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Systematic Review

Adjunctive photodynamic therapy to non-surgical treatment of chronic periodontitis: a systematic review and meta-analysis

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Abstract

Aim: To investigate the efficacy of antimicrobial photodynamic therapy (aPDT) adjunctive to scaling root planing (SRP) in patients with chronic periodontitis.

Methods: A meta-analysis was conducted according to the PRISMA statement and Cochrane Collaboration recommendations. Two independent reviewers performed an extensive literature search and manual search on seven databases. Mean differences (MD) and 95% confidence intervals (CI) were calculated for clinical attachment level (CAL) gain and probing depth (PD) reduction. The I^2 test was used for inter-study heterogeneity. Publication bias was examined by Egger's regression test and the trim-and-fill method.

Results: Sensitivity analysis of 14 randomized clinical trials (RCTs) revealed differences in PD reduction (MD 0.19, 95% CI 0.07–0.31, $p = 0.002$) and CAL gain (MD 0.37, 95% CI 0.26–0.47, $p < 0.0001$) in favour of SRP + aPDT, with no evidence of heterogeneity. Subgroup analysis revealed the absence of heterogeneity in RCTs, with high risk of bias for PD reduction and CAL gain. No evidence of publication bias was detected.

Conclusions: The use of adjunctive aPDT to conventional SRP provides short-term benefits. The evidence to support its clinical medium/long-term efficacy is insufficient. Further high-quality RCTs are needed to investigate the influence of potential confounders on the efficacy of adjunctive aPDT.

Key words: chronic periodontitis; dental scaling; meta-analysis; photochemotherapy

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Conflict of interest and source of funding statement

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The main objective of periodontal treatment is the removal of supragingival and subgingival plaque biofilm from the root surface, to reduce or arrest the progression of periodontal disease by mechanical debridement (Cobb 1996, Greenstein 2000). Non-surgical treatment of chronic periodontitis (CP), which mainly consists of scaling and root planing (SRP), usually results in significant clinical improvement (Drisko 2001). However, SRP alone may fail to eliminate subgingival bacteria located in areas inaccessible to periodontal instruments, such as furcation sites,

concavities, inter-proximal areas and deep pockets (Bower 1979, Brayer et al. 1989). Therefore, adjunctive procedures to periodontal therapy, such as locally delivered (Matesanz-Pérez et al. 2013) or systemic antibiotics (Sgolastra et al. 2012a,b), have been evaluated. However, chemotherapy could be potentially accompanied by side effects or may lead to the development of bacterial resistance (Slots & Rams 1990, Feres et al. 2002).

Antimicrobial photodynamic therapy (aPDT) recently has been proposed as an adjunctive treatment strategy to SRP. The application of aPDT is based on the following principle. A photoactivatable agent (photosensitizer) that absorbs light is able to be taken up preferentially by bacteria. When the photosensitizer is exposed to light of an appropriate wavelength (such as that emitted by a low-power laser) in the presence of oxygen, it generates singlet oxygen and free radicals that are cytotoxic to microorganisms and their products (Dobson & Wilson 1992, Komerik et al. 2003). Many oral bacteria are susceptible to infrared laser in the presence of photosensitizers, such as toluidine blue O, methylene blue and malachite green. These findings suggest that aPDT could be potentially advantageous in periodontal therapy (Azarpazhooh et al. 2010), as well as in the treatment of peri-implantitis (Haas et al. 2000) and endodontic infections (Garcez et al. 2007). However, studies conducted on humans have reported contrasting results (Braun et al. 2008, Christodoulides et al. 2008, Chondros et al. 2009, Lulic et al. 2009), and systematic reviews (Atieh 2010, Azarpazhooh et al. 2010, Sgolastra et al. 2013) have not shown any adjunctive effect of aPDT. Nevertheless, this lack of effect in the meta-analyses might have been due to the paucity of available studies (Atieh 2010, Azarpazhooh et al. 2010) and potential methodological biases, such as the inclusion of only parallel-group studies (Sgolastra et al. 2013).

In light of these previous findings, the aim of this systematic review and meta-analysis was to evaluate any clinical adjunctive effect of aPDT to SRP when compared with SRP alone or in combination with placebo in the treatment of CP patients.

Materials and Methods

Protocol development

The protocol for this systematic review and meta-analysis was designed a priori, according to the Cochrane Collaboration (*Cochrane Handbook for Systematic Reviews of Interventions*, Version 5.1.0, http://www.cochrane-handbook.org/) and Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines (Moher et al. 2009).

Focused question

The following focused question was developed in accordance with the recognized Patient, Intervention, Comparison, and Outcome (PICO) format (Miller & Forrest 2001): "What is the clinical efficacy of aPDT as an adjunctive therapy to SRP, when compared with SRP alone or in combination with placebo aPDT, in terms of clinical attachment level (CAL) gain and probing depth (PD) reduction, for patients with CP?"

