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Clinical efficacy of photodynamic therapy as an adjunct to scaling and root planing in the treatment of chronic periodontitis among cigarette smokers: A systematic review and meta-analysis

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ABSTRACT

Background: The aim of the study was to evaluate the clinical efficacy of adjunctive photodynamic therapy (PDT) as compared to scaling and root planing (SRP) alone in the treatment of chronic periodontitis among cigarette smokers.

Methods: Electronic databases including EMBASE, MEDLINE, Cochrane Oral Health Group Trials Register and Cochrane Central Register of Controlled Trials were searched up to January 2019. Randomized clinical trials (RCTs) with data on comparison between adjunctive PDT compared to SRP in each group were included. Primary outcomes included clinical attachment level (CAL) gain, while secondary outcomes was probing depth (PD) reduction. The weighted mean differences (WMD) of outcomes and 95% confidence intervals (CI) for each variable were calculated using random and fixed effect models.

Results: A total of 5 RCTs were included. Two clinical trials were classified as having a low risk of bias and 3 clinical trials as high risk of bias. The overall effect for CAL gain (WMD= –0.088, 95% CI= –0.40 to 0.23, p = 0.58) and PD reduction (WMD= -0.35, 95% CI= -0.87 to -0.17, p = 0.18) was not statistically significant between PDT and SRP groups at follow-up, respectively.

Conclusion: Within the limitations of this study, it remains debatable whether PDT as an adjunct to SRP is more effective in clinical attachment level gain as compared to SRP alone in cigarette smokers given that the available scientific evidence is weak.

1. Introduction

Chronic periodontitis is an inflammatory disease of bacterial origin that involves the supporting structures of the teeth and results in a gradual destruction of soft tissue and alveolar bone with deep pocket formation, gingival recession, or both [1]. Several risk factors are associated with the progression of chronic periodontitis including bacterial plaque, systemic inflammatory disorders and tobacco smoking that affect prevalence, extent and severity of disease [2–6]. Research indicates that a dose-response relationship exists between cigarette smoking and the odds of periodontitis increasing the rate of destruction to 5–6 folds among smokers compared with never-smokers [7]. In addition, smoking affects the subgingival bacterial profile in healthy individuals and is responsible for the depletion of beneficial bacteria and the increase in periodontopathogenic bacteria [8].

In smoker with chronic periodontitis, subgingival debridement (in conjunction with supragingival plaque control) does not respond favourably well. Majority of clinical studies supports the observation that probing depth (PD) reduction and gains in clinical attachment level (CAL) are less pronounced in smokers than in non-smokers [9–11]. Based on such observations, it has been hypothesized that purely mechanical debridement may not be effective for patients with current smoking history. Several researchers have reported the use of different antibiotics for enhanced PD reduction and CAL gain in smokers [12,13]. In view of the bacterial etiology of the inflammatory periodontal diseases and smokers responding less favourably to non-surgical periodontal, adjunctive photodynamic therapy (PDT) would likely improve clinical periodontal outcomes.

Numerous studies have investigated the use of PDT in the treatment of chronic periodontitis [14–17]. The rationale for use of PDT in the

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treatment of periodontal inflammation is to rapidly suppress the target microbial species. The phenomenon involves the stimulation of photosensitizer dye molecules by laser light of specific wavelength. This is followed by transition of dye molecule from ground singlet state to excited triplet state which reacts with endogenous oxygen to form highly reactive and cytotoxic singlet oxygen that facilitates bacterial cell death [18,19]. Several studies reported the use of PDT in smokers with chronic periodontitis and have reported conflicting results [20–22]. For instance, Theodoro et al. [20] in their single blinded split-mouth randomized controlled clinical trial (RCT) showed significant improvement in clinical periodontal parameters with PDT as compared to scaling and root planing (SRP) alone. However, de Melo Soares et al. [21] and Queiroz et al. [22] showed no clinical significant differences in periodontal parameters between PDT and SRP groups at follow-up. For this purpose, a systematic review is deemed necessary to quantitatively analyse the clinical efficacy of adjunctive PDT as compared to SRP alone in the treatment of chronic periodontitis in cigarette-smokers.

The aim of the current systematic review was to answer the formulated PICOS question: In smokers with chronic periodontitis (***P**atients*), what is the clinical efficacy of adjunctive PDT (***I**ntervention*) as compared to SRP alone (***C**omparator*) on clinical attachment level gain (***O**utcome*) considering only RCTs (***S**tudy design*)?

