

# The effect of indocyanine green-mediated photodynamic therapy as an adjunct to scaling and root planing in the treatment of chronic periodontitis: A comparative split-mouth randomized clinical trial

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## ABSTRACT

**Objective:** The aim of this study was to assess the effect of adjunctive photodynamic therapy (PDT) (using 810 nm diode laser and Indocyanine green as photosensitizer) in chronic periodontitis.

**Materials and Methods:** Patients with untreated chronic periodontitis were included. Treatment was done according to a split mouth design. All sites received periodontal treatment comprising scaling and root-planing (SRP). Test group were additionally treated with PDT. Plaque Index (PI), Gingival Index (GI), Probing Pocket Depth (PPD) and Relative Attachment Level (RAL) were evaluated at baseline, 1 month and 3 months.

**Results:** Mean baseline values for PI, GI, PPD and RAL were not different in the test group and control group. Statistical significant difference in PPD and RAL, 3 months after treatment was seen in test group as compared to the control group.

**Conclusions:** In patients with chronic periodontitis, clinical outcomes of conventional SRP can be improved by adjunctive PDT.

**Key words:** Chronic periodontitis, diode laser, photodynamic therapy

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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.<sup>[1]</sup> As a result of a constant bacterial challenge, the periodontal tissues, i.e., gingiva, periodontal ligament, cementum, and supporting alveolar bone are continuously exposed to specific bacterial components that have the ability to alter many local functions.

Currently, the most widely accepted and effective treatment approach for periodontal disease is the mechanical removal of the bacterial biofilm and their toxins from the tooth surface by scaling and root planing (SRP), making it compatible

for biologic reattachment.<sup>[2]</sup> However, mechanical therapy alone may fail to eliminate periodontal pathogens located in the soft tissue, and in areas inaccessible to periodontal instruments, such as furcation areas, root depressions, concavities, grooves, and distal molar region.<sup>[3,4]</sup>

Methods that can be used as adjuncts to SRP have been proposed to promote reduction or elimination of periodontal pathogens. Although systemic and local administration of antibiotics into periodontal pockets may be effective for disinfection, the frequent usage of antibiotics bears the potential risk of producing resistant microorganisms. Furthermore, these locally delivered antibiotics are difficult to maintain at a therapeutic concentration in the periodontal pocket. Thus, the development of alternative antibacterial

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therapeutic strategies, therefore, becomes important in the evolution of methods to control microbial growth in the oral cavity. In the past decade, photodynamic therapy (PDT) has been suggested as an adjunct to conventional SRP to eliminate subgingival microbial species and treat periodontitis.<sup>[5]</sup>

PDT for human infections is based on the concept that an agent (a photosensitizer) which absorbs light (of a particular wavelength) can be preferentially taken up by the target cell/bacteria and subsequently activated by light of the appropriate wavelength in the presence of oxygen to generate singlet oxygen and free radicals that are cytotoxic to microorganisms. As a result of the cytotoxic nature of the singlet oxygen, it is unlikely that the microorganisms would develop resistance to it.<sup>[6]</sup>

Indocyanine green (ICG) as a photosensitizer has been proposed for PDT, which has an optimal peak absorption at 800–810 nm.<sup>[7-9]</sup> ICG has been proved to be an effective photosensitizer for antimicrobial PDT (aPDT), *in vitro*. ICG has been investigated against selected bacterial species (*Staphylococcus aureus* and *Pseudomonas aeruginosa*) *in vitro*, providing statistically significant reduction in bacteria of 95%–99%, depending on the fluence values.<sup>[10]</sup> PDT using ICG as photosensitizer resulted in significant reduction of *Porphyromonas gingivalis* and *Aggregatibacter actinomycetemcomitans* as <10% of bacteria remain viable.<sup>[8]</sup> Nagahara *et al.* stated ICG is a potential new photosensitizer for aPDT to achieve clearance of periodontal pathogens including *P. gingivalis* as the maximum absorption wavelength of ICG is approximately 800 nm, a tissue penetrating wavelength which might be useful for a potential photodynamic periodontal therapy.<sup>[9]</sup>

Thus, the study aims to compare the effect of PDT (using 810 nm diode laser and ICG as photosensitizer) with SRP versus SRP alone in the treatment of chronic periodontitis.

## MATERIALS AND METHODS

### Source of data

Patients were recruited from the outpatient Department of Periodontology. Ethical clearance was obtained before the start of the study from the Institutional Ethical Committee.

### Inclusion criteria

- Patients between the age group of 25 and 55 years
- Patients with minimum 20 teeth
- Patients with chronic periodontitis having at least 4 teeth with probing depth  $\geq 5$  mm (two teeth in contralateral quadrant)
- Patients who gave informed consent for the study.

### Exclusion criteria

- Consumption of tobacco in any form
- Patients who have undergone periodontal therapy in

the last 6 months

- Patients who have received antibiotic therapy in the previous 3 months
- Patients with any systemic disease
- Pregnant and lactating women.

