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REVIEW ARTICLE

Efficacy of antimicrobial photodynamic therapy (aPDT) for nonsurgical treatment of periodontal disease: a systematic review

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Abstract

Although the standard treatment for periodontal disease is based on scaling and root planing (SRP), the use of antimicrobial photodynamic therapy (aPDT) has been studied as a complement to obtain better clinical results. The purpose of this study was to evaluate the effect of aPDT as adjuncts to SRP, compared with SRP alone, on clinical parameters of chronic periodontal patients. Only randomized controlled trials with at least 3-month follow-ups, of SRP alone and in association with aPDT, were included. The MEDLINE (PubMed), Google Scholar, and LILACS databases were searched for articles published up to July 2020. Random-effects meta-analyses were conducted for clinical attachment level (CAL) and probing pocket depth (PPD) change after treatment. Of 141 potentially relevant papers, 22 were included. The association between SRP and aPDT promoted a significant CAL gain and PPD reduction. Periodontal treatment was partially improved by aPDT, and a favorable effect of indocyanine green–mediated aPDT was observed, and high concentrations of phenothiazine chloride presented clinical improvement as well.

Keywords Chronic periodontitis · Clinical trial · Photochemotherapy · Photodynamic antimicrobial chemotherapy (PACT) · Photosensitizer · Methylene blue · Indocyanine green · Therapy · Photodynamic · Antibacterial *photodynamic* therapy (*aPDT*)

Introduction

Periodontal disease is associated with an oral polymicrobial community, which provides an inflammatory host response. The bacterial colonization of the periodontium may create a dysbiosis environment and cause periodontal tissue destruction [1]. Periodontal treatment is based on root disinfection through scaling and root planing (SRP) [2, 3] and strict control of biofilm, which prevents recolonization of the subgingival area [4]. In some cases, the mechanical cleaning of tooth surfaces is not sufficient to solve periodontal infection [5]. Some periodontal pathogens may persist in connective tissue and epithelial cells, or dentine tubules, favorable to subgingival recolonization and disease recurrence [6]. Therefore, this clinical challenge involves some complementary therapy, such as periodontal surgery or antibiotics [7, 8].

Antimicrobial photodynamic therapy (aPDT) has been proposed as adjunctive to periodontal treatment in order to reduce the periodontal pathogenic community even more [9]. The antimicrobial photodynamic effect was attempted more than a hundred years ago, since Oscar Raab's and Hermann von Tappeiner's studies [10], but since the development of antibiotics, there was a lack of interest in light therapy, which reappeared recently to fill the gap left by antibiotic resistance. aPDT is a localized and noninvasive procedure that occurs through photophysical mechanisms. When a photosensitizer binds the target cell, it absorbs energy from light irradiation, in a specific and resonant wavelength, turning into an excited state. Then, the photosensitizer loses energy, which participates in reactive oxygen species (ROS) formation [11]. The oxidative stress from ROS may act on different cell structures (lipids, proteins, DNA, and carbohydrates) and lead to cell death (Fig. 1) [12, 13].

Photosensitizers have been undergoing constant evolution, and porphyrins, chlorines, phthalocyanines, and phenothiazines can target both Gram-positive and Gram-negative

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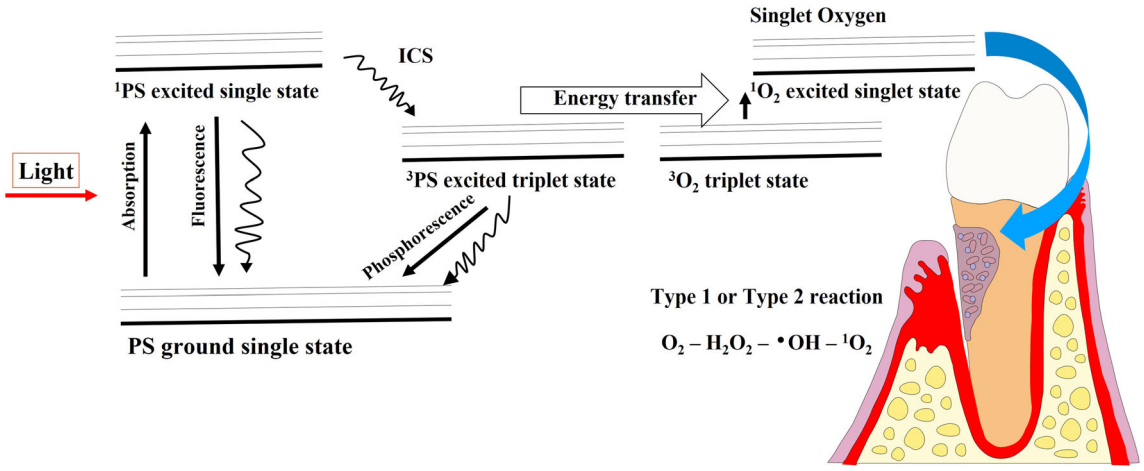

Fig. 1 Jablonski diagram

species [14–16]. Among phenothiazines, toluidine blue and methylene blue are the most used in dentistry, since they have a high absorption between 600 and 660 nm, and in this therapeutic window, there is low absorption by tissues [17–19]. Toluidine blue showed maximal absorption of energy at a wavelength of 630 nm, even in Gram-negative species in vitro [20]. Methylene blue showed maximal absorption when exposed to a wavelength of 660 nm [21, 22]. A recent promising photosensitizer is indocyanine green [23], which has high absorption at a wavelength of 800–805 nm and presented a great reduction of planktonic bacteria and biofilm of *Porphyromonas gingivalis* [24].

Its effect on dental biofilm was confirmed by Fontana et al., which associates a nontoxic dose of a photosensitizing agent with visible light [25]. The photosensitizer binds the target cells and is photoactivated by laser light at a specific wavelength. Oxygen singlet and other reactive oxygen species (ROS) are formed inside microbial cells, causing microbial death [15, 21, 26–28]. The methylene blue photosensitizer has a low molecular weight and a positive charge, which enable the passage across the porin-protein channels in the outer membrane of Gram-negative bacteria [29, 30].

Animal studies supported these results of bacterial reduction, with safety to the periodontal tissues [31–34]. Peron et al. investigated aPDT in animal data in the treatment of *P. gingivalis* infection, and the systematic review indicated some benefits of this therapy [15].

aPDT has also been investigated by several clinical trials as an adjunctive of periodontal treatment, which reported controversial results about the clinical benefits of PDT in the treatment of periodontal disease [35, 36]. In a clinical study, Malgikar et al. reported that aPDT associated with SRP may promote additional long-term clinical benefits to the patients [37]. However, Bassir et al. showed that the use of aPDT with periodontal treatment did not promote significant improvement compared with SRP alone [38]. In another research, Theodoro et al. showed that aPDT adjunctive to SRP was related to better microbiological results, but with no additional clinical benefits [39].

Therefore, the purpose of this study was to evaluate the effect of aPDT as an adjunct to SRP, compared with SRP alone, on the clinical treatment of chronic periodontal patients. The following question was addressed: "In systemically healthy periodontitis patients, is the use of aPDT as an adjunct to SRP more effective than SRP alone in reducing probing pocket depth (PPD) and improving clinical attachment level (CAL)?"

Material and methods

This review followed the guidelines from PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) and the *Cochrane Handbook of Systematic Reviews of Interventions* and was registered at the International Prospective Register of Systematic Reviews (National Institute for Health Research PROSPERO) (http://www.crd.york.ac.uk/PROSPERO; registration number CRD42020150364).

Study design

This is a systematic review of randomized controlled trials (RCTs) which aims to evaluate the effects of aPDT as an adjunct to SRP compared with SRP alone in CAL gain and in the reduction of PPD of patients with periodontitis.

Eligibility criteria

Inclusion criteria

Randomized controlled trials (parallel or split-mouth) with at least 3-month follow-ups with chronic periodontitis patients that receive SRP alone and in association with aPDT were included. Only English-version studies were included with no time restriction.

Exclusion criteria

Trials that included patients with systemic disease (e.g., diabetes) and/or current pregnancy, patients that were submitted to systemic or local antimicrobial treatment in the last 6 months, periodontal treatment in the last 6 months, patients with aggressive periodontitis. Studies that used photobiomodulation and/or inadequate wavelength.

Intervention and comparison

Use of aPDT adjunctive to SRP (test group) compared with SRP alone (control group).

Outcome measures

The primary outcomes were PPD and CAL change, and the secondary outcomes were bleeding on probing (BOP) change, plaque index (PI) change, and bacterial reduction.