2. Materials and methods

2.1. Study registration

The protocol for this systematic review was made a *priori* and registered in the PROSPERO (http://www.crd.york.ac.uk/PROSPERO), International Prospective Register of Systematic Reviews database. The record for the present protocol was published on January 21, 2019 with record number CRD42019121101. The outline of this systematic review followed the PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analysis) guidelines [23].

2.2. Eligibility criteria according to PICOS

Study design type: Only RCTs and/or controlled clinical trials (CCTs) were considered. Articles published in other than English language and non-RCTs were not incorporated in the current review.

Participants: Studies consisting at least 10 patients per group with smoking habit and clinically diagnosed with CP without any age restriction were included. Patients with no history of smoking were excluded from the current review.

Interventions: Efficacy of adjunctive antimicrobial PDT compared with root surface debridement. Treatment interventions other than PDT assessing main clinical outcome were excluded.

Outcome: Primary. Primary outcome measure included clinical attachment level gain. Secondary. Secondary outcome measures was probing depth reduction. Studies were excluded if the primary outcome (clinical attachment level gain) was missing.

2.3. Information sources and search plan

Searches in both electronic and manual literature were performed by two independent reviewers in the databases (MEDLINE, EMBASE, and Cochrane Central Register of Controlled Trials and Cochrane Oral Health Group Trials Register) between January 1st, 1984 and January 1st, 2019 for articles that focused the PICOS question using the following terms: (Photodynamic therapy) AND (chronic periodontitis) AND (scaling and root planning) AND (smokers).

The authors individually performed the screening of the titles and selection process for eligible articles. If data pertinent to the inclusion criteria was not found in the abstract, or if the abstract was missing, the article was chosen for full-text reading. Subsequently, full-text articles that satisfied the inclusion criteria were recognized and included in the systematic review. Reference lists from original studies were manually hand searched to identify papers that may have missed during the electronic data search. The search agreement between the reviewers was estimated by the Cohen's Kappa (κ) analysis. Manual hand searching of the following peer-reviewed journals was performed: *Lasers and Medical Science, Photodiagnosis and Photodynamic Therapy, Clinical Oral Investigations* and *Saudi Medical Journal*. Published studies that satisfied the inclusion criteria were handled for data abstraction. Reviewers planned and assessed the project in a way that the design of the proposal goes in accordance with the PRISMA guideline [23].

2.4. Data items and abstraction

Two reviewers executed the data abstraction independently. The details of the data from the accepted studies was charted according to the sample demographics, smoking habits, follow-up duration, main clinical outcomes and laser parameters. Data gathered were constructed on the focused PICO question summarized for the current review. The assessors crosschecked all collected data and any disagreements were resolved through discussion.

2.5. Risk of bias and quality assessment in individual studies

The revised recommendations of the Consolidated Standards of Reporting Trials statement was used to evaluate the risk of bias of RCTs [24]. The risk of bias was assessed for each selected RCT based on the Cochrane Handbook for Systematic Reviews of Interventions [25]. Following sections were deemed: randomization and allocation concealment, blinding of study participants and personnel with outcome assessment, reporting of all patients that completed the trial and withdrawals if any, and selective reporting. Sections for quality assessment were categorized as having (high) "high risk of bias", (low) "low risk of bias" or "unclear" for each of these sections. Overall, studies were considered as: (i) low risk of bias if all criteria were met; (ii) unclear risk of bias if one or more criteria were partly met; or (iii) high risk of bias if one or more criteria were not met.

2.6. Summary measures and approach to quantitative analysis

Quantitative analyses were performed separately for both primary (CAL gain) and secondary outcomes (PD reduction). Heterogeneity across the accepted studies for the outcome was assessed using the χ^2 and I^2 statistics. For analyses, if the test showed substantial heterogeneity ($I^2 > 50\%$), a random effects model was applied, or else ($I^2 \leq 50\%$), a fixed effects model would be used [26]. A *p*-value less than 0.05 represents significant heterogeneity. Forest plots were produced describing weighted mean difference (WMD) of outcomes and 95% confidence intervals (CI). Publication bias was statistically assessed across studies by generating funnel plots. Meta-analyses was performed using a specialized statistical software (MedCalc Software- B-8400 v 15.11.04, Ostend, Belgium). Data unsuitable for quantitative analysis were assessed descriptively.