### Study design

Patients who reported to the Department of Periodontology with generalized chronic periodontitis were selected. Patients were informed about the study protocol and informed consent was obtained before participating in the study.

Treatment was done according to a split-mouth design where the test and control sites were randomly divided with a flip of coin. Each group had thirty sites.

In each recruited patient, teeth with probing pocket depth (PPD)  $>5$  mm were allotted to either:

- Group A – Treated with SRP only (control site)
- Group B– Treated with SRP + PDT (test site).

All examinations were carried out by the same examiner. University of North Carolina-15 periodontal probe (Hu-Friedy, Chicago, IL, USA) was used to measure the clinical parameters.

The following clinical parameters were recorded for all the patients at baseline, 1, and 3 months.

- Plaque index (PI)<sup>[11]</sup>
- Gingival index (GI)<sup>[12]</sup>
- PPD
- Relative attachment level (RAL).<sup>[13]</sup>

### Initial therapy

On day 1, a brief history was recorded. Alginate impressions were recorded for the maxillary and mandibular arches. Custom acrylic stents were prepared [Figure 1].

On the next day, baseline measurement of clinical parameters was done. Custom acrylic stents were used to



**Figure 1:** Custom made acrylic stent on diagnostic cast

measure the RAL [Figure 2a]. Thereafter, all the patients enrolled in the study underwent a full mouth SRP using both hand and ultrasonic instruments.

Patients were recalled after 1 week of completion of SRP for PDT.

Teeth that were included in the test group received PDT, whereas the teeth that belonged to the control group were flushed with dye and treated with sham laser.

Patients were recalled at 1 and 3 month intervals for evaluation of clinical parameters of both test as well as control group. All the patients were assessed by the same examiner.

### Preparation of indocyanine green dye solution for photodynamic therapy application

ICG is available as a lyophilized sterile powder of 25 mg [Figure 3]. For its use as a photosensitizer, the dye solution has to be freshly prepared. The powdered ICG vial was reconstituted with 5 ml of sterile water (provided by the manufacturer) [Figure 4a]. It was shaken well for at least 3 min for complete dissolution of the dye, resulting in a final concentration of 5 mg/ml of water (i.e., 0.5% solution). The

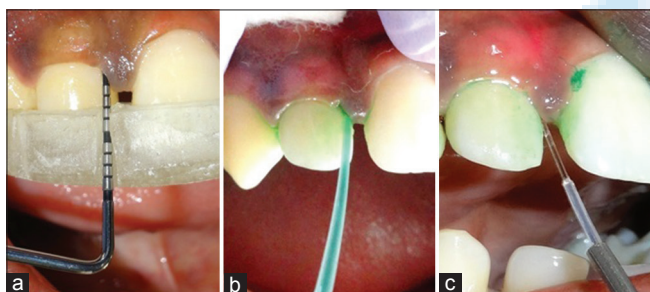
reconstitutes (dye solution) were withdrawn from the vial through the sterile syringe filter (0.2 micron) using a sterile syringe and 27-gauge needle [Figure 4b].

The purpose of using a sterile syringe filter is:

- To avoid any undissolved dye in the solution due to inadequate shaking/dissolution which cannot be observed visually since the dye solution is dark green in colour
- To avoid cross-contamination at the time of reconstitution.

Parker has advocated the use of ICG in a concentration of 1 mg/ml for PDT.<sup>[7]</sup> To achieve the desired concentration of ICG, only 1 ml of the dye solution was loaded in a 5 ml sterile syringe [Figure 5]. This was diluted with an additional 4 ml of sterile water so that the desired concentration of 1 mg/ml is achieved [Figure 4c].

The needle of the syringe was replaced with a blunt cannula [Figure 6] which was then used to fill the periodontal pocket with the dye. Periodontal pockets were rinsed



**Figure 2:** (a) Pocket probing with stent in position; (b) application of indocyanine green dye solution; (c) 810 nm diode laser used to activate the dye (photosensitizer)



**Figure 4:** Preparation of indocyanine green dye solution: (a) Powdered indocyanine green vial reconstituted with 5 ml of sterile water; (b) dye solution withdrawn from the vial through the sterile syringe filter; (c) syringe (with blunt cannula) loaded with dye solution (1 mg/ml)



**Figure 3:** Indocyanine green photosensitizer (Aurogreen®, Aurolab, Madurai, India)



**Figure 5:** Sterile water



with dye starting from the bottom of pocket to achieve complete filling of the pocket and coating of the root surface [Figure 2b].<sup>[14]</sup> Cotton rolls and a high vacuum suction were used to prevent ingestion of the dye solution. After 3 min, the patient was asked to rinse with water to remove excess photosensitizer.<sup>[14,15]</sup>

