

Effectiveness of Photodynamic Therapy as an Additional Treatment for Chronic Periodontitis/Generalized II-B Periodontitis in Conjunction with Scaling and Root Planing: A Split Mouth Case–control Study

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Abstract

Background: There are few clinical studies available in the literature on the impact of photodynamic treatment (PDT) as an adjunct to traditional scaling and root planning (SRP) on the management of periodontitis. This study compared the clinical parameters and interleukin (IL)-1 β levels in gingival crevicular fluid of patients with moderate chronic periodontitis (CP)/generalized II-B periodontitis treated with SRP alone or SRP + PDT. **Materials and Methods:** Twenty patients (12 males and eight females) with moderate-to-severe periodontitis were chosen for this split-mouth trial. After SRP, teeth were randomized and subjected to either to receive no further treatment or a single application of PDT using a 670 nm laser and 1% methylene blue. Outcomes such as a change in probing depth, % bleeding on probing, clinical attachment level, and IL-1 β were measured at baseline and 3 months after the intervention. **Results:** Statistical analysis was performed utilizing SPSS software version 19. All measurements showed significant improvements ($P < 0.05$) in the 3-month follow-up compared to the baseline in each group. All clinical parameters improved significantly in the PDT + SRP group compared to the SRP group. **Conclusion:** The adjunct use of PDT was supported by this study. CP patients treated with adjunct PDT to SRP showed greater improvement in both clinical and inflammatory parameters compared to SRP alone.

Keywords: Cytokines, Gingival crevicular fluid, Periodontitis, Photodynamic therapy.

INTRODUCTION

Chronic periodontitis (CP), that is, the destruction of the supporting structures of teeth is a host inflammatory response caused by microbial dysbiosis present in the plaque biofilm.^[1] Conventional scaling and root planning (SRP) using ultrasonic instruments and hand instruments has been the most effective nonsurgical treatment for periodontal disease.^[2] Although abundant research articles have demonstrated significant improvements in several clinical and biological indicators of periodontal health after SRP, residual pockets post-SRP present a challenge to this therapeutic approach. Residual periodontal disease is caused by rapid bacterial colonization, which is frequently associated with incomplete subgingival plaque removal, poor access to root concavities, furcation, and tissue-invasive periopathogens.^[3]

To overcome the limitations of SRP, various other modalities have been used as an adjunct in the literature with some amount of success. However, issues such as the development of microbial resistance, the modification of microbiota, cost factors, and patient compliance resulted in the introduction of photodynamic therapy (PDT), which was first used in 1904.^[4] Antimicrobial photodynamic therapy (aPDT) utilizes

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a particular light wavelength for the activation of a locally administered photosensitizer dye that produces toxic free oxygen radicals. Free radicals and singlet oxygen irreparably harm the cell elements and toxic products of bacteria. The major advantages of PDT are its specificity, with limited or no collateral damage and lack of resistance development among bacterial species.^[5]

In vitro and animal investigations using aPDT have demonstrated effective eradication of perio pathogens. However, in clinical trials on human subjects, the precise effect of aPDT on periodontal disease and its potential to alter clinical and inflammatory indicators remains less understood.^[6] Due to the paucity of available literature, the goal of the current study was to generate scientific evidence on the effectiveness of additional PDT therapy for SRP in the management of CP.

MATERIALS AND METHODS

Ethical statements

This study was conducted on patients selected from the outpatient department of a Government Medical and Dental College in South-west India. Before the start of the trial, the Institutional Ethical Committee granted ethical clearance (IEC/Oct/2018 Dt October 22, 2018). Before participating in this trial, all patients provided written informed consent.

Objectives

The study aimed to assess changes in the percentage of bleeding on probing (%BOP), clinical pocket probing depth (PD), clinical attachment level (CAL), and gingival crevicular fluid (GCF) levels of interleukin (IL)-1 β from baseline and 3 months after intervention.