Information sources and search strategy

Search strategies for each of the following bibliographic databases were developed: MEDLINE (PubMed), Google Scholar, and LILACS. Keywords were combined with Boolean operators (OR, AND) and used to search the databases. The search included all articles published on or before July 1, 2020, across all databases with no time restrictions. Only English-version articles were selected. The search strategy was (periodontal OR periodontal treatment OR periodontitis OR periodontal disease) AND (photodynamic OR pdt OR photosensitizer). We selected "clinical trial" as the article type. To complement the electronic search, manual searches were done. The reference manager software was used to remove the duplicated references (EndNote, Thomson Reuters). Moreover, unpublished studies were searched at OpenGrey (www.opengrey.eu).

Study selection

The selection of studies was conducted in two phases, as follows: (1) assessment of titles and abstracts and (2) assessment of the full text. Two authors (M.G.M. and R.A.P.) independently reviewed the titles and abstracts, and disagreements were discussed and solved by consulting a third author (C.T.K.). Studies that fulfilled the inclusion criteria were submitted to validity assessment and data extraction.

Data collection process

The same investigators (M.G.M. and R.A.P.) collected the data from the selected articles and a third author (C.T.K.) was consulted in case of disagreements. Also, if needed, the papers' authors were contacted to elucidate doubts or in order to obtain missing data.

Using extraction forms, the following data were collected: year of publication, author(s), country of the study, participants' characteristics, periodontal disease definition, follow-up duration, design of the study (parallel or split-mouth), characteristics of the aPDT (photosensitizer, concentration, dark toxicity, irradiation, wavelength, radiant exposure, output power, power density, irradiation time), sample size, outcome measures, conclusions, financial support, and conflicts of interest.

Risk of bias in individual studies

Selected studies were evaluated according to the Cochrane Collaboration's Tool for Assessing Risk of Bias. Two assessors (M.G.M. and R.A.P.) independently performed the quality assessment of each included trial, with disagreements solved by a third reviewer (C.T.K.). Studies were classified as adequate (+), inadequate (−), or unclear (?) as regards the risk of bias in the following domains: randomization and allocation concealment (selection bias), completeness of follow-up period/incomplete outcome data (attrition bias), blinding of patients and personnel (performance bias) and examiners (detection bias), selective reporting (reporting bias), and other forms of bias. Analyzing these domains, each study was rated with an overall risk of bias: (1) low risk, (2) unclear risk of bias, or (3) high risk of bias.

Summary measures and synthesis of results

Random-effects meta-analyses were conducted for changes in CAL and PPD, with a statistical package (Review Manager software, version 5.3, The Nordic Cochrane Center, The Cochrane Collaboration, Copenhagen, Denmark). Meta-analyses were analyzed by subgroups according to the photosensitizers (phenothiazine chloride $\leq$ 300 μM; phenothiazine chloride $\geq$ 10 mM; indocyanine green) and according to the risk of bias (low risk of bias; unclear risk of bias; high risk of bias). Pooled outcomes were expressed as weighted mean differences (WMD). Statistical heterogeneity among trials was assessed with I^2.

Results

A total of 141 potentially relevant papers were identified. After reading titles and abstracts, 104 were excluded, leaving 37 articles. After complete reading of the full text, 15 papers were excluded. At the end of the process, 22 papers were included in the review. The flowchart is shown in Fig. 2.

Included studies

The characteristics of the included studies are shown in Table 1. Initially, 680 patients with chronic periodontitis were enrolled, and 643 (94.55%) completed the follow-up. One paper did not mention the number of patients [40]. The age of the included patients ranged from 18 to 75 years old, and most of them were female. Eleven studies used a split-mouth design [38–48], and the other 11 used parallel groups [23, 49–58].

The follow-up periods of the trials were 3 [23, 38, 40, 43–45, 48, 49, 52, 54, 55, 57], 6 [39, 42, 46, 47, 50, 51, 56], and 12 months [41, 53, 58]. Twenty-eight participants dropped out of the respective studies because of relocation, one participant became pregnant, seven patients reported to have taken antibiotics, and the other participants refused to complete the research [44, 46, 50, 56]. The studies of Alwaeli et al., Tabenski et al., and Husejnagic et al. did not report the reasons for dropout [41, 48, 58].

Methodological quality of the studies

Three studies were considered to have a low risk of bias [38, 46, 48], fifteen studies were considered to have an unclear risk of bias [23, 39, 41–45, 47, 50–52, 54, 55, 57, 58], and four studies were judged to have a high risk of bias [40, 49, 53, 56] (Fig. 3a, b).

In six studies, treatment was randomly assigned by coin toss [40, 42, 44, 48, 51, 55], nine studies used computer-generated random sequences [38, 39, 41, 43, 46, 47, 50, 52, 56], two studies used a randomization list/table [54, 58], and one study did the randomization by drawing lots [57]. Four publications did not report how the random sequence was generated [23, 45, 49, 53]. Fourteen studies reported that allocation concealment was made properly [38, 39, 41–44, 46–51, 56, 58], and eight studies did not report this information [23, 40, 45, 52–55, 57].