An 810 nm diode laser was used to activate the photosensitizer [Figures 7 and 2c]. The diode laser was used at a power of 200 mW; pulse duration was fixed at 25  $\mu$ m for 30 s per site. This means that the laser was switched on 50% of the time which resulted in an average power of 100 mW delivered through an optic fiber tip of 400  $\mu$ m diameter during a period of 30 s per treatment site; this provided a fluence (energy density) value of 0.0125 J/cm<sup>2</sup> and 3.0 J of total energy delivered.<sup>[7]</sup> The laser was then applied to activate the dye.<sup>[7]</sup>

### Statistical analysis

A convenient sample size of sixty sites was included under 5% alpha error and 80% of power of the test to detect the significant difference. All data collected were entered in Microsoft Excel (MS Office version 2013) and tabulated. All the data was analyzed using the SPSS software version 17 (Illinois, Chicago, USA). These recordings were subjected to both intra- and inter-group comparisons. For intra-group comparison, one-way analysis of variance and *post hoc* Bonferroni test were used, and for intergroup comparison, Student's *t*-test was used. A statistical significance was set at 5% level of significance ( $P < 0.05$ ).

## RESULTS

The difference between the mean baseline values of both the control and test group for all the clinical parameters PI ( $1.71 \pm 0.29$ ;  $1.70 \pm 0.28$ ), GI ( $1.59 \pm 0.53$ ;  $1.72 \pm 0.56$ ), PPD ( $5.27 \pm 0.69$ ;  $5.13 \pm 0.34$ ), and RAL ( $9.30 \pm 2.32$ ;  $9.13 \pm 1.88$ ), respectively, were statistically insignificant. Thus, the randomization was successful.

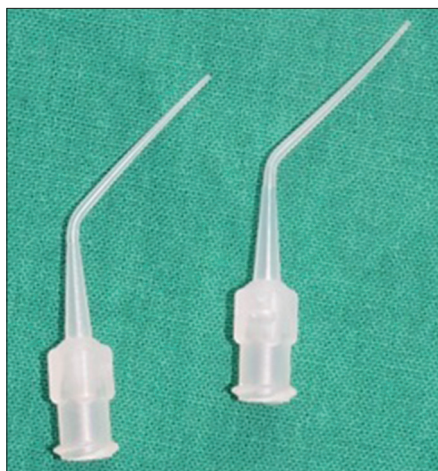


Figure 6: Blunt cannula

### Plaque index

The mean site-specific PI scores in the control group at baseline, 1 and 3 months were  $1.71 \pm 0.29$ ,  $0.35 \pm 0.34$ ,  $0.40 \pm 0.42$  and that in the test group were  $1.70 \pm 0.28$ ,  $0.35 \pm 0.33$ ,  $0.26 \pm 0.34$ , respectively.

Intergroup comparisons of PI at each follow-up carried out by Student's *t*-test revealed no statistical significant difference between the groups at any stage during the follow-up as seen in Table 1 and Graph 1.

Intragroup comparisons at different time interval during follow-up showed that there was a statistically significant reduction in the mean site-specific plaque scores at each follow-up as compared to the baseline. However, there was no statistical significant difference found between 1 and 3 months follow-up. These findings were true for both the test and control group [Table 2 and Graph 2].

### Gingival index

The mean site-specific GI scores in the control group at baseline, 1 and 3 months were  $1.59 \pm 0.53$ ,  $0.20 \pm 0.35$ ,

Table 1: Intergroup comparison of plaque index using Student's *t*-test

Group (n=30)	PI (mean $\pm$ SD)		p
	Group A (SRP only)	Group B (SRP + PDT)	
Baseline	$1.71 \pm 0.29$	$1.70 \pm 0.28$	0.825
1 month	$0.35 \pm 0.34$	$0.35 \pm 0.33$	1.000
3 months	$0.40 \pm 0.42$	$0.26 \pm 0.34$	1.09

Values significant ( $P \leq 0.005$ ) using Student's *t*-test. SD=Standard deviation, SRP=Scaling and root planning, PDT=Photodynamic therapy, PI=Plaque index

Table 2: Intragroup comparison of plaque index using repeated measures of analysis of variance

Group (n=30)	PI (mean $\pm$ SD)			p
	Baseline	1 month	3 months	
Group A (SRP only)	$1.71 \pm 0.29$	$0.35 \pm 0.34^*$	$0.40 \pm 0.42^*$	0.000
Group B (SRP + PDT)	$1.70 \pm 0.28$	$0.35 \pm 0.33^*$	$0.26 \pm 0.34^*$	0.000

\*Values highly significant ( $P < 0.001$ ) as compared to the baseline levels using multiple comparison test. SD=Standard deviation, SRP=Scaling and root planning, PDT=Photodynamic therapy, PI=Plaque index



Figure 7: 810 nm diode laser (AMD Picasso®)

$0.24 \pm 0.28$  and that in the test group were  $1.72 \pm 0.56$ ,  $0.18 \pm 0.27$ ,  $0.18 \pm 0.27$ , respectively.

