levels at baseline, 1 wk and 1 mo.

Results: The test teeth achieved greater reductions in the percentage of sites with bleeding on probing and in mean probing depth at 1 mo compared with the control teeth ($p < 0.05$). A significant decrease in gingival crevicular fluid volume was observed in both groups at 1 wk ($p < 0.001$), with a further decrease at 1 mo in the test sites ($p < 0.05$). The test sites showed a greater reduction of interleukin-1β levels in gingival crevicular fluid at 1 wk than the control sites ($p < 0.05$). No significant differences in periodontal parameters were found between the test and control teeth at 3 mo.

Conclusions: The present study suggests that a combined course of photodynamic therapy with low-level laser therapy could be a beneficial adjunct to nonsurgical treatment of chronic periodontitis on a short-term basis. Further studies are required to assess the long-term effectiveness of the combination of photodynamic therapy with low-level laser therapy as an adjunct in nonsurgical treatment of periodontitis.

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Periodontal disease is initiated by pathogenic plaque biofilm and characterized by bacteria-induced inflammatory destruction of tooth-supporting structures and alveolar bone. Mechanical scaling and root debridement have shown to be an effective treatment approach for periodontal disease (1,2). However, the limitations of scaling and root debridement have also been shown in management of initially deep periodontal pockets and furcation involved lesions (3,4). In recent years, various innovative adjunctive treatments have therefore been developed to improve the clinical effectiveness of scaling and root debridement (5).

Use of lasers in dentistry has been gaining popularity over the past few years. From the first ruby-based laser device developed by Theodore Maiman in 1960, various types of lasers with different systems are now available for clinical practice. Dental lasers have been classified based upon the difference in active medium, wavelength, delivery system, emission modes, tissue absorption and clinical applications, including argon and helium lasers, diode lasers, neodymium yttrium aluminium garnet (Nd:YAG) lasers, holmium:YAG and erbium family lasers and CO_2 lasers. In nonsurgical periodontal therapy, dental lasers have demonstrated the ability to remove calculus and decontaminate the root surfaces whilst inflicting minimal damage to root cementum (6–8). The Nd:YAG and CO_2 lasers have been successfully used in surgical treatment of periodontal diseases, with anticipated clinical benefits on excisions and coagulation of intraoral soft tissues, with minimal postoperative pain and bleeding (9,10). In recent years, there has been a growing interest in usage of diode lasers for periodontal treatment due to their antimicrobial and anti-inflammatory properties. It has been shown that use of the diode laser could contribute to significant reduction in bacterial populations and control of periodontal inflammation (11–13). The diode laser can be used safely in periodontal practice (14). An *in vitro* study showed that diode laser irradiation could stimulate the proliferation of periodontal ligament cells (15).

Photodynamic therapy is a technique combining laser energy with a photosensitizer to produce singlet oxygen molecules and free radicals to destroy targeted cells (16). It is an effective tool in treatment of oral lichen planus and periodontal diseases (17–19). Recently, a few studies have investigated the clinical effectiveness of photodynamic therapy as an adjunct in treatment of periodontitis (20–25). Low-level laser therapy, known as biostimulation, describes the effect of low-level laser energy on living cells determined by the wavelength of the laser and the total energy delivery measured as joules per square centimeter (26). It could affect the multi-staged process of wound healing, including the initial proinflammatory and vasoactive phase, formation of granulation tissue, angiogenesis and tissue remodelling. It is evident that low-level laser therapy can promote tissue repair by accelerating collagen production and can enhance the overall stability of connective tissues (27,28). Taken together, it is conceivable that photodynamic therapy in combination with low-level laser therapy might have biologically synergistic effects on control of microbial infections and the resultant inflammatory response as well as on promotion of tissue healing. Currently, there are no studies which combine photodynamic therapy and low-level laser therapy as an adjunctive 'package' in nonsurgical treatment of periodontitis. The present study was designed to evaluate the short-term effects of a combined course of photodynamic therapy with low-level laser therapy as an adjunct in treatment of chronic periodontitis.