2.7. Grading the 'body of evidence'

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) was employed to rank the evidence [27]. Two reviewers (ZA & MAR) rated the quality of the evidence and the strength and direction of the recommendations according to the following aspects [28]: risk of bias, consistency of results, directness of evidence, precision, and magnitude of the effect. Any disagreement between the two reviewers was resolved after additional discussion.

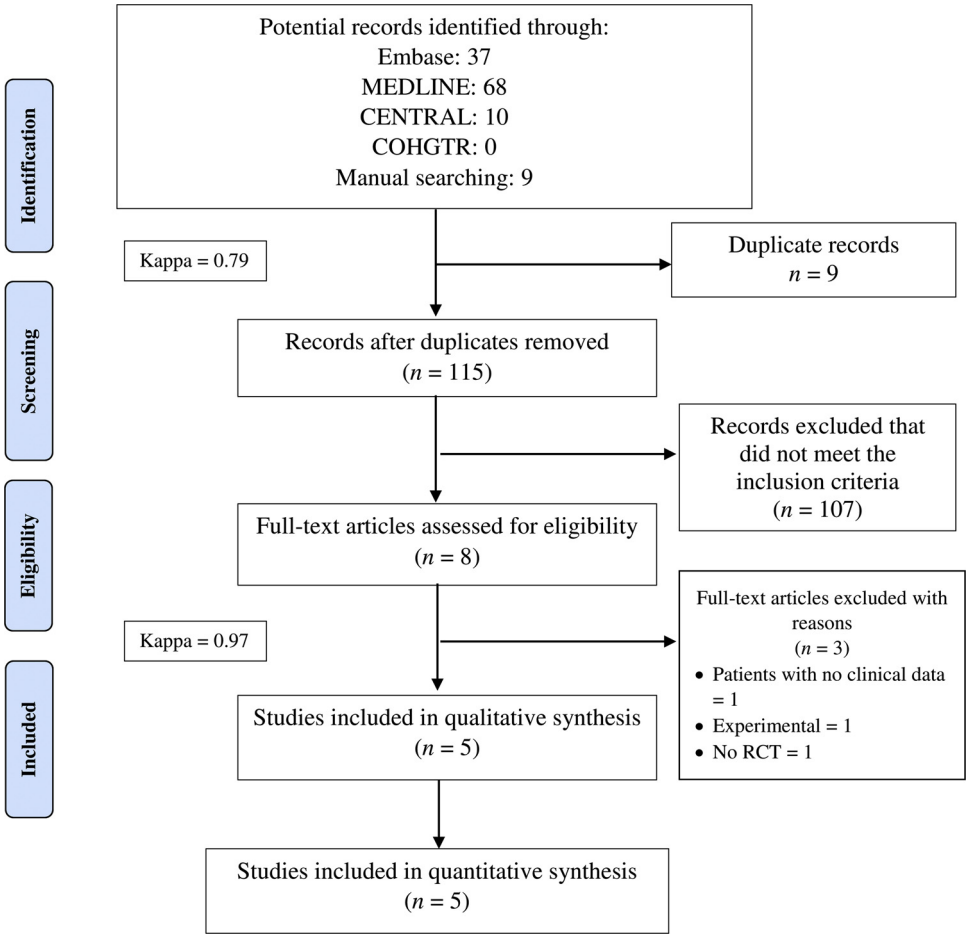

Fig. 1. PRISMA flow diagram for studies retrieved through the searching and selection process.

3. Results

3.1. Search results

A total of 124 study titles and abstracts were initially identified. After thorough analysis, 9 duplicate articles were omitted. Preliminary screening of titles and abstracts was completed, and 107 articles were excluded as they were considered irrelevant to the PICO question (κ score for inter-assessor agreement: 79%). A total of 8 papers were nominated for full-text reading. Of these 8 studies, 3 studies were further excluded. After the final stage of selection, 5 studies were included and processed for data extraction (κ score for inter-assessor agreement: 97%) [20–22, 29,30]. All studies were performed at university clinics. Fig. 1 shows the study identification flow chart according to PRISMA guidelines (Table 1).

3.2. General characteristics of the included studies

Five RCTs were included out of which 4 RCTs had split mouth design [20–22, 30], while 1 study had patient assignment [29]. Three studies were single-blinded RCTs [20,29,30], whereas 1 clinical study was double-blinded RCT [21]. Three studies were performed in Brazil [20–22], while 2 were undertaken in Saudi Arabia [29,30]. The number of participants in the included studies ranged from 20 to 51 with mean age ranging between 41.6 years to 48.0 years, respectively. The total number of males were 112 while total number of female participants were only 43. The smoking frequency and duration was also reported in the included studies, out of which three studies reported ≥ 10 cigarettes per day for ≥ 5 years [20,22,30], 1 clinical study only reported smoking frequency of 19 cigarettes per day [21], and the other clinical study only addressed the smoking duration which was 12.1 years respectively [29]. The follow-up period in all clinical studies ranged from 12 to 26 weeks [20–22, 30]. Funding was reported in 4 studies [20–22, 29].