Intergroup comparisons of GI at each follow-up carried out by Student's *t*-test revealed no statistical significant difference between the groups at any stage during the follow-up as seen in Table 3 and Graph 3.

Intragroup comparisons at different time interval during follow-up showed that there was a statistically significant reduction in the mean site-specific GI scores at each follow-up as compared to the baseline. However, there was no statistically significant difference found between 1 and 3 months follow-up. These findings were true for both the test and control group [Table 4 and Graph 4].

### Probing pocket depth

The mean PPDs at baseline, 1, and 3 months for the control group were  $5.27 \pm 0.69$ ,  $3.67 \pm 0.75$ , and  $3.67 \pm 0.75$ , and for the test group were  $5.13 \pm 0.34$ ,  $2.80 \pm 0.71$ , and  $2.23 \pm 0.67$ , respectively.

At the baseline, no statistical significant difference in the PPD was seen between the control and test group. However, there was statistically significant reduction in the probing depths in the test group as compared to the control group at both, 1 month ( $p = 0.000$ ) and 3 months ( $p = 0.000$ ) [Table 5 and Graph 5].

**Table 3: Intergroup comparison of gingival index using Student's *t*-test**

Group (n=30)	GI (mean±SD)		p
	Group A (SRP only)	Group B (SRP + PDT)	
Baseline	1.59±0.53	1.75±0.56	0.352
1 month	0.20±0.35	0.18±0.27	0.842
3 months	0.24±0.28	0.18±0.27	0.423

Values significant ( $p \leq 0.005$ ) using Student's *t*-test. SD=Standard deviation, SRP=Scaling and root planning, PDT=Photodynamic therapy, GI=Gingival index

**Table 4: Intragroup comparison of gingival index using repeated measures of analysis of variance**

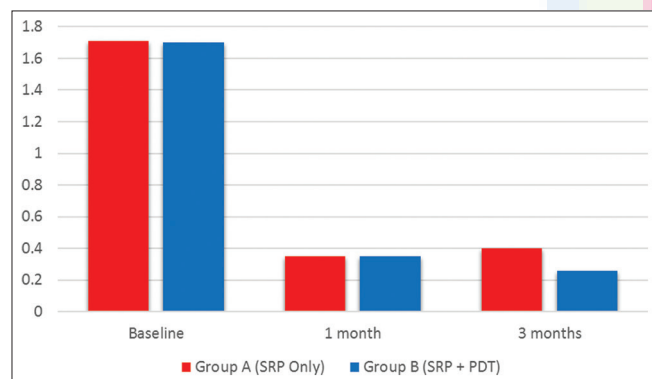
Group (n=30)	GI (mean±SD)			p
	Baseline	1 month	3 months	
Group A (SRP only)	1.59±0.53	0.20±0.35*	0.24±0.28*	0.000
Group B (SRP + PDT)	1.72±0.56	0.18±0.27*	0.18±0.27*	0.000

\*Values highly significant ( $p < 0.001$ ) as compared to the baseline levels using multiple comparison test. SD=Standard deviation, SRP=Scaling and root planning, PDT=Photodynamic therapy, GI=Gingival index

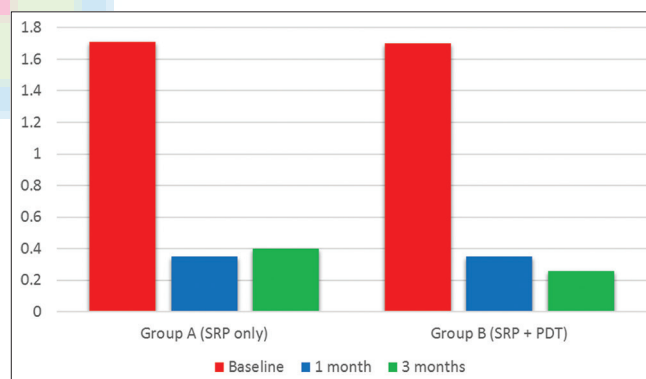
**Table 5: Intergroup comparison of probing pocket depth using Student's *t*-test**

Group (n=30)	PPD in mm (mean±SD)		p
	Group A (SRP only)	Group B (SRP + PDT)	
Baseline	5.27±0.69	5.13±0.34	0.349
1 month	3.67±0.75**	2.80±0.71**	0.000
3 months	3.67±0.75**	2.23±0.67**	0.000