Material and methods

Subjects

Twenty-four nonsmoking Chinese adults (10 males and 14 females with a mean age of 50 years) were recruited from the Prince Philip Dental Hospital, Hong Kong. Inclusion criteria were: (i) aged 18 years and above; (ii) healthy systemic condition; and (iii) presentation of untreated chronic periodontitis with at least two single-rooted teeth on each side of the mouth having probing depth ≥ 5 mm, interproximal attachment loss of ≥ 3 mm and radiographic signs of alveolar bone loss. Exclusion criteria were: (i) pregnancy; (ii) systemic diseases which could affect periodontal treatment outcomes; (iii) use of immunosuppressive agents; (iv) antibiotics or anti-inflammatory drugs taken within the preceding 3 mo;and (v) periodontal treatment within the past 6 mo. All subjects were given an information pamphlet about the study, and oral and written informed consent was obtained from all participants prior to the study. This study was approved by the Institutional Review Board of The University of Hong Kong/Hospital Authority Hong Kong West Cluster, and it was conducted in accordance with the provisions of the Declaration of Helsinki.

Study design and periodontal examination

The present study was a single-blinded, split-mouth design clinical trial. At baseline, all subjects underwent a full-mouth periodontal examination at six sites per tooth (excluding the third molars), including number of missing teeth, bleeding on probing, probing depth and gingival recession, which was measured as the distance from the cemento-enamel junction to the free gingival margin. Plaque scores were recorded at four sites per tooth. The examination was undertaken by a single investigator who was not involved in the treatment. In each subject, two single-rooted teeth having at least one site with probing depth ≥ 5 mm on either side of the mouth were randomly allocated as the test teeth (scaling and root debridement plus combined adjunctive laser treatments) or the control teeth (scaling and root debridement alone). The test teeth were matched clinically with the control teeth. Gingival crevicular fluid samples were collected from the test and control teeth at baseline, 1 wk and 1 mo after the treatment, whilst clinical data were obtained at baseline, 1 and 3 mo (Fig. 1).

Gingival crevicular fluid sampling and assay

Gingival crevicular fluid samples were collected from the test and control teeth following our previously established protocol (29). Briefly, after isolating the teeth with cotton rolls, a filter paper strip (Periopaper®; Oraflow Inc., New York, NY, USA) was gently inserted into the pocket until mild resistance was met and placed for 30 s. Gingival crevicular fluid volume was immediately measured by the Periotron 8000® (Oraflow Inc.) and then

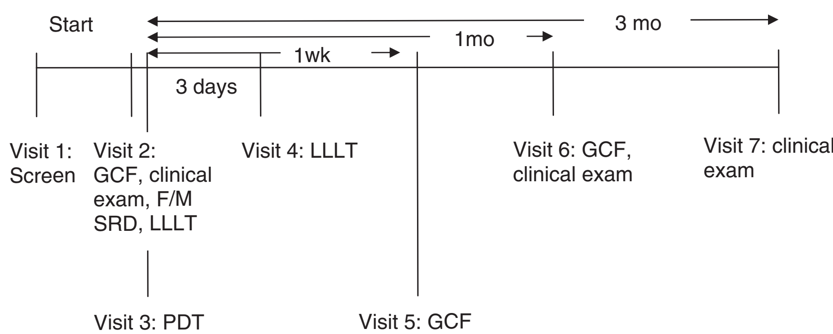

Fig. 1. Study design. Abbreviations: GCF, gingival crevicular fluid; F/M SRD, modified one-stage full-mouth scaling and root debridement; LLLT, low-level laser therapy; and PDT, photodynamic therapy.

converted to units of microlitres. Blood-contaminated samples were discarded. The two gingival crevicular fluid samples from each side of the mouth were then pooled together, placed in 200 μL of sterile phosphate-buffered saline (pH 7.2) for 30 min, and then consistently agitated by a vortex shaker for 60 min to elute the gingival crevicular fluid sample. The strips were then removed, and the eluent was centrifuged at 3000*g* for 5 min. The supernatants were stored at −70°C until further analysis. Interleukin-1β (IL-1β) was analysed using an ELISA kit (R&D Systems, Minneapolis, MN, USA), and values are presented as picograms per microlitre.