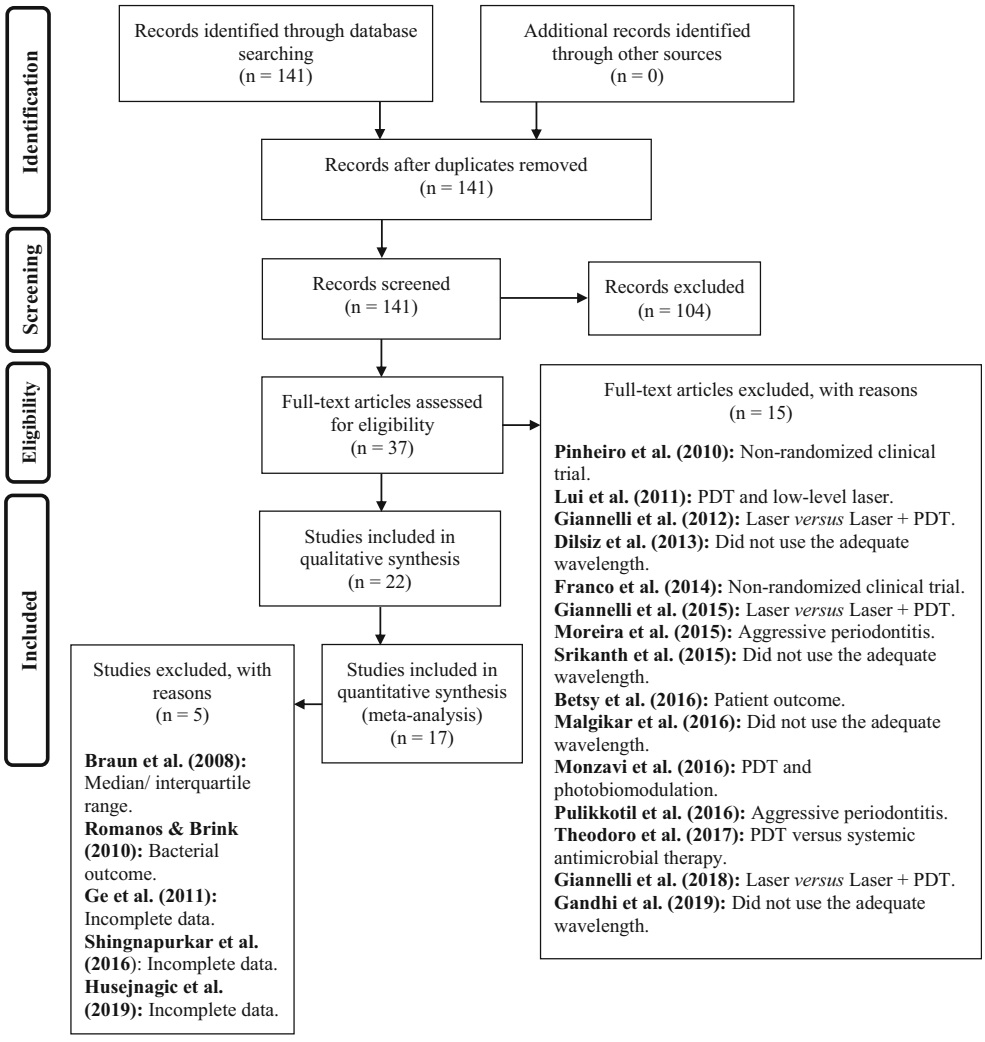

Fig. 2 Flowchart

Table 1 Characteristics of the studies

Study/country	Study design	Follow-up	Sample size (baseline)	Participants	Periodontitis definition and clinical examination	Source of funding
Alwaeli et al., 2015/Jordan	Split-mouth	12 months	*N* = 21 16 (5 male and 11 female) Age range 40.9 years (± 13.34 years)	Test group: *N* baseline = 21 *N* end of trial = 16 Control group: *N* baseline = 21 *N* end of trial = 16	At least 1 tooth with attachment loss of ≥ 4 mm in every quadrant	None
Andersen et al., 2007/USA	Parallel	3 months	*N* = 33 (11 male and 22 female) Age range 18–75 years (53 years)	Test group: *N* baseline = 14 *N* end of trial = 14 Control group 1: *N* baseline = 14 *N* end of trial = 14 Control group 2: *N* baseline = 5 *N* end of trial = 5	At least 4 or more sites with pocket depth of 6 mm or greater in at least 2 quadrants of the mouth, with bleeding on gentle probing	This research was supported by Ondine Biopharma Corporation
Balata et al., 2013/Brazil	Split-mouth	6 months	*N* = 22 (8 male and 14 female) Age range 31–62 years (43.18 years)	Test group: *N* baseline = 22 *N* end of trial = 22 Control group: *N* baseline = 22 *N* end of trial = 22	Presence of periodontal pockets with clinical attachment loss (CAL) ≥ 5 mm, bleeding on probing (BOP), and radiographic bone loss; minimum of 2 teeth with probing depth (PD) ≥ 7 mm and 2 other teeth with a PD ≥ 5 mm, all with BOP and located on opposite sides of the mouth	None
Bassir et al., 2013/Iran	Split-mouth	3 months	*N* = 16 (8 male and 8 female) Age range 40–63 years (50.3 ± 8.7 years)	Test group: *N* baseline = 16 *N* end of trial = 16 Control group: *N* baseline = 16 *N* end of trial = 16	Patients with clinical diagnosis of moderate to severe chronic periodontitis (Armitage 1999); presence of at least 2 teeth with a probing depth of 4–6 mm in each quadrant	This study was supported by the Laser Research Center in Dentistry (LRCD) of the Tehran University of Medical Sciences (No. 89-01-97-10245)
Betsy et al., 2014/India	Parallel	6 months	*N* = 88 (37 male and 51 female) Age range 39.6 years (± 8.7 years)	Test group: *N* baseline = 44 *N* end of trial = 40 Control group: *N* baseline = 44 *N* end of trial = 40	Probing pocket depths (PPD) between 4 and 6 mm at least in 2 different quadrants of the mouth	This study was supported by a grant from the Department of Science & Technology, Government of India
Braun et al., 2008/Germany	Split-mouth	3 months	*N* = 20 (9 male and 11 female) Age range 46.6 years (± 6.1 years)	Test group: *N* baseline = 20 *N* end of trial = 20 Control group: *N* baseline = 20 *N* end of trial = 20	At least 1 tooth with an attachment loss of > 3 mm in every quadrant	Helbo Photodynamic Systems provided the diode laser and photosensitizer
Christodoulides et al., 2008/Germany	Parallel	6 months	*N* = 24 (11 male and 13 female) Age range 36–56 years (45 ± 8.11 years)	Test group: *N* baseline = 12 *N* end of trial = 12 Control group: *N* baseline = 12 *N* end of trial = 12	Not reported	This study was partially supported by a grant from Helbo Photodynamic Systems, Grieskirchen, Austria

Table 1 (continued)

Study/country	Study design	Follow-up	Sample size (baseline)	Participants	Periodontitis definition and clinical examination	Source of funding
Ge et al., 2011/California	Parallel	3 months	*N* = 58 (30 male and 28 female) Age range 25–66 years (43 ± 10 years)	Test group 1: *N* baseline = 18 *N* end of trial = 18 Test group 2: *N* baseline = 20 *N* end of trial = 20 Control group: *N* baseline = 20 *N* end of trial = 20	With at least 4 sites of PDs of 6–9 mm in at least 2 quadrants of the mouth	This study was supported by the Loma Linda University School of Dentistry and the Ondine Biopharma Corporation
Harmouche et al., 2019/France	Split-mouth	6 months	*N* = 36 (14 male and 22 female) Age range 50.25 ± 5.98 years	Test group: *N* baseline = 36 *N* end of trial = 28 Control group: *N* baseline = 36 *N* end of trial = 28	Severe generalized chronic periodontitis ≥ 30% of sites with CAL > 5 mm and ≥ 5 sites with PPD ≥ 5 mm per quadrant	None
Hill et al., 2019/Germany	Split-mouth	6 months	*N* = 20 (3 male and 17 female) Average age 61.1	Test group: *N* baseline = 20 *N* end of trial = 20 Control group: *N* baseline = 20 *N* end of trial = 20	Presence of at least 1 single and 1 multi-rooted tooth with at least 4 mm probing depth in each quadrant	The work was supported by elexxion AG and by the Clinical Study Support Core (SZB) of University Hospital Bonn
Husejnagic et al., 2019/Austria	Split-mouth	3 months	*N* = 22 Age range 46.20 ± 6.96 years	Test group: *N* baseline = 22 *N* end of trial = 20 Control group: *N* baseline = 22 *N* end of trial = 20	Localized or generalized periodontitis of periodontal stage II, III, or IV with grade B or C, with probing depths above > 5 mm in at least 1 site in each quadrant, radiologically detectable alveolar bone loss in all quadrants	This study was supported by the Medical University of Vienna (EK 1860/2014)
Petelin et al., 2015/Slovenia	Parallel	12 months	*N* = 27 (15 male and 12 female) Age range 42–64 years	Test group: *N* baseline = 9 *N* end of trial = 9 Control group 1: *N* baseline = 9 *N* end of trial = 9 Control group 2: *N* baseline = 9 *N* end of trial = 9	The inclusion criteria were plaque index (PI) less than 20% and at least 4 teeth with increased PPD (≥ 4 mm) in each quadrant	The authors acknowledge the support of the Bredent–Medical, Germany, who provided the diode laser, photosensitizer, and fiber optic applicator used in this study
Polansky et al., 2009/Austria	Parallel	3 months	*N* = 58 (22 male and 36 female) Age range 25–67 years (48.7 years)	Test group: *N* baseline = 29 *N* end of trial = 29 Control group: *N* baseline = 29 *N* end of trial = 29	Moderate to severe as defined by the AAP	None
Pourabbas et al., 2014/Iran	Split-mouth	3 months	*N* = 24 (10 male and 14 female) Age range 18–70 years (46 ± 8 years)	Test group: *N* baseline = 24 *N* end of trial = 22 Control group: *N* baseline = 24 *N* end of trial = 22	≥ 3 mm attachment loss in about a minimum of 30% of the existing teeth and ≥ 1 site per quadrant with PD of ≥ 4 mm and BOP	None
Raj et al., 2016/India	Parallel	3 months	*N* = 20 (8 male and 12 female) Age range 35–50 years	Test group: *N* baseline = 10 *N* end of trial = 10 Control group:	Pocket depth ≥ 5 mm	None

Table 1 (continued)