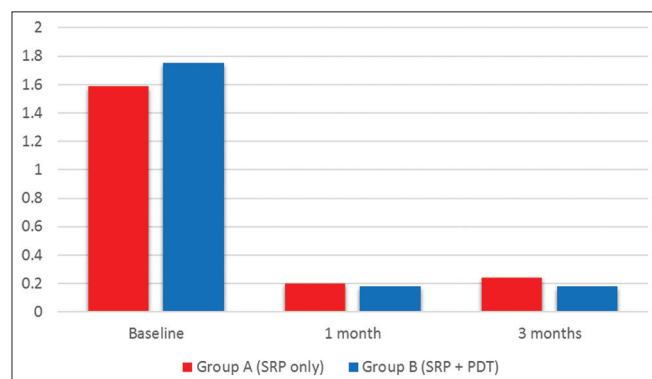
\*\*Values highly significant ( $p \leq 0.001$ ) using Student's *t*-test. PPD=Probing pocket depth, SD=Standard deviation, SRP=Scaling and root planning, PDT=Photodynamic therapy



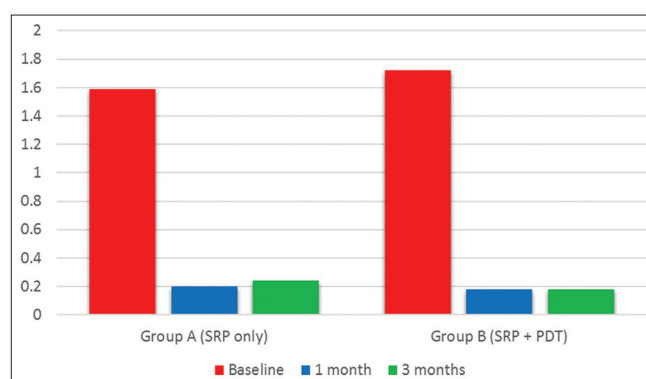
**Graph 1: Intergroup comparison of plaque index**



**Graph 2: Intragroup comparison of plaque index**



**Graph 3: Intergroup comparison of gingival index**



**Graph 4: Intragroup comparison of gingival index**

Intragroup comparisons showed a statistically significant reduction in the pocket depth at 1 and 3 months, in both control and test group, when compared to the baseline. In test group, statistically significant reduction was seen between 1 and 3 months follow-up, whereas no significant results were seen between 1 and 3 months follow-up in the control group [Table 6 and Graph 6].

### Relative attachment level

The mean RAL at baseline, 1 and 3 months for the control group was  $9.30 \pm 2.32$ ,  $8.07 \pm 2.42$ , and  $8.07 \pm 2.42$ , and for the test group was  $9.13 \pm 1.88$ ,  $7.40 \pm 1.52$ , and  $6.60 \pm 1.49$  respectively.

At the baseline and 1 month follow-up, no statistical significant difference in the RAL was seen between the control and test group. However, there was statistically significant reduction in the RAL in the test group as compared to the control group at 3 months ( $P = 0.007$ ) [Table 7 and Graph 7].

Intragroup comparisons showed a statistically significant reduction in the RAL at 1 and 3 months, in test group, when compared to the baseline. No statistical significant result was seen in the control group at 1 and 3 months when compared to the baseline.

No statistical significant result was seen in the control and test group when 1 and 3 months were compared [Table 8 and Graph 8].

**Table 6: Intragroup comparison of probing pocket depth using repeated measures of analysis of variance**

Group (n=30)	PPD in mm (mean±SD)			p
	Baseline	1 month	3 months	
Group A (SRP only)	5.27±0.69	3.67±0.75*	3.67±0.75*	0.000
Group B (SRP + PDT)	5.13±0.34	2.80±0.71*	2.23±0.67*	0.000

\*Values highly significant ( $p < 0.001$ ) as compared to the baseline levels using multiple comparison test. PPD=Probing pocket depth, SD=Standard deviation, SRP=Scaling and root planning, PDT=Photodynamic therapy

**Table 7: Intergroup comparison of relative attachment level using Student's t-test**

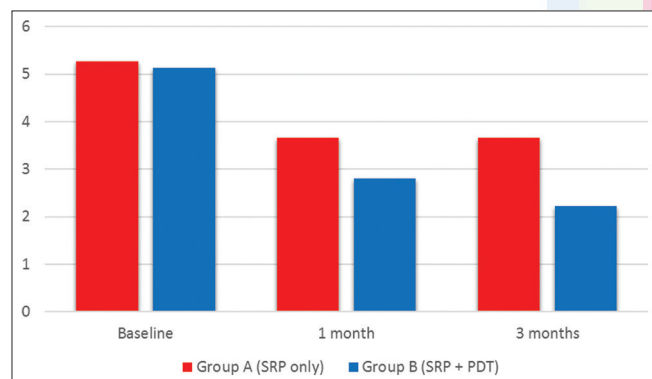
Group (n=30)	RAL in mm (mean±SD)		p
	Group A (SRP only)	Group B (SRP + PDT)	
Baseline	9.30±2.32	9.13±1.88	0.761
1 month	8.07±2.42	7.40±1.52	0.234
3 months	8.07±2.42*	6.60±1.49*	0.007

\*Values significant ( $p \leq 0.05$ ) using Student's t-test. RAL=Relative attachment level, SD=Standard deviation, SRP=Scaling and root planning, PDT=Photodynamic therapy