Eligibility criteria

A study was considered eligible for inclusion in this systematic review if it met the following criteria: (1) randomized controlled clinical trial (RCT), (2) conducted on adult (age >18 years) human subjects affected by CP irrespective of its severity, (3) compared SRP + aPDT *versus* SRP ± Placebo aPDT and (4) reported CAL gain and probing depth (PD) reduction. An article was excluded if it included patients with systemic disease or who were assumed to be taking antibiotics or medications or undergoing treatments that are known to affect periodontal tissue or periodontal treatment; if patients had a follow-up time <3 months; if the study reported additional treatments (e.g. local or systemic antimicrobial therapy, adjunctive laser therapy, periodontal surgical therapy) other than SRP + aPDT; or if it was a duplicate or ancillary study. To be as inclusive as possible, no restrictions were applied with regard to the year of publication of the studies or to language.

Information sources and search

The following databases were searched from their earliest records through August 22, 2012: MEDLINE, Cochrane Controlled Clinical Trial Register, Cochrane Database of Systematic Reviews, CINAHL, Science Direct, ISI Web of Knowledge and SCOPUS. The following search algorithm was used to explore the databases, using Boolean operators and an asterisk symbol (*) as truncation: ((("Periodontitis"[Mesh] OR "Chronic Periodontitis"[Mesh] OR "Periodontal Diseases"[Mesh] OR "Periodontal Pocket"[Mesh] OR "Periodontal Attachment Loss"[Mesh] OR "Tooth Mobility"[Mesh] OR periodontitis OR periodontal disease* OR periodontal pocket* OR attachment loss OR alveolar bone loss OR pocket depth OR clinical attachment level) AND (therapy OR treatment OR intervention)) OR (periodontal non surgical treatment OR periodontal non surgical therapy OR scaling root planing OR dental scaling OR periodontal treatment OR periodontal therapy OR calculus remov* OR calculus debridement OR dental debridement OR periodontal debridement OR "Dental Scaling"[Mesh] OR "Root Planing"[Mesh] OR "Dental Prophylaxis"[Mesh])) AND ("Photochemotherapy"[Mesh] OR photodynam* therapy OR photodynam* treatment OR photochem* therapy OR photodynam* OR phototherapy OR photochem* treatment). In the CINAHL, SCOPUS and Science Direct databases, the MeSH terms were not used.

In addition, a manual search was performed of issues of the last 15 years of the following journals: *Journal of Clinical Periodontology*, *International Journal of Periodontics and Restorative Dentistry*, *Journal of Periodontology*, *Journal of Dental Research*, *Journal of Periodontal Research*, *Periodontology 2000*, *Journal of Dentistry*, *Journal of the American Dental Association*, *Journal of Clinical Dentistry*, *Lasers in Medical Science*, *Lasers in Surgery and Medicine*, *Clinical Oral Investigations*, *Photomedicine and Laser Surgery*, *Photodiagnosis and Photodynamic Therapy*, and

Journal of Photochemistry and Photobiology B.

The references of all selected full-text articles and related reviews were checked for potentially relevant additional studies. The corresponding authors were contacted to find unpublished material, obtain missing data or clarify paramount methodological issues.

Study selection and data collection

To minimize the potential for reviewer bias, two blinded reviewers (F.S. and M.S.) independently screened all of the titles and abstracts retrieved by electronic and hand searches. Inter-reviewer reliability in the study selection process was determined by the Cohen κ test, assuming an acceptable threshold value of 0.61 (Landis & Koch 1977a, b). Discrepancies with regard to the inclusion or exclusion of studies were resolved by discussion between the reviewers who selected the studies (F.S. and M.S.). Data of the included articles regarding patient demographic characteristics, presence of smokers, laser settings and reported outcomes were extracted by two independent reviewers (A.P. and A.M.) with a specific extraction form. A separate *ad hoc* extraction sheet that focused on the study quality was used by two independent reviewers (F.S. and R.G.).

Outcome measures

Primary outcome measures of interest were CAL gain and PD reduction. The CAL gain and PD reduction were defined as the difference between the CAL and PD levels, respectively, measured at baseline and at the end of follow-up. Secondary outcomes of interest were changes in the following parameters: reduction of bleeding on probing (BoP) index, increase of gingival recession (REC). Changes in REC increase and BoP indexes were defined as the difference between the baseline and end of follow-up measurements.