3.3. Parameters of photodynamic therapy in the included studies

Four studies used diode lasers [21,22,29,30], while only 1 clinical study reported the use of GaAlAs (gallium-aluminium arsenide) [20]. The wavelengths ranged from 660 to 670 nm. Three studies reported power density [21,22,29] and energy fluence [20–22] which ranged from 16.72–160 J cm^{-2} and 28–75 m W cm^{-2}, respectively. Power output, duration of irradiation and optic fibre diameter was reported in four studies which was 150 mW, 60 s and 0.6 mm, respectively [20–22, 29]. Three studies reported the use of methylene blue (MB) [20,29,30], whereas 2 clinical studies reported phenothiazine chloride (PC) as photosensitizers (PS) [21,22]. Pre-irradiation time ranged from 10 to 60 s. Concentration of PS was reported in all 5 studies, in which 3 studies reported 10 mg/ml [20–22], whereas 1 study each reported 0.01% [30] and 0.005% [29], respectively. Four studies reported the total number of laser sessions which ranged from 1 to 4 applications throughout the study period (Table 2) [20–22, 29].

3.4. Clinical periodontal parameters of the included studies

The results for four clinical parameters (CAL gain, PD reduction, PI and BOP) are presented in Table 3. A total of 5 clinical trials reported CAL gain which ranged from 4.11 mm to 9.24 mm in the PDT group and

Table 1
General description of the included studies in chronological order.

Author et al., Year; Journal name	Study Design	Country of study	Sample demographics *n*; Mean age (Age range); M/F	Smoking frequency and duration	Follow-ups (Weeks)	Main Outcome	Funding
Al-Zahrani et al., [30] 2011; *Saudi Medical Journal*	Single-blinded RCT; Split-Mouth	Saudi Arabia	20; 41.6 (30-56); 20/0	≥ 10 cigarettes per day for ≥ 5 years	Up to 12	Significant improvement in clinical periodontal parameters with PDT as compared to the SRP were observed	Not stated
Queiroz et al., [22] 2015; *Lasers in Medical Science*	RCT; Split-Mouth	Brazil	23; 46.05 (35-55); 9/11	≥ 10 cigarettes per day for ≥ 5 years	Up to 12	No statistical significant differences in clinical periodontal parameters between PDT and SRP groups were observed	Government
Theodoro et al., [20] 2018; *Photodiagnosis and Photodynamic Therapy*	Single-blinded RCT; Split-Mouth	Brazil	51; 48 (35-65); 35/16	≥ 10 cigarettes per day for ≥ 5 years	Up to 26	Significant improvement in clinical periodontal parameters with PDT as compared to the SRP were observed	Government
de Melo Soares et al., [21] 2018; *Clinical Oral Investigations*	Double-blinded RCT; Split-Mouth	Brazil	22; 48 (39-61); 6/16	19 cigarettes per day (NA)	Up to 13	No statistical significant difference in clinical periodontal parameters between PDT and SRP groups were observed	Private
Al-Ahmari et al., [29] 2018; *Photodiagnosis and Photodynamic Therapy*	Single-blinded RCT; Patient Assignment	Saudi Arabia	42; 46.8 (NA); 42/0	NA; 12.1 years	Up to 13	No statistical significant difference in clinical periodontal parameters between PDT and SRP groups were observed	University

RCT; Randomized clinical trial, PDT; photodynamic therapy, SRP; scaling and root planing.

Table 2
Photodynamic therapy related parameters of the included studies.