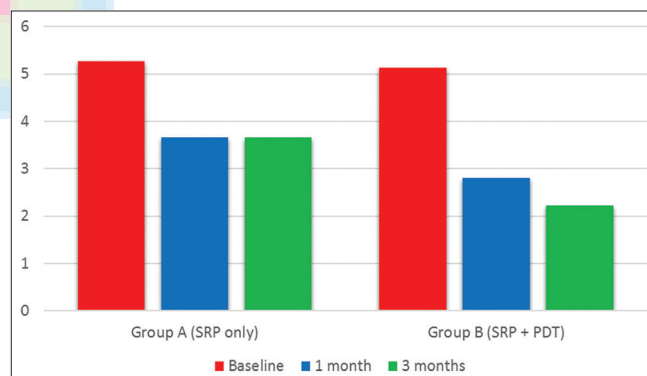
**Table 8: Intragroup comparison of relative attachment level using repeated measures of analysis of variance**

Group (n=30)	RAL in mm (mean±SD)			p
	Baseline	1 month	3 months	
Group A (SRP only)	9.30±2.32	8.07±2.42	8.07±2.42	0.075
Group B (SRP + PDT)	9.13±1.88	7.40±1.52*	6.60±1.49*	0.000

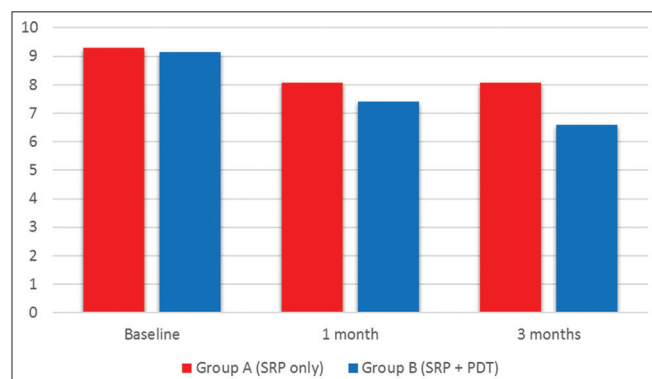
\*Values highly significant ( $p < 0.001$ ) as compared to the baseline levels using multiple comparison test. RAL=Relative attachment level, SD=Standard deviation, SRP=Scaling and root planning, PDT=Photodynamic therapy



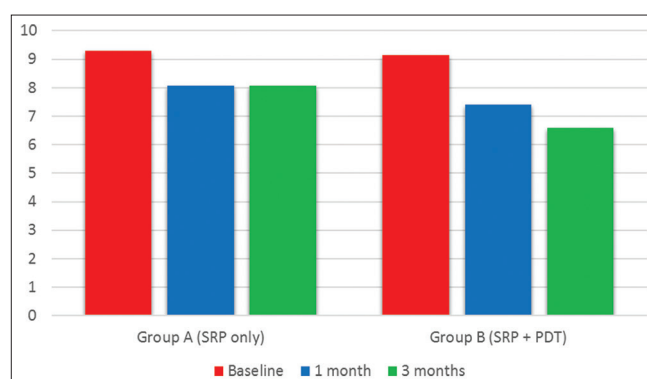
**Graph 5: Intergroup comparison of probing pocket depth**



**Graph 6: Intragroup comparison of probing pocket depth**



**Graph 7: Intergroup comparison of relative attachment level**



**Graph 8: Intragroup comparison of relative attachment level**

## DISCUSSION

Conventional mechanical instrumentation of the root surface is considered as a prerequisite for long-term treatment success.<sup>[16]</sup> Bonito *et al.* showed that mechanical debridement cannot completely remove pathogenic bacteria.<sup>[17]</sup> In addition, mechanical debridement alone only temporarily reduces the bacterial infection and may result in a return to pretreatment levels in <2 weeks.<sup>[3,18]</sup> Hence, treatments adjunct to mechanical debridement have been advocated.

In aPDT, photodestruction is mainly caused by damage to the cytoplasmic membrane and DNA.<sup>[6]</sup> The polysaccharides present in the extracellular matrix of polymers of a bacterial biofilm are susceptible to photodamage.<sup>[19]</sup> Such dual activity is not exhibited by antibiotics and may represent a significant advantage of aPDT. Moreover, development of resistance to the cytotoxic action of singlet oxygen or free radicals seems to be unlikely.

PDT is equally effective against antibiotic-resistant and antibiotic-susceptible bacteria, and repeated photosensitization has not induced the selection of resistant strains.<sup>[14]</sup>

Over the past decade, a number of studies have been carried out to evaluate PDT as an adjunct to SRP for the nonsurgical management of chronic periodontitis, aggressive periodontitis, and patients on periodontal maintenance therapy. Efforts were made in four systematic reviews,<sup>[20-23]</sup> to evaluate the benefit of PDT for the treatment of periodontitis, either as a primary mode of treatment or as an adjunct to mechanical debridement. The results of these systematic reviews were not definitive and in part contradictory with regard to the clinical and microbiological effects. Hence, it was clearly indicated from these reviews that more primary research is necessary to assess the value of PDT and to determine the factors influencing the outcomes.