Study/country	Study design	Follow-up	Sample size (baseline)	Participants	Periodontitis definition and clinical examination	Source of funding
				N baseline = 10 *N* end of trial = 10		
Romanos & Brink, 2010/USA	Split-mouth	3 months	*N* = 10 Age range 40–50 years	Test group: *N* baseline = 10 *N* end of trial = 10 Control group: *N* baseline = 10 *N* end of trial = 10	Pocket depth ≥ 5 mm	The authors would like to thank Dr. M. Yunker for his support in the preparation of this manuscript
Segarra-Vidal et al., 2017/Spain	Parallel	6 months	*N* = 40 (12 male and 28 female) Age range 33–74 years (55 ± 2 years)	Test group: *N* baseline = 20 *N* end of trial = 18 Control group: *N* baseline = 20 *N* end of trial = 19	Periodontal involvement of at least 30% and a clinical attachment loss of ≥ 3 mm (moderate 3–4 mm, advanced ≥ 5 mm)	This study was supported by a grant from SEPA (Madrid, Spain) and was funded by Periowave® (Ondine Biopharma Corp., Vancouver, British Columbia, Canada)
Sethi & Raut, 2019/India	Parallel	3 months	*N* = 30(14 male and 16 female) Age range 30–55 years (47.8 ± 5.1 years)	Test group: *N* baseline = 15 *N* end of trial = 15 Control group: *N* baseline = 15 *N* end of trial = 15	PPD > 5 mm and CAL > 4 mm	None
Shingnapurkar et al., 2016/India	Split-mouth	3 months	*N* = 60 sites Age range 25–55 years	Test group: *N* baseline = 30 sites *N* end of trial = 30 sites Control group: *N* baseline = 30 sites *N* end of trial = 30 sites	At least 4 teeth with probing depth ≥ 5 mm	None
Sigusch et al., 2010/Germany	Parallel	3 months	*N* = 24 (7 male and 17 female) Age range 32–58 years	Test group: *N* baseline = 12 *N* end of trial = 12 Control group: *N* baseline = 12 *N* end of trial = 12	Patients with LCP (localized chronic periodontitis) were characterized by < 30% of sites with PDs > 3.5 mm	This study was partially supported by Helbo Photodynamic Systems, Grieskirchen, Austria
Tabensky et al., 2017/Germany	Parallel	12 months	*N* = 54 (21 male and 24 female) Age range 48–63 years	Test group: *N* baseline = 18 *N* end of trial = 15 Control group: *N* baseline = 18 *N* end of trial = 15	Minimum of 4 teeth with PPD ≥ 6 mm, approximal plaque index (API) ≤ 25%, papillary bleeding index (PBI) ≤ 25%	The authors thank Nina-Kristin Hullmann and Vanessa Vogl for their contribution in the initial phase of the study. Helbo® Photodynamic Systems, Walldorf, Germany, supported this study in part
Theodoro et al., 2012/Brazil	Split-mouth	6 months	*N* = 33 (12 male and 21 female) Age range 35–55 years (43.12 ± 8.2 years)	Test group: *N* baseline = 33 *N* end of trial = 33 Control group: *N* baseline = 33 *N* end of trial = 33	At least 3 nonadjacent sites with BOP and a PD of 5 to 9 mm	Glaucia Helena G. Soares received a scholarship from São Paulo State Foundation for Research (FAPESP 2007/039001). The authors would like to thank Bruno Theodoro Luciano, graduate student at the Institute of International Relations, University of Brasilia, DF, Brazil, for the English translation and review

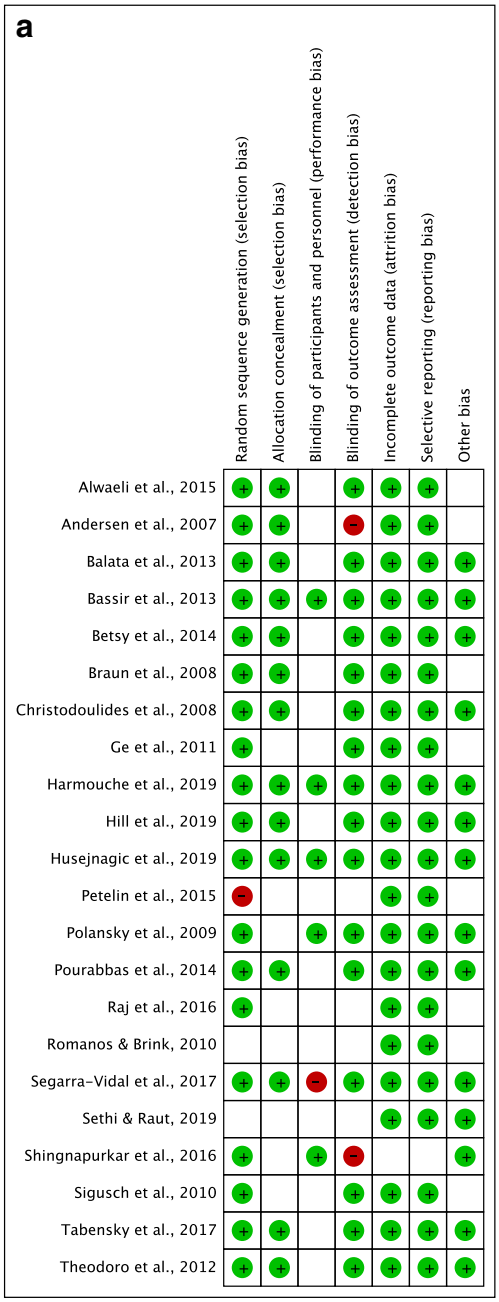

Fig. 3 Risk of bias. **a** Table. **b** Graph

Effects of interventions

Individual outcomes of studies

The individual outcomes of studies are presented in Table 2. One of the included trials did not use PPD and CAL as the primary outcomes [45]. Another paper did not use PPD gain as a clinical outcome [57]. Seven of the included studies showed that periodontal treatment in association with aPDT promotes a significant PPD reduction [23, 40, 41, 43, 49, 50, 57], and eight of them showed CAL gain [23, 40, 41, 43, 47, 49, 50, 55].

Six studies showed that the test group presented a significantly greater BOP change than the control group [23, 41, 43, 51–53]. Harmouche et al., Hill et al., and Husejnagic et al. did not report the statistical differences between groups for BOP changes [46–48]. There were no differences between groups for PI [23, 38–40, 46, 48, 50, 51, 56, 58].

Twelve studies were used as outcome bacterial reduction [23, 39, 45, 47, 48, 51, 53–58]. Three studies did not show statistical bacterial alterations between groups [51, 54, 58]. Petelin et al., Theodoro et al., and Hill et al. analyzed the proportion of *Aggregatibacter actinomycetemcomitans*, *Porphyromonas gingivalis*, *Prevotella intermedia*, *Tannerella forsythia*, and *Treponema denticola* [39, 47, 53]. The use of SRP and PDT reduced the proportion of *T. denticola and T. forsythia;* the proportion of all bacterial species; and the proportion of *P. gingivalis*, *P. intermedia*, and *T. denticola*, respectively, compared with SRP alone [39, 47, 53]. Romanos and Brink analyzed the same bacterial species and two others (*Peptostroptococcus micros* and *Fusobacterium nucleatum*). The test group promoted a statistical reduction of bacteria compared with the control group [45]. Raj et al. analyzed the proportion of *P. gingivalis*, *T. forsythia*, and *T. denticola* and showed a statistical bacterial reduction of all three in the test group [55]. In the studies of Segarra-Vidal et al. and Sigusch et al., the use of PDT promoted a significant reduction of *A. actinomycetemcomitans* and *F. nucleatum*, respectively [56, 57]. Husejnagic et al. investigated by PCR the concentration of *A. actinomycetemcomitans*, *P. gingivalis*, *T. forsythia*, *T. denticola*, *P. intermedia*, *P. micros*, *F. nucleatum*, *C. rectus*, *Eubacterium nodatum*, *Eikenella corrodens*, and *Capnocytophaga* species on the subgingival plaque. As result, test and control groups promoted a reduction in the pathogen concentration after treatment. The use of PDT promoted a slightly higher reduction of *P. gingivalis* and *T. denticola* [48]. Sethi and Raut showed an expressive reduction of bacterial colonies after PDT [23].

Pooled outcomes

The association between SRP and aPDT suggested a significant overall CAL gain (overall 0.29 mm, 95% CI 0.11–0.46 mm; heterogeneity—$I^2 = 77\%$, $p = 0.001$; phenothiazine chloride ≤ 300 μM 0.15 mm, 95% CI − 0.06–0.36 mm, heterogeneity—$I^2 = 71\%$, $p = 0.15$; phenothiazine chloride ≥ 10 mM 0.45 mm, 95% CI 0.06–0.84 mm, heterogeneity—$I^2 = 85\%$, $p = 0.03$; indocyanine green 0.69 mm, 95% CI 0.23–1.15 mm, heterogeneity—$I^2 = 0\%$, $p = 0.003$) (Fig. 4) and PPD reduction (overall 0.28 mm, 95% CI 0.10–0.46 mm, heterogeneity—$I^2 = 90\%$, $p = 0.002$; phenothiazine chloride ≤ 300 μM 0.09 mm, 95% CI − 0.10 to 0.28 mm, heterogeneity—$I^2 = 87\%$, $p = 0.37$; phenothiazine chloride ≥ 10 mM 0.47 mm, 95% CI − 0.09 to 1.04 mm, heterogeneity—$I^2 = 94\%$, $p =$