Author et al.	Laser type	Wavelength (nm)	Energy fluence (J cm^{-2})	Power output (mW)	Power density (mW cm^{-2})	Duration of irradiation (seconds)	Optic fiber diameter (mm)	Type of photosensitizer	Pre irradiation time (seconds)	Photosensitizer concentration	Number of laser sessions
Al-Zahrani et al. [30]	Diode laser	670	NA	NA	NA	NA	NA	Methylene blue	NA	0.01%	NA
Queiroz et al. [22]	Diode laser	660	16.72	60	28	60	0.6	Phenothiazine chloride	60	10 mg/ml	1
Theodoro et al. [20]	GaAlAs	660	160	100	NA	48	0.03	Methylene blue	60	10 mg/ml	3
de Melo Soares et al. [21]	Diode laser	660	16.72	70	28	60	0.6	Phenothiazine chloride	60	10 mg/ml	4
Al-Ahmari et al. [29]	Diode laser	660	NA	150	75	60	0.6	Methylene blue	10	0.005%	1

GaAlAs; gallium-aluminum-arsenide, nm; nanometers, *J* cm^{-2}; joules per square centimeters, mW; milliwatts, mW cm^{-2}; milliwatts per square centimeters, mg/mL; milligram per milliliter, μm; micrometer, cm^2; square centimeters, NA; not available.

Table 3
Clinical periodontal outcomes of the included studies in chronological order (Data is presented as mean ± SD).

Author et al.	Clinical attachment level gain	Probing depth reduction	Plaque Index	Bleeding on Probing
Al-Zahrani et al. [30]	PDT + SRP Baseline: 6.30 ± 1.44 Follow up: 4.70 ± 1.27 SRP Baseline: 6.18 ± 1.40 Follow up: 4.80 ± 1.45	PDT + SRP Baseline: 5.60 ± 0.83 Follow up: 3.84 ± 0.85 SRP Baseline: 5.35 ± 0.46 Follow up: 3.90 ± 0.75	PDT + SRP‡ Baseline: 78.50 ± 16.10 Follow up: 41.90 ± 17.90 SRP‡ Baseline: 75.90 ± 15.80 Follow up: 43.60 ± 16.60	PDT + SRP‡ Baseline: 74.50 ± 21.50 Follow up: 41.90 ± 22.30 SRP‡ Baseline: 68.00 ± 23.00 Follow up: 45.60 ± 19.50
Queiroz et al. [22]	PDT + SRP Baseline: 10.83 ± 1.45 Follow up: 9.24 ± 1.91 SRP Baseline: 11.12 ± 1.52 Follow up: 9.72 ± 1.86	PDT + SRP Baseline: 5.39 ± 0.74 Follow up: 3.58 ± 1.05 SRP Baseline: 5.35 ± 0.70 Follow up: 3.77 ± 1.06	NA	NA
Theodoro et al. [20]	PDT + SRP Baseline: 4.55 ± 0.39 Follow up: 4.11 ± 0.34 SRP Baseline: 4.68 ± 0.94 Follow up: 4.47 ± 0.80	PDT + SRP Baseline: 4.02 ± 0.42 Follow up: 3.54 ± 0.33 SRP Baseline: 4.19 ± 0.85 Follow up: 3.85 ± 0.73	NA	PDT + SRP‡ Baseline: 87.88 ± 9.61 Follow up: 59.69 ± 17.97 SRP‡ Baseline: 76.48 ± 22.68 Follow up: 68.89 ± 22.02
de Melo Soares et al. [21]	PDT + SRP ¶ Baseline: 5.25 ± 0.59 Follow up: 4.40 ± 1.16 SRP Baseline: 5.34 ± 0.95 Follow up: 4.53 ± 1.18 PDT + SRP ¥ Baseline: 7.59 ± 1.02 Follow up: 5.87 ± 1.13 SRP Baseline: 7.47 ± 0.67 Follow up: 5.70 ± 1.46	PDT + SRP ¶ Baseline: 5.17 ± 0.45 Follow up: 3.87 ± 0.86 SRP Baseline: 5.33 ± 0.43 Follow up: 5.14 ± 1.06 PDT + SRP ¥ Baseline: 7.29 ± 0.95 Follow up: 5.13 ± 1.15 SRP Baseline: 7.72 ± 0.43 Follow up: 5.50 ± 1.11	PDT + SRP† Baseline: 67.85 Follow up: 34 SRP† Baseline: 70.90 Follow up: 25	PDT + SRP† Baseline: 71.42 Follow up: 62 SRP† Baseline: 65.45 Follow up: 53.06
Al-Ahmari et al. [29]	PDT + SRP Baseline: 7.4 ± 0.7 Follow up: 6.2 ± 0.5 SRP Baseline: 7.1 ± 0.7 Follow up: 6 ± 0.4	PDT + SRP Baseline: 6.4 ± 0.8 Follow up: 5.8 ± 1.1 SRP Baseline: 6.1 ± 0.5 Follow up: 5.5 ± 1.2	PDT + SRP‡ Baseline: 55.2 ± 5.6 Follow up: 35.2 ± 3.9 SRP‡ Baseline: 52.6 ± 9.3 Follow up: 38.5 ± 5.6	PDT + SRP‡ Baseline: 31.6 ± 4.5 Follow up: 28.2 ± 1.6 SRP‡ Baseline: 35.3 ± 6.9 Follow up: 32.7 ± 2.4