Periodontal and adjunctive laser treatments

On the first day, all patients received routine oral hygiene instructions and a modified one-stage full-mouth scaling and root debridement under local anaesthesia of 2% lidocaine with 1:80000 adrenaline (Xylestesin^{TM} -A; 3M ESPE AG, Seefeld, Germany). On completion of scaling and root debridement, the test teeth received low-level laser therapy using a 940 nm diode laser (Ezlase™; BIOLASE Technology Inc. Irvine, CA, USA). The laser was fired at the orifice of the gingival margin at a distance of 1 cm, using a setting of 1.5 W as a continuous wave. Each tooth received 5–10 s of exposure, giving no more than 4 J/cm^2 of energy. The patients returned on the next day, and the same test teeth underwent photodynamic therapy. Topical anaesthetic gel (20% benzocaine, Topex®; Sultan Healthcare, Englewood, NJ, USA) was initially applied and then washed off. The periodontal pockets were filled with a 1% methylene blue solution, which was left for 3 min before any excess was gently rinsed away. The diode laser was operated at a peak power of 5.0 W, with a pulse length of 0.05 ms and pulse interval of 0.2 ms (average 1.0 W), using a 300 μm fibre-optic tip (30). The tip was initiated and introduced into the pocket with a smooth stroking action, starting coronally and working towards the bottom of the pocket. No more than 30 s were allocated to each tooth. The patients returned after 3 d for the final low-level laser therapy on the test teeth. Oral hygiene instructions were reinforced at 1 and 3 mo after the treatment. The laser therapy was performed by a trained operator who was not involved in clinical examination and data collection. Specially designed safety glasses were provided to the patient, operator and dental assistant for protection of the eyes from the laser beam. The laser treatment was carried out in a closed room, with an appropriate warning sign at the door to inform those outside.

Statistical analysis

The mean or percentage (percentage of sites) of clinical and gingival crevicular fluid data was calculated for test and control teeth in each subject. Student's paired *t*-test was used to determine the significance of the differences between the test and control groups. When the data showed a skewed distribution, the median differences were compared using the Wilcoxon signed rank test. Differences between data sets with a probability of < 0.05 were regarded as statistically significant. The statistical analysis was carried out using a statistics package (SPSS for Windows, release 16.0; SPSS Inc., Chicago, IL, USA).

Results

All 24 patients completed the 3 mo clinical trial, with no patients reporting any postoperative pain, discomfort or complications at any of the follow-up appointments. At the subject level, the overall periodontal condition was significantly improved after treatment. There was a reduction in the percentage of sites with bleeding on probing from 84 ± 14% at baseline to 35 ± 8% at 1 mo and 27 ± 8% at 3 mo ($p < 0.001$), and a reduction in the percentage of sites with probing depth ≥ 5 mm from 34 ± 10% at baseline to 14 ± 6% at 1 mo and 11 ± 6% at 3 mo ($p < 0.001$).

A total of 96 teeth and 576 sites were evaluated, and the clinical data are shown in Table 1. At baseline, no significant differences were found between the test and control teeth, while significant improvements in clinical condition were observed after treatment ($p < 0.05$). In addition, the test teeth exhibited a greater reduction in mean probing depth ($p < 0.05$) and percentage of sites with bleeding on probing ($p < 0.05$) at 1 mo (Figs 2 and 3) compared with the control teeth. No significant differences were found between the test and control teeth at 3 mo.

Gingival crevicular fluid data are shown in Table 2. At baseline, no significant difference in gingival crevicular fluid volume was found between test

Table 1. Clinical data (means ± SD) in test and control teeth

	Test			Control		
	Baseline	1 mo	3 mo	Baseline	1 mo	3 mo
Plaque (% of sites)	83 ± 28	31 ± 38**	27 ± 33	88 ± 27	38 ± 42*	27 ± 36†
Bleeding on probing (% of sites)	94 ± 06	40 ± 18**	39 ± 14	92 ± 10	49 ± 15**	43 ± 12†
Probing depth (mm)	4.7 ± 0.8	3.3 ± 0.4**	3.1 ± 0.5†	4.5 ± 0.7	3.4 ± 0.4**	3.2 ± 0.3†
Recession (mm)	0.8 ± 1.2	1.6 ± 1.1**	1.8 ± 1.2	1.0 ± 1.1	1.6 ± 1.1*	1.8 ± 1.3

*$p < 0.05$, **$p < 0.001$, significant difference from baseline.
†$p < 0.05$, significant difference from 1 mo.