Table 2 Participants, interventions, outcomes, and results

Study	Interventions	Photosensitizer	Irradiation parameters	CAL (mm)	PPD (mm)	Bacterial outcome
Alwaeli et al., 2015	Test group: SRP + PDT Control group: SRP	Photosensitizer: phenothiazine chloride Concentration 1% Dark toxicity 1–3 min	Irradiation: diode laser Wavelength 660 nm Radiant exposure 357.1 J/cm^2 Output power 100 mW Power density 35 W/cm^2 Irradiation time 10 s	Test 1.48 ± 1.89* Control 0.13 ± 1.7	Test 1.51 ± 1.54* Control 0.6 ± 1.66	Not reported
Andersen et al., 2007	Test group: SRP + PDT Control group 1: SRP Control group 2: PDT	Photosensitizer: phenothiazine chloride Concentration 0.005% Dark toxicity 5 min	Irradiation: diode laser Wavelength 670 nm Radiant exposure 10–20 J/cm^2 Output power 150 mW Power density 166.7 mW/cm^2 Irradiation time 60 s	Test 0.86 ± 0.61* Control 1 0.36 ± 0.35 Control 2 0.14 ± 0.65	Test 1.11 ± 0.53* Control 1 0.74 ± 0.43 Control 2 0.67 ± 0.44	Not reported
Balata et al., 2013	Test group: SRP + PDT Control group: SRP	Photosensitizer: phenothiazine chloride Concentration 0.005% Dark toxicity 2 min	Irradiation: low-power laser—AsGaAl Wavelength 660 nm Radiant exposure 320 J/cm^2 Output power 100 mW Power density 3214.3 W/cm^2 Irradiation time 90 s	Test 2.08 ± 0.51 Control 2.14 ± 0.33	Test 2.28 ± 0.33 Control 2.32 ± 0.27	Not reported
Bassir et al., 2013	Test group: SRP + PDT Control group: SRP	Photosensitizer: phenothiazine chloride Concentration 0.01% Dark toxicity: -	Irradiation: light-emitting diode (LED) Wavelength 625–635 nm (628 nm) Radiant exposure 40 J/cm^2 Output power: - Power density 2000 mW/cm^2 Irradiation time 20 s	Test 1.39 ± 0.53 Control 1.3 ± 0.04	Test 1.3 ± 0.04 Control 1.38 ± 0.28	Not reported
Betsy et al., 2014	Test group: SRP + PDT Control group: SRP	Photosensitizer: phenothiazine chloride Concentration 1% Dark toxicity 3 min	Irradiation: diode laser Wavelength 655 nm Radiant exposure 3.6 J/cm^2 Output power 1 W Power density 60 mW/cm^2 Irradiation time 60 s	Test 2.5 ± 1.21* Control 1.5 ± 1.2	Test 2.7 ± 0.63* Control 1.5 ± 0.63	Not reported
Braun et al., 2008	Test group: SRP + PDT Control group: SRP	Photosensitizer: phenothiazine chloride Concentration 1% Dark toxicity 3 min	Irradiation: diode laser Wavelength 660 nm Radiant exposure 357.1 J/cm^2 Output power 100 mW Power density 35 W/cm^2 Irradiation time 10 s	Test − 0.67 mm, inter-quartile range 0.36, maximum − 1.89, minimum − 0.20* Control − 0.35 mm, inter-quartile range 0.21, maximum − 0.81, minimum − 0.11	Test: median 3.6 mm, inter-quartile range 0.6, maximum 5.3, minimum 3.2* Control: median 3.7 mm, inter-quartile range 0.6, maximum 6.0, minimum 3.4	Not reported
Christodoulides et al., 2008	Test group: SRP + PDT Control group: SRP	Photosensitizer: phenothiazine chloride Concentration 1% Dark toxicity: -	Irradiation: diode laser Wavelength 670 nm Radiant exposure 3.6 J/cm^2 Output power 75 mW Power density 60 mW/cm^2 Irradiation time 60 s	Test 0.7 ± 0.3 Control 0.5 ± 0.5	Test 0.9 ± 0.3 Control 0.7 ± 0.7	No statistically significant difference was observed between the 2 treatment groups at the baseline and post-treatment examinations
Ge et al., 2011	Test group: SRP + PDT (1 time) Test group: SRP + PDT (2 times) Control group: SRP	Photosensitizer: phenothiazine chloride Concentration 0.01% Dark toxicity: -	Irradiation: diode laser Wavelength 670 nm Radiant exposure 21 J/cm^2 Output power 140 mW Power density 0.35 W/cm^2 Irradiation time 60 s	Not reported	Not reported	Not reported
	Test group: SRP + PDT		Irradiation: LED	Test 0.85 ± 1.28	Test 1.13 ± 1.02	Not reported

Table 2 (continued)

Study	Interventions	Photosensitizer	Irradiation parameters	CAL (mm)	PPD (mm)	Bacterial outcome
Harmouche et al., 2019	Control group: SRP	Photosensitizer: phenothiazine chloride Concentration 0.01% Dark toxicity 1 min	Wavelength 625–635 nm (628 nm) Radiant exposure: - Output power: - Power density 2000 mW/cm^2 Irradiation time 10–30 s	Control 0.85 ± 1.26	Control 1.16 ± 1.03	
Hill et al., 2019	Test group: SRP + PDT Control group: SRP	Photosensitizer: indocyanine green Concentration 0.01% Dark toxicity: -	Irradiation: diode laser Wavelength 808 nm Radiant exposure 2829 J/cm^2 Output power 100 mW Power density: - Irradiation time 60 s	Test 2.31 ± 1.73* Control 1.33 ± 1.59	Test 2.2 ± 1.19 Control 1.38 ± 1.1	Test: reduction of Pi*, Td*, and Pg Control: reduction of Pg
Husejnagic et al., 2019	Test group: SRP + PDT Control group: SRP	Photosensitizer: phenothiazine chloride Concentration 0.01% Dark toxicity 1 min	Irradiation: LED Wavelength 635 nm Radiant exposure 14 J/cm^2 Output power 750 mW Power density: - Irradiation time 60 s	Not reported	Not reported	Test and control: reduction in the pathogen concentration Test: reduction in Pg and Td
Petelin et al., 2015	Test group: SRP with ultrasonic scaler + 3 episodes of aPDT Control group 1: SRP with Gracey curettes Control group 2: SRP with ultrasonic scaler	Photosensitizer: phenothiazine chloride Concentration 1% Dark toxicity 3 min	Irradiation: diode laser Wavelength 660 nm Radiant exposure 3.6 J/cm^2 Output power 75 mW Power density 60 mW/cm^2 Irradiation time 60 s	Test 0.5 ± 0.18 Control 1 0.7 ± 0.18 Control 2 0.6 ± 0.18	Test 0.5 ± 0.12 Control 1 0.5 ± 0.12 Control 2 0.6 ± 0.12	Test: reduced proportion of Aa, Pg, Pi, Tf, and Td Control 1: reduced proportion of Pg, Pi, Tf and Td Control 2: reduced proportion of Aa, Pg, and Pi
Polansky et al., 2009	Test group: SRP + PDT Control group: SRP	Photosensitizer: phenothiazine chloride Concentration 1% Dark toxicity: -	Irradiation: diode laser Wavelength 680 nm Radiant exposure 3.6 J/cm^2 Output power 75 mW Power density 60 mW/cm^2 Irradiation time 60 s	Test 1.35 ± 0.87 Control 1.35 ± 0.88	Test 1.24 ± 0.68 Control 1.03 ± 0.8	No significant inter-group difference at baseline or 90 days after treatment. Pg was signifi-cantly reduced in both groups. No significant reductions in Tf and Td were observed in either group
Pourabbas et al., 2014	Test group: SRP + PDT Control group: SRP	Photosensitizer: phenothiazine chloride Concentration 0.1% Dark toxicity: -	Irradiation: handy laser sprint Wavelength 638 nm Radiant exposure 8–10 J/cm^2 Output power 150 mW Power density 0.06 W/cm^2 Irradiation time 120 s	Test 1.47 ± 0.06 Control 1.35 ± 0.2	Test 1.34 ± 0.04 Control 1.27 ± 0.08	Not reported
Raj et al., 2016	Test group: SRP + PDT Control group: SRP	Photosensitizer: phenothiazine chloride Concentration: - Dark toxicity 1 min	Irradiation: light source (Lit 600) Wavelength 635 nm Radiant exposure: - Output power 0.5 W Power density: - Irradiation time 60 s	Test 1.0 ± 0.56 Control 0.2 ± 0.14	Test 1.7 ± 0.16* Control 0.9 ± 0.33	Td = Test 0.4 ± 0.06* Control 0.1 ± 0.03 Pg = Test 0.6 ± 0.00* Control 0.2 ± 0.17 Tf = Test 0.4 ± 0.09* Control 0.1 ± 0.06
Romanos & Brink, 2010	Test group: SRP + PDT Control group: SRP	Photosensitizer: phenothiazine chloride Concentration 1%	Irradiation: low-intensity laser Wavelength 670 nm Radiant exposure 79,577 J/cm^2	Not reported	Not reported	Test group: reduction of 91.37%*