‡ Denotes percentage of means.
† The figures denotes the percentage of subjects.
¶ Clinical data represents moderate probing depths.
¥ Clinical data represents deep probing depths.
PDT; photodynamic therapy, SRP; scaling and root planing, NA: not available.

4.47 mm–9.72 mm in the SRP group at follow-up [20–22, 29,30]. PD reduction was also reported in all 5 clinical trials which ranged from 3.54 mm to 5.8 mm in the PDT group and 3.77 mm to 5.5 mm in the SRP group at follow up [20–22, 29,30]. Plaque index was reported in 3 studies which ranged from 34.0%–41.90% and 25.0%–43.60% in the PDT and SRP groups, respectively [21,29,30]. Four clinical trials reported data for BOP [20,21,29,30], which ranged from to 28.2%–62.0% and 32.7%–68.89% in the PDT and SRP groups, respectively.

3.5. Quality of the clinical studies

All the clinical studies were subjected to critical analysis following the Cochrane Handbook for Systematic Reviews of Interventions for evaluating the risk of bias. We categorized 2 clinical trials as having a low risk of bias [20,21] and 3 clinical trials as having high risk of bias [22,29,30]. These 2 studies were judged to have lower risk of bias due to adequate reporting of sequence generation and randomization technique, blinding of study participants/personnel and patients withdrawal. In contrast, the domain classified as having high risk of bias was allocation concealment, blinding methods in 3 clinical trials (Table 4).

3.6. Main outcomes of the clinical studies

All included clinical studies reporting the use of PDT as an adjunct to SRP showed significant improvement in clinical periodontal parameters with PDT in the treatment of chronic periodontitis in cigarette smokers at follow-up. However, intergroup comparisons showed only two studies reported significant improvements with adjunctive PDT as compared to SRP [20,30], whereas three clinical trials showed no statistical significant differences in CAL gain and PD reduction between adjunctive PDT and SRP at follow-up [21,22,29].

Considering the effects of PDT on CAL gain and PD reduction, all 5 studies presented data to be included in the quantitative assessment. The overall effect for both clinical parameters were calculated using WMD. Random effect model was used for CAL gain as the heterogeneity was statistically significant ($\chi^2 = 12.72$, $P = 0.012$, $I^2 = 68.57\%$), while fixed effect model was employed for PD reduction as there was no significant heterogeneity observed ($\chi^2 = 4.94$, $P = 0.29$, $I^2 = 19.08\%$). The overall effect for CAL gain (WMD = –0.088, 95% CI = –0.40 to 0.23, $p = 0.58$, Fig. 2A) and PD reduction (WMD = -0.35, 95% CI = -0.87 to -0.17, $p = 0.18$, Fig. 2B) was not statistically significant between PDT and SRP groups at follow-up, respectively.

3.7. Evidence profile

Table 5 shows a summary of the various factors used to rate the quality of evidence and strength of recommendations according to GRADE [27]. Taken together, the strength of a recommendation based on the quality of the evidence emerging from this review is estimated to be moderate. Given that the effect is small, the direction of recommendation emerging from this systematic review is weak in favour

Table 4
Risk of bias of the included studies.

Author et al.	Sequence generation	Allocation concealment	Blinding of study participants and personnel	All patients accounted for at the end of study	Clear explanation of withdrawals	Selective reporting	Over risk of bias
Al-Zahrani et al. [30]	Low	High	High	Low	Low	Low	**High**
Queiroz et al. [22]	Low	High	High	Low	Low	Low	**High**
Theodoro et al. [20]	Low	Unclear	Low	Low	Low	Low	**Low**
de Melo Soares et al. [21]	Low	Low	Low	Low	Low	Low	**Low**
Al-Ahmari et al. [29]	Low	High	High	Unclear	Unclear	Low	**High**

of the use of PDT in the treatment of chronic periodontitis in patients with smoking habit.

3.8. Publication bias

All the randomized clinical studies were inside the confidence interval area and showed symmetry. This suggests there was no significant publication bias related to the clinical efficacy of PDT in the treatment of chronic periodontal inflammation in smokers (Online supplementary file S1 and S2).