Patient selection

A total of 23 participants (12 men and 11 women) were enrolled with ages ranging from 35 to 60 years old (mean age: 41.44 years). The sample size was calculated to test the null hypothesis at a significance level of 5% and statistical power of 90%. The number of samples determined as per statistics in this split-mouth study was 14 subjects; however, this study included 23 patients to cover loss to follow-up. All the selected subjects had chronic generalized periodontitis (AAP 1999 Classification) or generalized II-B periodontitis as per the 2017 classification. The study's participants had the following inclusion criteria: (1) good overall general health; (2) at least 20 natural teeth, with a minimum of five in each of the four quadrants; (3) attachment loss of a minimum of 3 millimeters in at least 30% of the existing teeth; and (4) at least three sites in each of the quadrants with a minimum of pocket PD (PPD) ranging from 4 to 5 millimeters and the presence of BOP on such sites. Subjects who were current or former smokers, pregnant women, treated for periodontitis within the last 12 months, having extensive restorations, diabetic/suffering from liver disease/cancer/receiving radiation, or allergic to photosensitizer dye were excluded from the study. To ensure an adequate level of plaque control, all participants

were given comprehensive oral hygiene instructions 7 days before the treatment.

Study design

In this split-mouth study, every patient's anatomical mouth was divided into two subunits. The halves of the patient's mouth were distributed at random into either of the groups, that is, Group A (Test Group, i.e., SRP+PDT group) and Group B (Control Group, i.e., SRP alone group), by block randomization. The selection of the patient and charting of clinical parameters and collection of GCF both at the initial assessment and subsequent visits were performed by a lone clinician who was not aware of the study's methodology, while another experienced periodontist performed SRP and PDT.

Treatment protocol

All patients selected for this research underwent full-mouth conventional nonsurgical periodontal therapy, that is, supragingival and subgingival SRP with ultrasonic scalers and periodontal hand instruments, that is, Gracey curettes (Figure 3a). The PDT protocol was performed in addition to SRP on the TEST side. Each patient underwent PDT and SRP in a single session within 24 h. A HELBO Theralite (Bredent medical™) diode laser (Figure 1) with a wavelength of 670 nm and a power output value of 75 mW/cm² was used to carry out photodynamic therapy. The spot size for the laser was 0.6 mm. The dye used in this study was the HELBO blue photosensitizer, which contains methylthioninium hydrochloride, scientifically known as 3,7-bis phenothiazine-5-ium chloride, which has a peak absorbance at 670 nm and a concentration of 10 mg/mL, or 1%. For the application of the photosensitizer dye, a viscoelastic Cannula was used. The dye was applied beginning at the bottom of the pocket and followed apico-coronally until the gingival margin (Figure 2b). Extra caution was taken to minimize bubble entrapment during dye application. The dye was left *in situ* for 60 s, allowing it to be absorbed. The extra dye was then properly removed from the pocket by rinsing it with sterile water to facilitate easy laser irradiation (Figure 2c). After rinsing for 1 min (10 s for each site), the pocket surface of the tooth was subjected to HELBO Theralite diode laser light using circular movements (Figure 2d). Circular movements promote the most effective laser light activation of dye molecules and transfer of resulting energy to nearby oxygen. The singlet oxygen that results is sufficiently reactive and effective to kill bacterial cells.

Clinical parameters

Changes in plaque index (PI) (Silness and Loe, 1964), %BOP, PPD, and height of CAL were assessed at the initial intervention visit and subsequent follow-up visit at 3 months by means of a graduated William's periodontal probe placed at the mesiobuccal, mesiolingual, distolingual, and distobuccal interdental locations.

Immunological parameter

Collection of GCF Samples for interleukin (IL)-1 β assay

Cotton rolls were used to isolate GCF collection sites, that is, the maxillary posterior tooth with the deepest pocket depth on