Table 2 (continued)

Study	Interventions	Photosensitizer	Irradiation parameters	CAL (mm)	PPD (mm)	Bacterial outcome
		Dark toxicity 1 min	Output power 2 W Power density 3978 W/cm^2 Irradiation time 20 s			Control group: reduction of 54.22%
Segarra-Vidal et al., 2017	Test group: SRP + PDT Control group: SRP	Photosensitizer: phenothiazine chloride Concentration 0.005% Dark toxicity: -	Irradiation: diode laser Wavelength 670 nm Radiant exposure 10–20 J/cm^2 Output power 150 mW Power density 166.7 mW/cm^2 Irradiation time 60 s	Test 1.52 ± 1.09 Control 2.28 ± 1.01	Test 1.9 ± 0.81 Control 2.07 ± 0.69	Control group: reduction of Pg and Tf Test group: reduction of Aa*, Pg, and Tf
Sethi & Raut, 2019	Test group: SRP + PDT Control group: SRP	Photosensitizer: indocyanine green Concentration 0.5% Dark toxicity 1 min	Irradiation: diode laser Wavelength 810 nm Radiant exposure 5.4 J/cm^2 Output power 0.8 W Power density: - Irradiation time 60 s	Test 1.41 ± 0.68* Control 0.79 ± 0.75*	Test 1.86 ± 0.61* Control 0.7 ± 0.8	Test: reduction in bacterial colonies
Shingnapurkar et al., 2016	Test group: SRP + PDT Control group: SRP	Photosensitizer: indocyanine green Concentration 0.5% Dark toxicity: -	Irradiation: diode laser Wavelength 810 nm Radiant exposure 0.0125 J/cm^2 Output power 200 mW Power density: - Irradiation time 30 s	Test 2.53 ± 1.12* Control 1.23 ± 1.5	Test 2.9 ± 0.44* Control 1.6 ± 0.45	Not reported
Sigusch et al., 2010	Test group: SRP + PDT Control group: SRP	Photosensitizer: phenothiazine chloride Concentration 1% Dark toxicity 1 min	Irradiation: diode laser Wavelength 660 nm Radiant exposure 0.6 J/cm^2 Output power 75 mW Power density 60 mW/cm^2 Irradiation time 10 s	Test 0.95 ± 0.41* Control 0.2 ± 0.34	Not reported	Test group: reduction of Fn*
Tabensky et al., 2017	Test group: SRP + PDT Control group: SRP	Photosensitizer: phenothiazine chloride Concentration 1% Dark toxicity 3 min	Irradiation: diode laser Wavelength 670 nm Radiant exposure: - Output power: - Power density 75 mW/cm^2 Irradiation time 10 s	Test 2.13 ± 1.45 Control 1.4 ± 1.43	Test 2.6 ± 1.27 Control 1.94 ± 1.31	Total bacterial reduced in test and control groups*
Theodoro et al., 2012	Test group: SRP + PDT Control group: SRP	Photosensitizer: phenothiazine chloride Concentration 0.01% Dark toxicity 1 min	Irradiation: GaAlAs LLLT laser Wavelength 660 nm Radiant exposure 64.28 J/cm^2 Output power 30 mW Power density 0.4 W/cm^2 Irradiation time 150 s	Test 1.56 ± 1.32 Control 1.98 ± 1.04	Test 2.33 ± 0.86 Control 2.71 ± 0.62	Reduction of all periodontopathogens (Aa, Pg, Pi, Pn, and Tf) in the PDT group compared with that in the SRP group*

* indicates $p < 0.05$

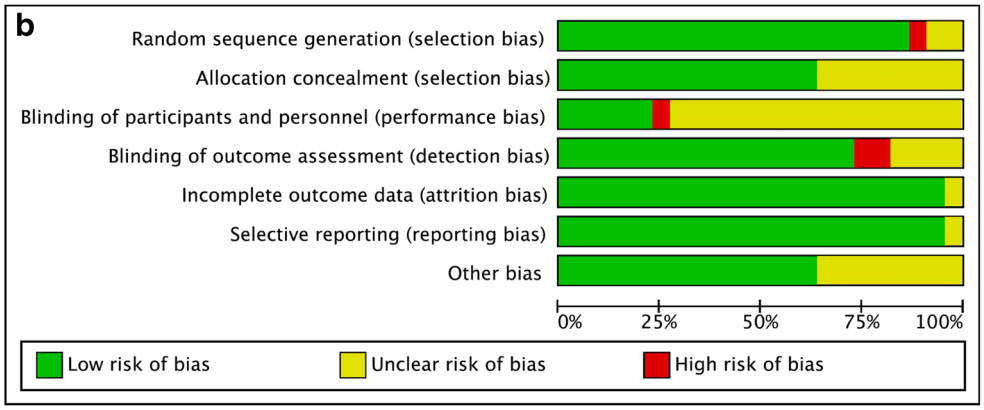

Fig. 4 Forest plot of random-effects meta-analysis evaluating CAL gain according to photosensitizer

0.10; indocyanine green 1.04 mm, 95% CI 0.63–1.46 mm, heterogeneity—I^2 = 0%, p < 0.00001) (Fig. 5).

Still, two more meta-analyses were conducted according to the risk of bias. The association between SRP and aPDT suggested a significant overall CAL gain (overall 0.29 mm, 95% CI 0.11–0.46 mm; heterogeneity—I^2 = 77%, p = 0.001; low risk of bias 0.08 mm, 95% CI − 0.16 to 0.32 mm, heterogeneity—I^2 = 0%, p = 0.53; unclear risk of bias 0.40 mm, 95% CI 0.16–0.64 mm, heterogeneity—I^2 = 80%, p = 0.001; high risk of bias 0.09 mm, 95% CI − 0.36–0.53 mm, heterogeneity—I^2 = 77%, p = 0.70) (Fig. 6) and PPD reduction (overall 0.28 mm, 95% CI 0.10–0.46 mm, heterogeneity—I^2 = 90%, p = 0.002; low risk of bias − 0.08 mm, 95% CI − 0.21 to 0.06 mm, heterogeneity—I^2 = 0%, p = 0.26; unclear risk of bias 0.46 mm, 95% CI 0.16–0.75 mm, heterogeneity—I^2 = 93%, p = 0.002; high risk of bias 0.03 mm, 95% CI − 0.29 to 0.34 mm, heterogeneity—I^2 = 68%, p = 0.87) (Fig. 7).

Meta-analysis for PI and BOP was not conducted.

Adverse effects

Six trials did not report information about the presence of complications [43, 45, 53–55, 57]. The other sixteen trials reported the absence of adverse effects after SRP and/or PDT [23, 38–42, 44, 46–52, 56, 58].

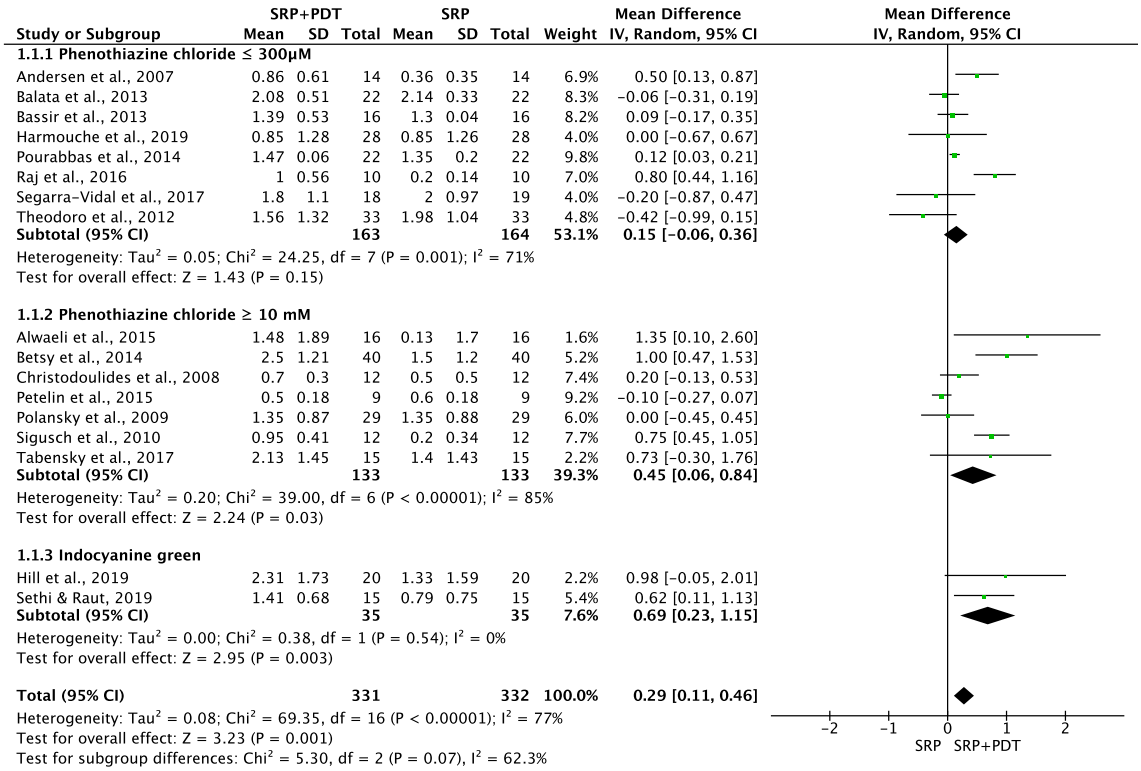

Fig. 5 Forest plot of random-effects meta-analysis evaluating PPD reduction according to photosensitizer