4. Discussion

4.1. Summary of the main outcomes

We systematically reviewed the clinical efficacy of adjunctive PDT as compared to SRP alone in the treatment of chronic periodontitis among cigarette smokers. Overall, only 2 clinical studies reported significant improvement in clinical periodontal parameters with the use of PDT as compared to SRP alone [20,30]. However, the quantitative findings of the present study suggests no significant differences between the effect of PDT and SRP alone at follow-up.

4.2. Response of smokers to periodontal treatments

Tobacco smoking contributes to a poor clinical response to periodontal therapy and including other regenerative and periodontal plastic techniques [11,31,32]. Manual debridement alone provides a modest efficacy in enhancing clinical parameters and in declining the subgingival microbial niche in smokers [7]. The poor response of smokers to periodontal therapies may very well be described by the undesirable effects of tobacco smoking on the immunoinflammatory pathways and healing phases [7]. Overall, smoking may affect periodontal breakdown through different pathways, including dysfunction in the microcirculatory, inflammatory and immune systems [33]. Therefore, it is believed that a better understanding of the mechanisms of actions of cigarette smoke and its products in the microbiota and host responses is essential to develop more efficient therapeutic approaches for smokers. For this purpose, evaluation of treatment outcomes using PDT among cigarette smokers is critical.

Table 5
Summary of findings table on body of the estimated evidence profile (GRADE, 2015) and appraisal of the strength of the recommendation regarding the effectiveness of adjunctive PDT in the treatment of chronic periodontitis in smokers.

Determinants of quality	Photodynamic therapy
Study design	RCTs
Number of studies n = 5 (Fig. 1) Comparison n = 6	5
Risk of bias	High
Consistency (Figure 2 and 3)	Rather not consistent
Directness	Generalizable
Precision	Rather precise
Magnitude of the effect	Moderate
Strength of the recommendation based on the body of evidence	Moderate
Direction of recommendation	Weak in favour of the use of PDT

4.3. Comparison of studies

The main purpose of the PDT is to effectively target pathogenic bacteria from deep periodontal pockets to limit the severity of periodontal infection. A plethora of evidence suggests that PDT is highly

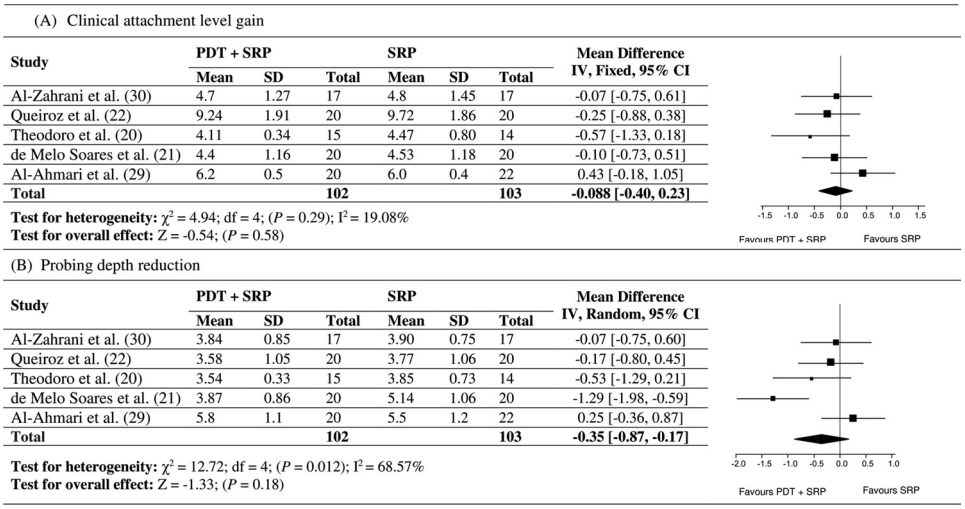

Fig. 2. (A) Forest plot presenting post-therapy clinical attachment level gain by comparing PDT versus SRP in cigarette smokers with chronic periodontitis, (B) Forest plot presenting post-therapy probing depth reduction by comparing PDT versus SRP in cigarette smokers with chronic periodontitis.

efficacious in reducing the periodonto-pathogenic bacteria from deep probing depths [34]. In addition, the subgingival bacterial niche differs in smokers from that of non-smokers indicating that cigarette smoking considerably affects subgingival bacterial species [8,35]. It is notable from the included studies that only 2 clinical trials evaluated the levels of bacterial species in subgingival plaque samples (data not shown in this review) [20,21]. Insufficient data exists which may be impossible to give a conclusive recommendation if PDT is effective in the reduction of bacterial species in periodontitis with smokers. However, from a recent microbiological study by Queiroz et al. [35], they concluded that periodontal therapy with adjunctive PDT or SRP alone did not reduce the levels of various pathogenic subgingival bacteria in smokers with chronic periodontal disease.