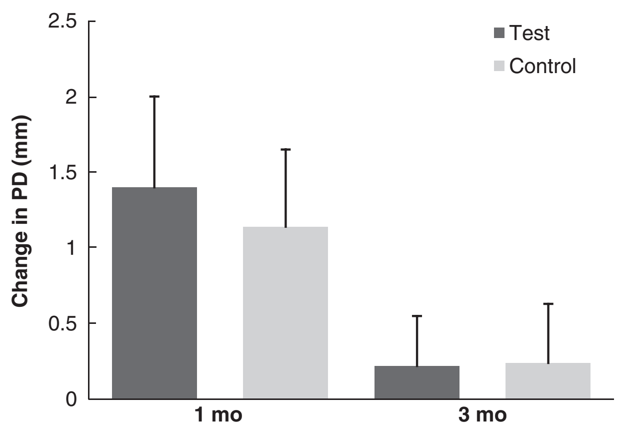

Fig. 2. Change in probing depth (means + SD) from baseline to 1 mo and from 1 mo to 3 mo after the treatment in test and control teeth. Test teeth show a significantly greater reduction in probing depth compared with the control teeth at 1 mo ($p < 0.05$).

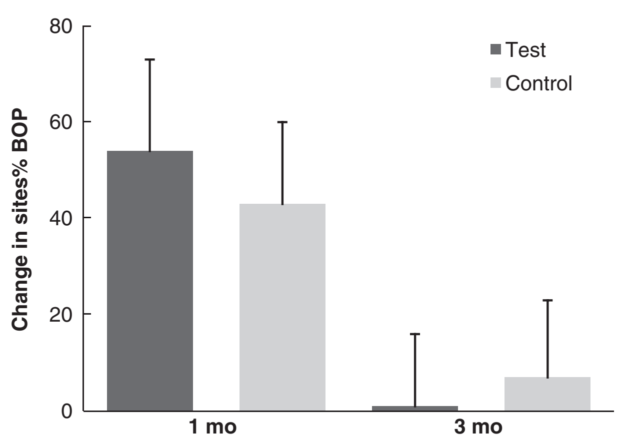

Fig. 3. Change in percentage of sites with bleeding on probing (means + SD) from baseline to 1 mo and from 1 mo to 3 mo after the treatment in test and control teeth. Test teeth show a significantly greater reduction in percentage of sites with bleeding on probing compared with control teeth at 1 mo ($p < 0.05$).

and control sites. Compared with the baseline, gingival crevicular fluid volume reduced significantly at 1 wk in the test and control sites ($p < 0.001$), whilst further reduction at 1 mo was observed only in the test sites ($p < 0.05$). At baseline, there was no significant difference in gingival crevicular fluid IL-1β levels between the test and control sites. Compared with the control sites, a significantly greater reduction of IL-1β levels was found in the test sites at 1 wk (346.0 ± 127.4 vs. 274.5 ± 162.0 pg/mL, $p < 0.05$; Fig. 4.). No significant differences were found between the test and control sites at 1 mo.

Discussion

The primary objective of initial periodontal therapy is the disturbance, disruption and control of the pathogenic plaque biofilms on the tooth surface. Nonsurgical periodontal therapy with use of both hand and powered instruments has shown to be an effective and predictable treatment approach (1,2,31–33). Mechanical debridement can create significant changes in the microbiological environment of periodontal pockets by shifting the pathogenic biofilm to a beneficial one. This leads to a decrease in microbial loading and concentration of its products, such as lipopolysaccharide, thereby resulting in a better control of host immuno-inflammatory responses, reduction in gingival crevicular fluid flow and a more neutral subgingival environment compatible with periodontal health. Nonsurgical subgingival debridement significantly decreases the population of bacteria associated with chronic periodontitis, including *Porphyromonas gingivalis*, *Aggregatibacter actinomycetemcomitans*, *Prevotella intermedia*, *Tannerella forsythia* and *Treponema denticola* (34,35). However, certain pathogens, such as *A. actinomycetemcomitans* and *P. gingivalis*, are particularly resistant to the effects of subgingival debridement (36). This has been linked with their ability to invade the pocket epithelium and underlying connective tissues (34,37). Harbouring pathogenic bacteria in the pockets is associated with residual deep pockets, persistent