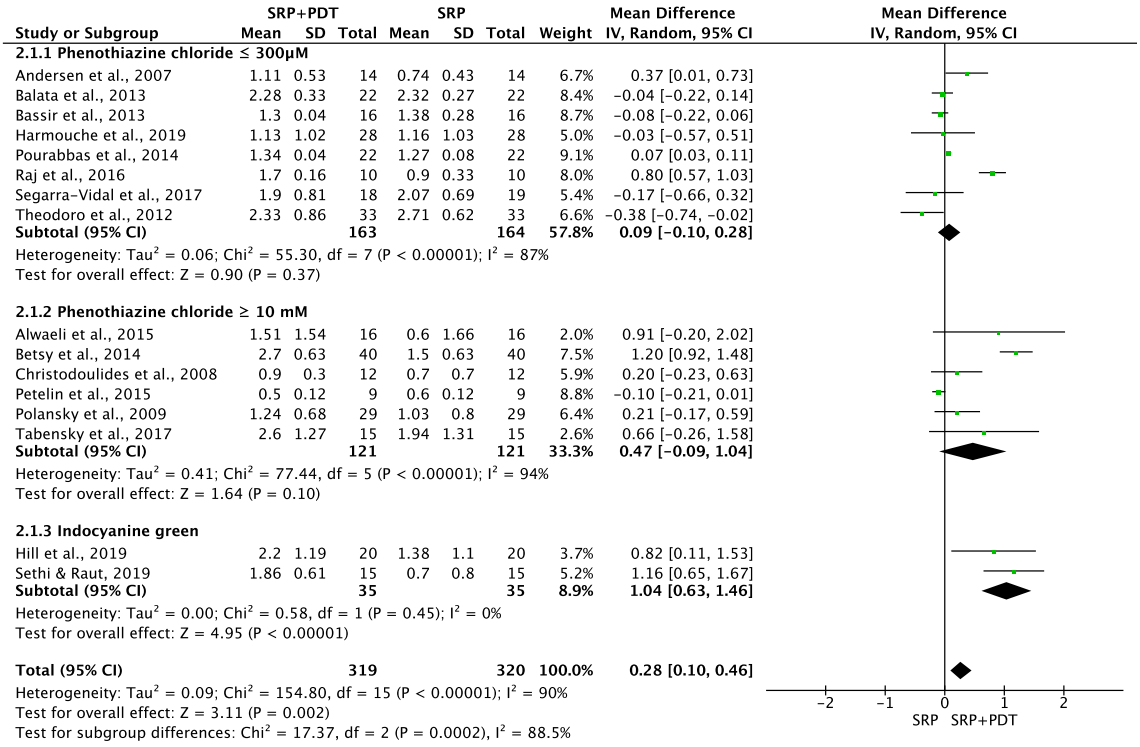

Fig. 6 Forest plot of random-effects meta-analysis evaluating CAL gain according to risk of bias

Discussion

The findings of this systematic review suggest that aPDT has a beneficial influence on clinical outcomes in SRP. Periodontal treatment performed with the adjunctive use of aPDT may result in higher CAL gain and PPD reduction than the ones performed alone. The use of aPDT was associated with approximately 0.3 mm and 0.3 mm more CAL gain and PPD

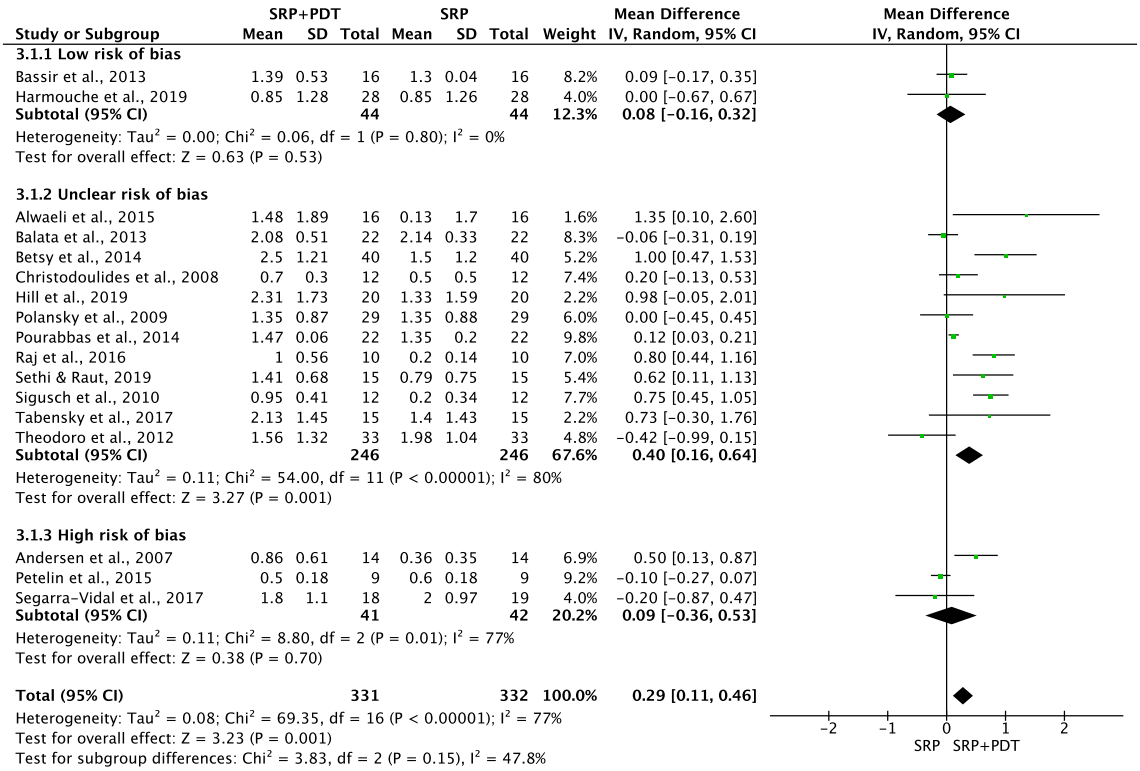

Fig. 7 Forest plot of random-effects meta-analysis evaluating PPD reduction according to risk of bias

reduction, respectively, than SRP alone. Although these values were considered statistically significant, the clinical relevance of these improvements must be discussed. The clinician should analyze if it is worth investing in aPDT for these clinical improvements.

A subgroup meta-analysis was made to compare different types and protocols of aPDT (studies that use phenothiazine chloride at concentrations of ≤ 300 μM versus phenothiazine chloride ≥ 10 mM versus studies that used indocyanine green). When CAL gain was analyzed, the use of indocyanine green promoted better results (phenothiazine chloride ≤ 300 μM 0.15 mm, 95% CI − 0.06 to 0.36 mm, $p = 0.15$; phenothiazine chloride ≥ 10 mM 0.45 mm, 95% CI 0.06–0.84 mm, $p = 0.03$; indocyanine green 0.69 mm, 95% CI 0.23–1.15 mm, $p = 0.003$). When PPD reduction was analyzed, the use of indocyanine green was also associated with better results (phenothiazine chloride ≤ 300 μM 0.09 mm, 95% CI − 0.10 to 0.28 mm, $p = 0.37$; phenothiazine chloride ≥ 10 mM 0.47 mm, 95% CI − 0.09 to 1.04 mm, $p = 0.10$; indocyanine green 1.04 mm, 95% CI 0.63–1.46 mm, $p < 0.00001$).