PDT has been explored for periodontal therapy using a variety of photosensitizing dyes (methylene blue, toluidine blue, and chlorines), and with lasers of various wavelengths. Methylene blue (10 mg/ml) and 660–680 nm diode laser appear to be the most commonly tested combination.<sup>[6]</sup> Recently, *in vitro* studies have shown the efficacy of a new photosensitizer dye, ICG, against *A. actinomycetemcomitans* and *P. gingivalis*, when activated by an 810 nm diode laser.<sup>[8,9]</sup> ICG is a water soluble, anionic tricarboxyanine that belongs to the large family of cyanine dyes. The ICG molecule exhibits a molecular structure with amphiphilic properties that have both hydrophilic and lipophilic properties. Through photon-induced electron transfer, ICG is able to produce powerful photosensitized cellular damage.<sup>[7,10]</sup>

ICG in therapeutic concentrations has almost no host toxicity and is approved by the United States Food and Drug Administration (FDA) for medical applications to observe liver function, cardiac output, and blood volume.<sup>[8]</sup> ICG binds to plasma protein, is not chemically altered in the body, exists in a stable state, and is rapidly excreted in the bile. Thus, ICG has been shown to satisfy most of the requirements of an ideal photosensitizer.<sup>[9]</sup>

ICG has a wide optical absorption band from 600 to over 800 nm with optimal peak at 805–810 nm near-infrared wavelength, which is close to the emission of commercially available diode lasers used for soft tissue surgery.<sup>[7,24]</sup> In addition, the wavelength of 805–810 nm has more capacity to penetrate biological tissue than rest of the spectrum. Penetration depth in biological tissue for visible-red wavelengths (650 nm) is 3–3.5 mm, whereas for near-infrared light (800–1100 nm), it reaches up to 6 mm.<sup>[25]</sup>

Thus, in the present study, we evaluated the effect of PDT using an 810 nm diode laser and ICG as photosensitizer as an adjunct to SRP in the treatment of chronic periodontitis.

Our study design was a randomized controlled trial in accordance with the recommendations by Pihlstrom.<sup>[26]</sup> It was legitimate to employ a split-mouth design to eliminate bias that would arise due to variation in healing pattern among individuals. Furthermore, the photosensitizer alone is not capable of generating an antimicrobial effect.<sup>[14]</sup>

PDT was carried out 1 week after the completion of SRP. The rationale behind this was that a bleeding sulcus would have a reductive effect on the dye penetration into the pocket. The dye would be rinsed from the sulcus or diluted to invalid levels by the bleeding, which would end up neutralizing its effect completely. This might affect the final treatment outcome; hence, a time shift is recommended in this treatment.<sup>[15]</sup>

The mechanism of uptake of ICG by periodontal bacteria appears to be unclear. However, it has been demonstrated that this uptake appears to be more specific to periodontal bacteria as another Gram-negative bacterium (*Escherichia coli*) and cultured gingival cells take up 10-fold lesser amounts of ICG.<sup>[7,8]</sup>

The PDT procedure comprises the photosensitizer dye (ICG dye) being activated by laser energy. The photosensitizer alone is not capable of generating an antimicrobial effect. As only the test sites were irradiated by laser light, a damaging effect on bacteria in the control sites was not possible. For the control sites, photosensitizer was flushed in periodontal pocket, and sham laser was used. Hence, the patients were blinded for the procedure.

The results of the present study are in accordance with those of studies evaluating the effect of photodisinfection alone



and in combination with conventional SRP.<sup>[14,27]</sup> Assessing 33 patients with chronic periodontitis, Andersen *et al.*<sup>[27]</sup> reported a clinical attachment gain of  $0.36 \pm 0.35$  mm in the group treated with SRP alone after 12 weeks. A gain of  $0.86 \pm 0.61$  mm was observed for SRP with adjunctive aPDT. These values are in agreement with those reported in the present study. The difference in RAL values in control group (mean difference 1.233 mm) at 3 months was lower than those in the test group (mean difference 2.533 mm).