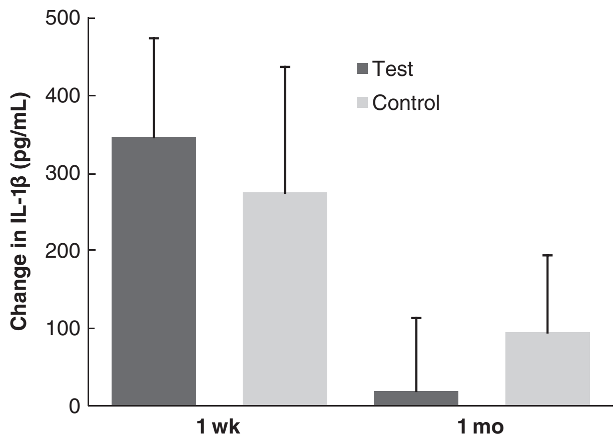

Fig. 4. Change in interleukin-1β (IL-1β) concentration (means + SD) from baseline to 1 wk and from 1 wk to 1 mo after the treatment in test and control sites. Test sites show a significantly greater reduction in IL-1β concentration compared with control sites at 1 wk ($p < 0.05$).

bleeding and an increased risk of further disease progression (38). Clinicians who recognize the impact of specific bacteria on periodontal conditions have incorporated antimicrobials as a part of periodontal therapy. Systematic reviews have shown that systemic and local delivery of antimicrobials can significantly improve the microbiological and clinical outcomes of periodontal therapy, especially when it is timed correctly with thorough subgingival debridement (39–41). However, frequent use of antimicrobials may lead to antimicrobial resistance, development of opportunistic infections, such as candidosis, and unwanted systemic effects, such as hypersensitivity and gastrointestinal reactions, which limits their clinical usage. Clinicians are therefore in search of alternative adjunctive therapies that might provide similar benefits to antimicrobial therapy with fewer side-effects.

Dental lasers have been shown to be potentially advantageous in nonsurgical and surgical periodontal treatments. They have been advocated in the removal of root surface deposits, soft and hard tissue ablation combined with haemostatic and bactericidal effects. The Er:YAG laser has been shown to have similar root debridement results to an ultrasonic scaler (7,42,43). Diode lasers produce wavelengths corresponding to the absorption coefficient of haemoglobin, oxygenated haemoglobin and melanin. Diode lasers have often been compared with Nd:YAG lasers, as they both emit energy within the infrared range at very similar wavelengths (11). The antibacterial property of diode lasers against *A. actinomycetemcomitans* has been recognized (12,44). Photodynamic therapy combines the use of a photosensitizer with laser light energy to produce either free radicals or singlet oxygen molecules (45), which have a cytotoxic effect against periodontopathogens, such as *P. gingivalis*, *Fusobacterium nucleatum* and *Capnocytophaga gingivalis* (46). Photodyamic therapy has been claimed to have a broad spectrum of action, with efficacy against antibiotic-resistant strains without evidence of development of photoresistant strains, extensive reduction in the bacterial population with limited damage to host tissues, the ability to target infected tissues, and overall beneficial economic factors (47). Clinical studies combining photodynamic therapy with nonsurgical periodontal therapy have reported mixed outcomes (22). Some studies showed that photodynamic therapy in combination with scaling and root debridement led to a significant improvement in clinical parameters compared with scaling and root debridement alone (20,21,24), whilst others found that the adjunctive use of photodynamic therapy showed no significant benefits (23,25,48).