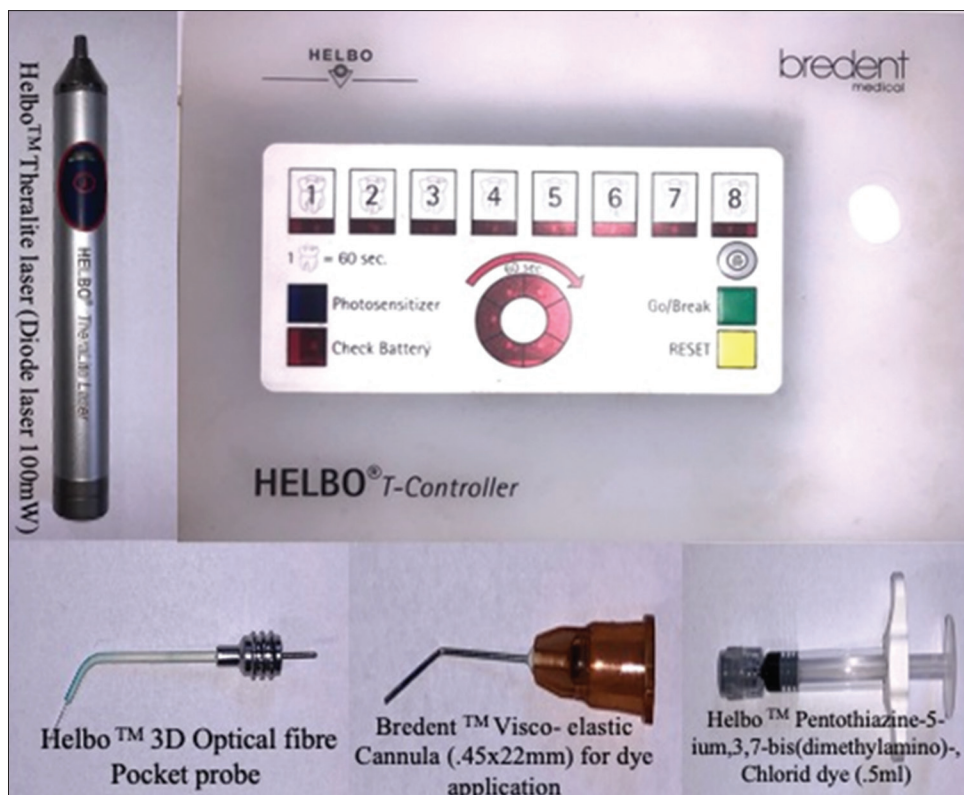


Figure 1: Helbo PDT kit



Figure 2: PDT application. (a) After SRP. (b) After application of methylene blue. (c) Washing off the dye. (d) 670 NM diode laser probe inserted and activated into the periodontal pocket



Figure 3: IL-1 β Kit. (a and b) Diaklone kit with reagents. (c) Collected patient samples. (d) ELISA microplate reader

the test and control sides. The areas were then gently air-blown to dry any saliva. The supragingival plaque was removed before collecting GCF. The sterile plastic micropipette tip attached to the micropipette set in a 5 μ L position was positioned on the point of exposure of the periodontal pocket. The plunger

of the micropipette was then slowly released (30 s) to draw at least 2 μ L–5 μ L of GCF. The blood-adulterated sample was discarded upon withdrawal. The sample was immediately transferred to 100 μ L of phosphate-buffered saline in a labeled Eppendorf tube and placed on ice. To prevent the loss of bioactive human IL-1, samples in Eppendorf tubes were kept frozen at -20°C .

Methodology to determine the levels of IL-1 β

A commercially available human IL-1 beta Enzyme-linked immunosorbent assay (ELISA) reagent kit (Diaklone™) was used to measure the amount of IL-1 in the GCF (Figure 3a and b). Before starting the assay, the frozen GCF samples were gradually warmed to room temperature (Figure 3c). Thawing of the sample was avoided by heating it at 37°C . Kit reagents such as buffer, standard, control, and anti-IL-1 β were diluted and prepared as per the instructions given with the kit. 100 μ L of the samples, control, diluted standard, and 50 μ L of diluted anti-IL-1 β were transferred to the wells of the ELISA plate in duplicate. The plate was then capped with a plastic lid and left to sit for 3 h at room