Indocyanine green is a molecule from the tricarbocyanine dye family, and it was developed by Kodak Research Laboratories in 1955 and approved by the US Food and Drug Administration in 1956 for medical diagnosis. ICG has been used as photosensitizer over the years, and more recently, it was proposed as a PS candidate for aPDT in periodontal tissue. It absorbs infra-red light and under high concentration presents J-aggregates packed in a head-to-tail manner. Phenothiazine chloride also aggregates in high concentrations and over 100 μM presents more dimmers than monomers in water solution [59, 60]. Dimerization of phenothiazinium dyes may lead to impaired photosensitizing efficacy, and a more effective photosensitizer or a better method or vehicle will be important to improve the antimicrobial effect and consequently improve clinical outcomes provide by this technique [61].

Among 12 studies that used bacterial reduction as an outcome [23, 39, 45, 47, 48, 51, 53–58], three of them did not observe a statistically significant difference between groups related to the bacterial parameters, and also to clinical outcomes (CAL and PPD) [51, 54, 58]. Interestingly, those three studies used a concentration of phenothiazine chloride greater than or equal to 10 mM. From the other 9 studies that observed statistically significant reduction of microorganisms, 3 of them used a concentration of phenothiazine chloride greater than or equal to 10 mM [45, 53, 57]. Only Sigusch et al. showed CAL gain; nevertheless, they did not report PPD [57]. From the studies that used a concentration of phenothiazine chloride less than or equal to 300 μM, only Raj et al. observed a difference in PPD between groups [55].

When the studies that used indocyanine green were analyzed, both of them showed statistically significant CAL gain compared with the control group [23, 47]. The study of Sethi and Raut also reported a difference in PPD between groups, with better values in the test group [23]. Although bacterial load reduction was observed in most of the studies of this systematic review, aPDT groups did not provide great improvement for the clinical outcomes in some studies. On the other hand, the results of this meta-analysis showed an additional benefit within the use of aPDT as an adjunct to SRP. Our results are partially in agreement with a previous meta-analysis [62], which presented inconclusive data about microbiological findings. Thus, additional clinical studies on indocyanine green–mediated aPDT would be welcome in the literature to complete antimicrobial and clinical outcomes information.

Another subgroup meta-analysis was made to compare the results according to the risk of bias (studies with a low risk of bias versus those with an unclear risk of bias versus those with a high risk of bias). When CAL gain and PPD reduction were analyzed, papers with an unclear risk of bias were associated with better results (CAL gain—low risk of bias 0.08 mm, 95% CI − 0.16 to 0.32 mm, $p = 0.53$; unclear risk of bias 0.40 mm, 95% CI 0.16–0.64 mm, $p = 0.001$; high risk of bias 0.09 mm, 95% CI − 0.37–0.53 mm, $p = 0.70$; PPD reduction—low risk of bias − 0.08 mm, 95% CI − 0.21–0.06 mm, $p = 0.26$; unclear risk of bias 0.46 mm, 95% CI 0.16–0.75 mm, $p = 0.002$; high risk of bias 0.03 mm, 95% CI − 0.29 to 0.34 mm, $p = 0.87$).

Just three of the selected papers have a low risk of bias [38, 46, 48]. This is an important fact to consider when interpreting the results of this review since bias can subvert the validity of the conclusions of clinical trials. Studies that present an unclear or high risk of bias tend to overestimate the effect of treatment and decrease the reliability of the trials' conclusions.

Most of the papers judged as having an unclear risk of bias failed to report the blinding of participants. The authors did not mention if patients know which treatment they received. However, as the systematic review did not use patient outcomes, this bias does not interfere in the interpretation of the meta-analysis. Still, another important problem associated with the risk of bias was the uncertainty or lack of blinding of the researcher responsible for data analysis. As the researcher knows the groups, there may be a tendency to find better results in the test group. This fact may have occurred in the study of Andersen et al. and Shingnapurkar et al.. Both reported that evaluators were not blinding, and they were found statistically significant results favorable to the test group [40, 49]. However, we did not include the last study in the meta-analysis because it did not report the number of patients. Another two papers that did not report the information about the blinding of research also demonstrated that SRP with PDT is associated with the best results [45, 55].

The information about allocation concealment is not present in most papers classified as having an unclear or high risk of bias. Allocation is made to organize the volunteers' sequence. As the studies did not report this information, the researchers may have influenced the choice of participants in the test group. This fact

may be associated with the best results found in the subgroup named "unclear risk of bias" of the meta-analysis.

Furthermore, the meta-analysis showed that the papers with an unclear risk of bias and a high risk of bias had the highest heterogeneity (low risk of bias: $I^2 = 0\%$; unclear risk of bias: $I^2 = 80\%$—CAL gain and 93%—PPD reduction; high risk of bias: $I^2 = 77\%$—CAL gain and 68%—PPD reduction). It was assumed that the main cause for the occurrence of heterogeneity is due to the different protocols of aPDT and different definitions of periodontal disease. Still, data of meta-analysis could be influenced by publishing bias. The published results may be systematically different from reality.

Studies with an unclear risk of bias and a high risk of bias should have their quality questioned. This fact can compromise the reliability of the results [63]. The greater the heterogeneity, the greater the question about the validity of the results. In our review, studies with a low risk of bias and low heterogeneity showed favorable results for basic periodontal treatment alone. This makes us question the effectiveness of using PDT adjunctive to basic periodontal treatment. Is the use of PDT really effective? It seems not.

The sample size can also change the effect of the results. Six studies with an unclear risk of bias [41, 43, 45, 52, 55, 57] and two studies with a high risk of bias [49, 53] did not report about sample size calculation. Inaccurate studies, generally performed with small sample sizes, may find positive or negative results (statistically significant or not) due to chance.

The majority of the studies presented a follow-up of 3 months, while the ideal would be a longer period of observation, around 12 months, to analyze the stability of the clinical results [41, 53, 58]. Nevertheless, this review showed more studies with a long-term follow-up than the previous systematic review [62] that included one study with a 12-month follow-up [64].

Another point that must be discussed is the difference between split-mouth and parallel design. Half of the studies used a split-mouth design [38–48], and the other half used parallel groups [23, 49–58]. In split-mouth study, test and control interventions are randomly allocated to different areas in the oral cavity. This design removed most of the variability of outcomes among patients. Since the subject is his own control, there is a potential increase in statistical power. [65]. When only studies with split-mouth were analyzed, there was no statistical difference between the test (SRP + PDT) and control groups (SRP), regardless of the risk of bias and the photosensitizer used ($p > 0.05$). Thus, we must question once again the real effectiveness of PDT.

Thirteen papers excluded smokers [23, 39–41, 43–45, 47, 50, 53, 55–57], one paper did not report this information [49], three papers included patients that smoked ≤ 10 cigarettes/day [38, 46, 58], and five papers included smokers [42, 48, 51, 52, 54]. Cigarettes are considered a risk factor for periodontal disease. The association between smoking and periodontal destruction is dose-dependent [66]. Worst results would be expected in the papers that included smokers. However, this association did not occur. It can be explained by the randomization, which includes the same number of smokers in each experimental group.

The reviewer's calibration and reproducibility are extremely important to analyze the results. Calibration is the degree of the results' consistency from the repetition of the procedure. Still, low reproducibility is associated with low validity of the study. It is recommended to perform these procedures to reduce the discrepancy of data [67]. Most of the selected papers did report reviewers' calibration and reliability [38, 39, 41–44, 46, 48, 50, 51, 53, 54, 56, 58], and eight papers did not report this information [23, 40, 45, 47, 49, 52, 55, 57]. As these last studies present a high or unclear risk of bias, we must question the results found.

The greatest difficulty in comparing aPDT studies is the lack of standardization of clinical protocols that include different light sources, wavelengths, and irradiation times and different photosensitizers and their concentrations. Due to the absence of a clinical protocol for aPDT in periodontics, there is a high heterogeneity between works that use phenothiazine photosensitizers (71 to 94%). This study limitation makes it difficult to accurately compare data and to interpret the real benefit of aPDT for those patients. In this sense, more studies with standard irradiation and photosensitizer protocols based on photochemical knowledge would improve data comparison. Well-controlled and randomized clinical trials would also improve data in this field.

Conclusion

While overall analysis indicates that aPDT partially improves periodontal treatment, many clinical protocols were described in the literature. A favorable effect of indocyanine green–mediated aPDT was observed, and high concentrations of phenothiazine chloride presented clinical improvement as well.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent Informed consent is not applicable in this study.

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