The present study combines photodynamic therapy with low-level laser therapy as an adjunct to scaling and root debridement. Low-level laser therapy is a laser technique with over 30 years of documentation, and many of these reports have shown its benefits in clinical dentistry (49). Initially, low-level laser therapy was provided by helium–neon gas lasers, but nowadays they have been replaced by gallium arsenide-based diode lasers (26). Animal experiments have shown that oral tissues could benefit from 2–4 J/cm^2 of irradiation two to three times a week (50,51). The mechanism of low-level laser therapy involves photoreceptors in the electron transport chain within the membrane of cell mitochondria. Absorbtion of light creates a short-term activation of respiratory chain components, promoting ATP production and activation of nucleic acid synthesis (52). Low-level laser therapy has an additional effect on fibroblasts by promoting proliferation and increasing cell numbers, secretion of growth factors and differentiation of

Table 2. Gingival crevicular fluid data (means ± SD) in test and control sites

	Test			Control		
	Baseline	1 wk	1 mo	Baseline	1 wk	1 mo
Gingival crevicular fluid volume (μl)	1.1 ± 0.4	0.5 ± 0.2**	0.4 ± 0.2†	1.1 ± 0.4	0.6 ± 0.3**	0.5 ± 0.2
Interleukin-1β (pg/ml)	534.5 ± 155.2	188.5 ± 106.4**	169.21 ± 82.2	537.9 ± 200.2	263.3 ± 113.2**	168.6 ± 88.3††

**$p < 0.001$, significant difference from baseline.
†$p < 0.05$, ††$p < 0.001$, significant difference from 1 wk.

fibroblasts into myofibroblasts (53,54). This collectively results in improved wound contraction and accelerated wound healing (26,28).

Two recent reviews (22,55) suggest that photodynamic therapy has limited effects on clinical parameters, subgingival bacteria loads and gingival crevicular fluid levels. As yet, no study has combined photodynamic therapy with low-level laser therapy as an adjunct to nonsurgical periodontal therapy. The present clinical trial shows that the adjunctive use of photodynamic therapy and low-level laser therapy could significantly improve early clinical outcomes, whereas no significant differences were found between the test and control teeth at 3 mo. These observations may illustrate that the periodontal changes after one course of photodynamic therapy and low-level laser therapy might be short term. Overall pocket reduction achieved in this study is slightly better than the outcome achieved in a previous study by comparison of the treatment response following scaling and root debridement and photodynamic therapy or scaling and root debridement alone (20).

Gingival crevicular fluid analysis serves as a noninvasive method of assessing inflammatory conditions of periodontal tissues (56). Several host response mediators in gingival crevicular fluid have been proposed as possible diagnostic indices for periodontal disease, such as IL-1β and prostaglandin E_2 (57–59). The present study showed that test sites had a greater reduction in IL-1β levels compared with the control sites 1 wk after the treatment, implying that photodynamic therapy with low-level laser therapy might have a beneficial effect in controlling periodontal inflammation during the early healing period. However, it is notable that no significant difference was found in gingival crevicular fluid volume or IL-1β levels in gingival crevicular fluid 1 mo after the treatment, which is partly in contrast to the study by Qadri *et al.* (13). Further study is warranted to confirm the present findings and clarify the potential mechanisms involved.

This study had several limitations. Firstly, it should be noted that photodynamic therapy was combined with low-level laser therapy as a synergistic treatment modality, and no attempt was made to distinguish their respective therapeutic effects. Secondly, the overall beneficial effects of one course of photodynamic therapy with low-level laser therapy may be limited, as they appear to wash out by 3 mo. Currently, there is a lack of an established protocol for adjunctive laser treatment with scaling and root debridement. Further study is therefore needed to determine a more effective treatment protocol by using photodynamic therapy and low-level laser therapy as an adjunct to nonsurgical treatment of periodontitis.

Within the limitations of the study, it is concluded that a course of combined photodynamic therapy with low-level laser therapy could be a beneficial adjunct to nonsurgical treatment of chronic periodontitis on a short-term basis. The benefits can be seen in terms of greater reduction of probing depths, bleeding sites and periodontal inflammation as measured by the levels of IL-1β in gingival crevicular fluid. Further studies are required to assess the long-term effectiveness of the combination of photodynamic therapy with low-level laser therapy as an adjunct in nonsurgical treatment of periodontitis.

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