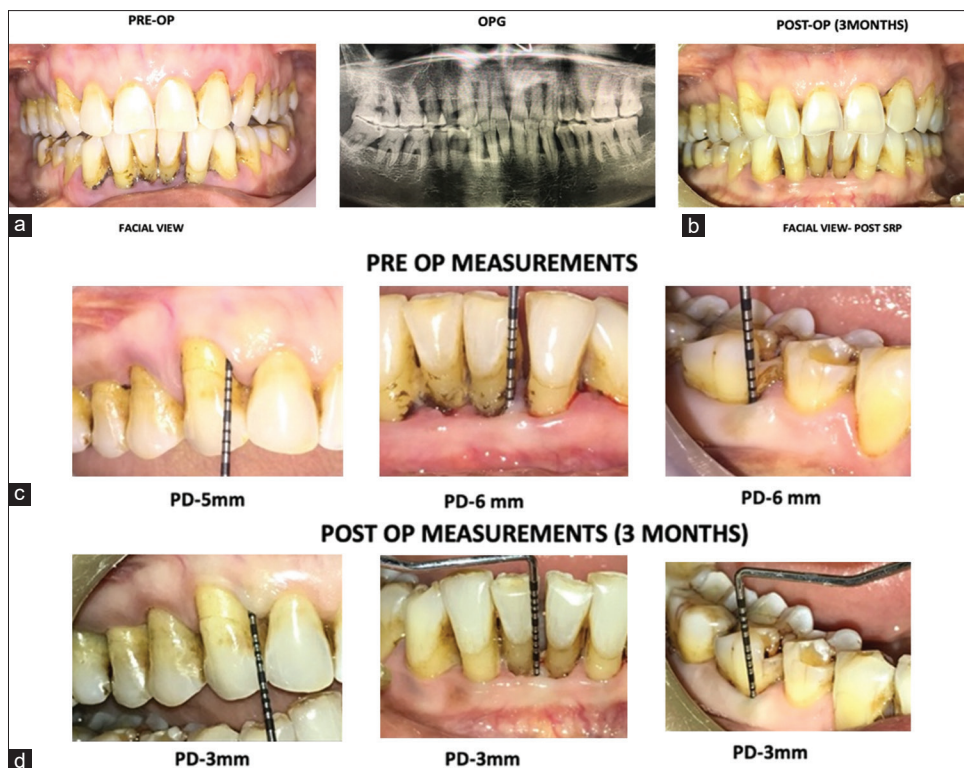


Figure 4: Appearance of the gingiva before and after PDT. In Case 1 at (a) baseline and (b) 3 months. (c) Pre-operative PD. (d) PD after 3 months of PDT

temperature (18–25°C). The lid was removed, and with buffer, the ELISA plate was washed 3 times. The wells received an additional 100 μ L of diluted streptavidin-HRP, and the plate was once more incubated for 30 min. After another three passes of buffer washing, 100 μ L of TMB substrate was applied to each well, and the color was allowed to develop for 15 min. The last step was to add 100 μ L of H₂SO₄ (Stop Reagent) to each well. Using a spectrophotometer with 450 nm as the primary wavelength and, optionally, 620 nm as the reference wavelength, the average absorbance values of each of the wells were read (Figure 3c). The total duration of the entire procedure was 3 h 45 min.

The average absorbance of each of the standards was first plotted against the corresponding concentration of the IL-1 β standard on the vertical and horizontal axes to create a linear standard curve.

Using the aforementioned standard curve and estimating values of optical density against IL-1 standard reference concentrations, IL-1 levels in each sample were computed.

Statistical analysis

The assessment of statistical data was completed utilizing SPSS software Version 19 (IBM, Chicago, USA). The Chi-square test was applied to determine whether there were any categorical data variances among the test and control groups, while the Mann–Whitney test was employed for continuous data. Similarly, Wilcoxon's signed rank test was utilized to identify significant variations between baseline and subsequent visits among the test and control groups. Any p values below the

threshold of 0.05 were considered to be statistically significant for the current investigation.

RESULTS AND FINDING

Out of 23 people enrolled, three were left to follow up, and twenty were considered for final result compilation. Among the test and control groups, there were no significant variations in the baseline clinical parameter values ($P > 0.05$) or IL-1 levels (Table 1).

The mean PI was 2.11 and 0.77 at baseline and post-90 days, respectively. The $P < 0.05$ suggests that both therapies were successful in lowering the plaque scores in patients with CP. As it was a split-mouth clinical trial and the PI being a full-mouth index, there was no need for intragroup or intergroup comparison.