Another important aspect that evaluates the overall clinical efficacy of periodontal therapy is the understanding of immune inflammatory pathways of periodontal disease with its target therapy against immuneinflammatory response. When periodontal infection is established, the recognition of pathogen associated molecular patterns by pathogen recognition receptors stimulates innate immune responses, including the stimulation of elastases, proteinases, metalloproteinases, inflammatory cytokines, including interleukin (IL)-1beta, IL-8, IL-6, and tumor necrosis factor-alpha [36,37]. From the included studies, only 1 study evaluated the levels of proinflammatory cytokines at follow-up and showed comparable outcomes between PDT and SRP [21]. Therefore, further studies are needed to explore immunological aspect which may further help to extrapolate therapeutic strategy (including PDT) among cigarette smokers.

Another important aspect that is worth documenting is that the included studies either lacked data or had significant heterogeneity pertinent to laser parameters. Parameters including energy fluence and power density of laser light either varied considerably or were not reported in some studies. It is well-known that number of laser applications also influence the overall efficacy of laser treatment. The studies with PDT showing no statistical significant differences between groups may be related with the frequency of laser application [21,22,29]. In these studies, PDT was performed only in one session. It is impossible for a single application of laser to sustain antimicrobial effect for 12 weeks and hence comparable outcomes were observed. Among other factors, fiber diameter has an overall effect on power density and energy output during laser application in photomodulation and can modify the actual amount of energy released during the process, potentially affecting the antimicrobial efficacy of photodynamic therapy [38]. There were numerous irradiation protocols and parameters that were not described in full. For instance, Al-Zahrani et al. [30] did not describe several parameters including energy fluence, duration of irradiation, power output and density. The missing data on irradiation protocol may also have an effect on the periodontal outcomes. Therefore further studies with standardized laser parameters are required to interpret the efficacy of PDT in the treatment of chronic periodontitis in smokers.

4.4. Limitations and future implications

There are certainly some important limitations associated with the present systematic review. Firstly, the present study included less number of clinical trials for both qualitative and quantitative analysis. This is partially because of the lack of studies in the chosen area and due to the required parameters for the inclusion criteria for quantitative analysis. As a consequence of this, the results showed no significant difference within the assessed clinical parameters between groups. Worthy-of-note, the overall risk of bias was high in majority of the studies assessed which could possibly gave skewed results [22,29,30]. Furthermore, there was a short follow-up period described within the included studies. The authors suggest that to determine the clinical outcomes in the management of periodontitis, the follow-up period seems inadequate in the included studies and longer follow-up periods could have yielded different outcomes. In addition, the present systematic review did not consider studies in any other language except English. This may have resulted in publication bias with potential relevant studies published in other language being missed [39]. These inadvertent methodological shortcomings should be taken into account when interpreting the findings of the current review.

It is yet arduous to give recommendations to the clinicians since large follow-up RCTs are scarce, and hence the generalizability of the present systematic review findings are limited. Also, it should be kept in mind that meta-analyses of small trials do not always predict the outcome of large trials [40]. These results should be interpreted with extreme caution as a number of factors (e.g. significant heterogeneity in laser parameters, follow-up duration, and limited number studies) may have influenced the results. Therefore, ideally, future robust RCTs should include data with long follow-up periods, standard laser parameters, immunological and microbiological parameters that could help evaluate the true efficacy of PDT among cigarette smokers with chronic periodontitis.

5. Conclusion

Within the limitations of this study, it remains debatable whether PDT as an adjunct to SRP is more effective in clinical attachment level gain as compared to SRP alone given that the available scientific evidence is weak. Further well-designed robust RCTs are warranted in order to evaluate the impact of PDT on clinical attachment level gain in chronic periodontitis with smokers.

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There was no external funding for the present study.

Ethical approval

Not required. The manuscript does not contain clinical studies or patient data

Conflict of interest statement

The authors declare that they have no conflict of interest and all authors have read and approved the final draft.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.pdpdt.2019.04.027.

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