A number of studies have been conducted evaluating the adjunctive use of PDT for the nonsurgical management of chronic periodontitis. Human studies have produced contrasting results and some systematic reviews have only partly discussed the adjunctive effect of PDT. A meta-analysis by Atieh<sup>[22]</sup> revealed supportive data for the potential improvements of using aPDT in conjunction with SRP in periodontal treatment. They found that adjunctive aPDT resulted in significantly greater clinical attachment gain and a reduction in probing depth. Sgolastra *et al.*<sup>[23]</sup> also conducted a systematic review indicating that the adjunctive use of aPDT and subgingival SRP can provide additional benefits in terms of reductions in PD and gains in the clinical attachment level. These benefits of combined treatment were observed only at the 3-month follow-up time point. In contrast, no significant differences were observed at 6 months posttreatment. However, this finding is likely related to the small number of included studies that reported a follow-up time of 6 months.<sup>[23]</sup>

The most recent systematic review by Smiley *et al.* concluded that PDT with a diode laser adjunctive to SRP has beneficial effects with a moderate level of certainty and it resulted in a mean attachment gain of 0.53 mm.<sup>[20]</sup>

To the best of our knowledge, as of now, only one clinical trial has been reported in literature where ICG and an 810 nm diode laser has been used for adjunctive PDT treatment.<sup>[24]</sup> The authors reported that additional PDT resulted in a significantly higher change in CAL after 3 months posttreatment than the sites receiving SRP alone. The same was not seen with respect to probing depth. Furthermore, lactate dehydrogenase levels were measured to identify any potential toxic effect and the dye showed good tissue acceptability.

In the present study, the patients did not report any adverse effect posttreatment. It was also noted that ICG did not stain the teeth or restorations with the exception of plaque, which stained green, presumably due to the bacterial content.<sup>[8]</sup>

In our current study and also in most studies carried out so far, the PDT procedure was applied just once. The concept of repeated application and activation of the photosensitizer have been addressed in only a few studies. In one trial, three rounds of PDT within 1 week had no significant effect

on clinical and microbiological parameters.<sup>[28]</sup> In another trial, five rounds of adjunctive PDT yielded better clinical outcomes than mechanical debridement only in residual pockets of maintenance patients; reductions of pocket depth and bleeding on probing and gains in clinical attachment level were greater in the test as compared to the control group.<sup>[29]</sup>

In a trial, PDT procedure was carried out once in Group A and twice in Group B, in a 1-week interval. The treatment outcomes in terms of pocket depth reduction and clinical attachment gain were significant to the groups which receive PDT. However, among the Group A (PDT application once) and Group B (PDT application twice,) there was no statistically significant difference on subsequent follow-up.<sup>[30]</sup>

The variation in the reported treatment outcome to PDT, in the literature, can be attributed to several factors such as drug ion concentration, period of retention of the drug within the tissue, time for biological response, pH of the environment (tissue/tooth interface), presence of exudates and gingival fluid, and mode of drug application.<sup>[31]</sup>

A possible concern for the clinical application of PDT is the potential photocytotoxicity to host cells. However, it has been demonstrated that the doses of light needed for killing bacteria in PDT are much lower than those that are toxic for keratinocytes and fibroblasts.<sup>[32]</sup>

Concern has been raised regarding the safety of ICG for periodontal application. It is to be noted that for medical purposes, ICG is administered as 10 ml intravenous solution of 2.5 mg/ml and is used to determine cardiac output, hepatic function and liver blood flow, and ophthalmic angiography. In the present study, ICG is used at a concentration of 1 mg/ml and in a smaller volume and is flushed into the periodontal pocket. Therefore, the safety issues should be comparable or less than for the existing FDA-approved formulation.<sup>[8]</sup> Furthermore, ICG is not absorbed by the intestinal mucosa, which is why the danger of uncontrolled swallowing of the material is nonexistent.<sup>[15]</sup>

### Limitations

- This was a single-blinded study; hence, the examiner was not blinded for the test and control sites. This could have resulted in a potential bias in the findings
- Microbiologic parameters were not assessed to find exact alterations in the periodontal pathogens following treatment
- The sample size used in this study is small and larger sample size would be required to compare the effects of PDT in a more comprehensive manner.

### CONCLUSION

In spite of the limitations of our study, statistically significant results were seen with respect to reduction in pocket depth



and gain in the attachment level with adjunct use of PDT in the treatment of chronic periodontitis. The use of ICG as a photosensitizer seems to be safe and no adverse effect was reported postoperatively. The overall treatment was well tolerated by the patients.

Use of PDT (using ICG and 810 nm diode laser) should be seen as an adjunct for the reduction of bacterial pathogens and as a part of the overall treatment necessary to address causative factors and repair, remodel, or restore the tissue site as required. The use of PDT is not intended as a substitute for the best practice in periodontics, i.e., patient evaluation, assessment of local and systemic factors, and formulation of an overall and specific treatment plan. Oral hygiene instruction and SRP should be carried out and any progress should be quantified using the accepted treatment outcome protocols.

Within the limits of our study, we conclude that PDT using ICG and 810 nm diode laser resulted in significant clinical improvement when used in patients with chronic periodontitis. PDT can be used as an adjunct for the nonsurgical treatment of chronic periodontitis. More studies with sufficient statistical power should be conducted to assess the possibilities of using PDT in various forms of periodontitis. In addition, further studies are required to elucidate the beneficial properties of ICG.

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### Conflicts of interest

There are no conflicts of interest.

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