For the intragroup comparison (i.e., both the groups), PD, CAL, the percentage of BOP sites, and IL-1 levels at intervals of 3 months from baseline showed $P < 0.05$, suggesting significant improvements (Tables 2 and 3). When compared to the SRP group, the SRP + PDT group showed statistically significant improvements in every clinical and immunological variable (Table 4).

DISCUSSION

This study is among the few case–control studies in India to assess PDT's effectiveness as a supplement to SRP in the management of CP. Only one incidence of PDT was performed. Only a few studies have addressed the idea of PDT being

Table 1: Intergroup comparison of mean of clinical parameters and GCF IL-1 β at baseline between control and test group

Variable	Group A (n=10)	Group B (n=10)	P-value	Remarks
% of Bleeding sites	85.71 $\pm$ 5.16	84.88 $\pm$ 5.41	0.08	Non-significant
PPD (in mm)	5.81 $\pm$ 0.67	5.71 $\pm$ 0.70	0.10	Non-significant
CAL (in mm)	6.60 $\pm$ 0.64	6.66 $\pm$ 0.69	0.96	Non-significant
IL-1 β levels (pg/mL)	609.12 $\pm$ 193.60	605.47 $\pm$ 176.45	0.64	Non-significant

Table 2: Intragroup comparison of mean of clinical and GCF IL-1 β at baseline and 90 days post-intervention with SRP in control group (Group B)

Variable	Baseline (Mean $\pm$ SD)	90 days (Mean $\pm$ SD)	P-value	Remarks
% of Bleeding sites	84.88 $\pm$ 5.41	25.67 $\pm$ 4.49	0.00	Significant
PPD (in mm)	5.71 $\pm$ 0.70	3.52 $\pm$ 0.68	0.00	Significant
CAL (in mm)	6.66 $\pm$ 0.69	5.29 $\pm$ 0.85	0.00	Significant
IL-1 β levels (pg/mL)	605.47 $\pm$ 176.45	246.28 $\pm$ 85.39	0.00	Significant

Table 3: Intragroup comparison of mean of clinical parameters and GCF IL-1 β at Baseline and 90-day post-intervention with SRP+aPDT in test group (Group A)

Variable	Baseline (Mean $\pm$ SD)	90 days (Mean $\pm$ SD)	P-value	Remarks
% of Bleeding sites	85.71 $\pm$ 5.16	19.52 $\pm$ 4.15	0.00	Significant
PPD (in mm)	5.81 $\pm$ 0.67	2.91 $\pm$ 0.58	0.00	Significant
CAL (in mm)	6.60 $\pm$ 0.64	4.78 $\pm$ 0.56	0.00	Significant
IL-1 β levels (pg/mL)	609.12 $\pm$ 193.60	196.38 $\pm$ 72.9	0.00	Significant

Table 4: Intergroup comparison of mean of differences of clinical parameters and GCF IL-1 β at 90-day post-interventions between control and test group

Variable	Group A (SRP+aPDT) Difference between before and after intervention (Mean $\pm$ SD)	Group B (SRP) Difference between before and after intervention (Mean $\pm$ SD)	P-value	Remarks
% of Bleeding sites	66.19 $\pm$ 1.84	59.20 $\pm$ 2.68	0.00	Significant
PPD (in mm)	2.9 $\pm$ 0.17	2.18 $\pm$ 0.24	0.00	Significant
CAL (in mm)	1.88 $\pm$ 0.36	1.265 $\pm$ 0.23	0.00	Significant
IL-1 β levels (pg/mL)	412.73 $\pm$ 133.82	359.188 $\pm$ 102.67	0.00	Significant

applied repeatedly. In one of the trials, the application of three rounds of PDT in 1 week had an insignificant effect on microbiological and clinical parameters.^[6,7] Each subject serves as its own control in the split mouth method, which eliminates the majority of patient outcome variability from the assessment of the intervention impact. Potentially fewer subjects are needed for the split-mouth strategy compared to for parallel trials having the same level of power. The “spilling” of the outcomes of one intervention from one side to another could lead to bias; however, suction and delivery of dye through a cannula and further activation using laser application using a fiberoptic tip directly to the pocket prevented bias.^[8] A 3-month evaluation time was chosen, as studies have demonstrated that perio-pathogens rebound to before treatment levels in 9–11 weeks, and a number of studies in the PDT literature used 3 months of evaluation time.^[9]

In line with earlier research, both therapies at 3 months resulted in a statistically evident decrease ($P = 0.05$) in the percentage of bleeding locations (%BOP) (Tables 2 and 3).^[10,12] In the intergroup comparison, SRP+ aPDT (Group A) demonstrated a statistically higher decrease in the percentage of bleeding locations ($P = 0.05$) than SRP alone (Group B) (Table 4). These results concur with earlier research.^[10]

This study found that SRP+ aPDT resulted in higher gains in CAL and PD reduction than SRP alone when intergroup comparisons were made Figure 4(a,b,c,d), (Table 4). The positive clinical outcomes are in agreement with the previously reported findings of *in vitro* studies, animal studies, and in vivo studies with different concentrations of methylene blue, different wavelengths of lasers, and different resident times of photosensitizers.^[11–20] Contrary to our findings in many clinical trials, aPDT provided no additional

benefits in PPD reduction and CAL as an adjunct to SRP in the management of CP.^[21,22]

Immunological parameters, that is, IL-1 β levels in GCF at baseline, were comparable and showed no statistically significant difference ($P > 0.05$) (Table 1) among both groups. A statistically significant ($P < 0.05$) reduction in IL-1 β levels in GCF was observed in both the control (Group B) and test groups (Group A) (Tables 2 and 3), which was in agreement with previously reported studies.^[20,24,25] Compared with the control sites, a significantly greater reduction in IL-1 β levels was found in the test sites at 90 days ($P < 0.05$) (Table 4), showing that photodynamic therapy might have a beneficial effect in controlling periodontal inflammation, which was in line with many studies in recent literature.^[19-21]

There are inadequate data in the literature about the effect of PDT on the modulation of immune biomarkers.^[10,26] Three studies reported lower IL-1 β levels in the GCF of patients treated with adjunct aPDT to SRP.^[20,24,25] Conversely, other studies showed no significant difference in the IL-1 β concentrations among patients with and without adjunctive PDT to SRP.^[25-27] It is relevant to comment here that there was noteworthy heterogeneity among all the studies.

One possible reason for the reduction in IL-1 β is the ability of aPDT to reduce the stimulation of T lymphocytes, interfere with the immunostimulatory function of antigen-presenting cells, and inactivate pro-inflammatory mediators.^[23,29] Another explanation for the reduction of IL-1 β could be due to the production of reactive oxygen species, which are singlet oxygen molecules and are toxic to pathogenic microbes and their toxic lipopolysaccharides. PDT has also been linked to the activation of other immune processes, including the acute phase response, complement cascade, and production of chemokines.^[28]

The controversial reports available in the literature regarding the success of PDT as an adjunct to non-surgical periodontal therapy in improving clinical and immunological parameters might be due to the diverse concentrations and residence time for photosensitizers used, distinct wavelengths and irradiation time of the laser and the appliance skills of the clinician.^[6,30]

The limitation of this randomized controlled split-mouth clinical trial is the short duration of follow-up and comparatively smaller sample size. As aPDT is based on the eradication of microorganisms, a microbiological analysis could have assessed changes in periodontal pathogens. Only a single inflammatory biomarker, IL-1 β , was evaluated, whereas the current knowledge states that the host response is the primary driver of periodontal disease. Hence, it is proposed that more inflammatory and immune mediators may be included in future studies to have more diversified knowledge on the role of aPDT as an adjunct to SRP.

In this study, it was found that the use of PDT as an adjunct to SRP produces better results than SRP alone. A plausible explanation could be due to bacterial load reduction and

inactivation of bacterial virulence factors and cytokines. The following advantages were observed: relatively short treatment time, no need for anesthesia, and precise laser application.

CONCLUSION

The use of a PDT as an adjunct to SRP produced better results compared to SRP alone. A plausible explanation could be due to bacterial load reduction and inactivation of bacterial virulence factors and cytokines. The following advantages were seen: relatively short treatment time, no need for anaesthesia, and precise laser application.

CONFLICTS OF INTEREST

No potential conflicts of interest relevant to this article were reported.

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None.

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