Risk of bias in individual studies

Two blinded reviewers (F.S. and R.G.) independently performed the quality assessment of the methodology of all included studies, according to the revised recommendation of the CONSORT statement (Moher et al. 2001). The level of agreement between reviewers was calculated as described above. Quality assessment was performed in two phases. During the first phase, quality assessment was based on the published full-text articles; in the second phase, all studies were reconsidered according to the additional information provided by the corresponding authors. After determining the scores at the conclusion of the second phase of quality assessment, an overall estimation of plausible risk of bias (low, moderate or high) was performed for each selected study. Low risk of bias was estimated when all of the criteria were met, moderate risk was estimated when one or more criteria were partly met, and high risk of bias was estimated when one or more criteria were not met (*Cochrane Handbook for Systematic Reviews of Interventions*, Version 5.1.0, http://www.cochrane-handbook.org/).

Summary measures and synthesis of the results

The CAL gain and PD reduction were analysed with the generic inverse variance statistical method on a patient basis. Mean differences (MDs), 95% confidence intervals (CIs) and standard errors (SEs) were taken from all studies to combine data from parallel and split-mouth studies (Lesaffre et al. 2009). If the standard deviation (SD) of the MD was not available and could not be calculated from the raw data reported in the study, then variance imputation methods were used to estimate the appropriate variance values. The intra-patient correlation coefficient (r = Pearson correlation) was used to calculate the SE for the remaining split-mouth studies.

If a study provided medians and interquartile ranges instead of means and SDs, then the means and SDs were imputed as described by Hozo et al. (Hozo et al. 2005). The overall estimate effect was considered significant for $p < 0.05$. Meta-analysis was performed with the statistical software package RevMan [Review Manager (Computer program). Version 5.1. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2011].

Risk of bias across studies

Intra-study heterogeneity was assessed with the χ^2-based Q-statistic method, and inter-study heterogeneity was evaluated with the I^2 statistic. A significant heterogeneity was indicated by $p < 0.1$ because of the moderate insensitivity of the Q-statistic (Lau et al. 1997). The value of I^2 ranged 0–100, with larger values ($\geq 75\%$) suggesting high heterogeneity (Higgins & Thompson 2002). Due to expected inter-study heterogeneity, a random effect model (Der Simonian & Laird model) was used.

Additional analyses

The presence of publication bias was investigated for each outcome of interest using two methods. Visual detection was used to analyse the funnel plots (Sterne & Egger 2001), and quantitative analysis was performed by the regression asymmetry test (Egger et al. 1997) and the trim-and-fill method (Duval & Tweedie 2000). Quantitative analysis was undertaken only on meta-analyses including more than 10 studies, due to the low power of the tests. Publication bias analysis was performed with Stata 10.0 (Stata Corp. LP., College Station, TX, USA). For cases in which significant heterogeneity was identified ($p < 0.1$ for the Q-statistic; Lau et al. 1997) or I^2 was $\geq 75\%$ (Higgins & Thompson 2002), Galbraith radial plots were used to detect the studies that were outliers (i.e. non-homogeneous with the results of other included RCTs; Chambrone et al. 2011), using the NCSS 8 statistical software (Number Cruncher Statistical System, NCSS, Kaysville, UT, USA). A subgroup analysis was performed according to the level of risk of bias and to different times of follow-up.

Results

Study selection

The electronic search identified 438 articles without overlap in the screened databases. The hand search did not provide any additional studies (Appendix S1). Of the 438 collected articles, 45 articles were considered

relevant. After full-text examination, 31 studies were excluded for the following reasons: 20 articles were not human RCTs, four did not focus on aPDT, two did not include patients with CP, two used additional therapy other than SRP + aPDT, two were duplicate studies and one included patients with systemic disease (Appendix S2). Therefore, 14 articles were included in the systematic review.

Study characteristics

The characteristics of the included studies are shown in Table 1.

Design of the studies

The included studies were RCTs published between 2007 and 2012. Of these, four were split-mouth two-arm (Braun et al. 2008, Al-Zahrani & Austah 2011, Berakdar et al. 2012, Campos et al. 2013), three were split-mouth three-arm (Cappuyns et al. 2012, Dilsiz et al. 2012, Theodoro et al. 2012), two were parallel three-arm (Andersen et al. 2007, Ge et al. 2011) and five were parallel two-arm studies (Christodoulides et al. 2008, Chondros et al. 2009, Lulic et al. 2009, Polansky et al. 2009, Sigusch et al. 2010).

Sample size

Quantitative analysis was performed on 360 patients. The number of patients included in the studies ranged from 10 to 58.

Antimicrobial photodynamic therapy

Most of the included studies performed a single session of aPDT (Christodoulides et al. 2008, Chondros et al. 2009, Polansky et al. 2009, Sigusch et al. 2010, Al-Zahrani & Austah 2011, Berakdar et al. 2012, Campos et al. 2013, Dilsiz et al. 2012, Theodoro et al. 2012). One study (Ge et al. 2011) included one session of aPDT in one arm and two session of aPDT in another arm. Another study (Lulic et al. 2009) performed multiple applications of aPDT. The number of aPDT sessions was not reported in three studies (Andersen et al. 2007, Braun et al. 2008, Cappuyns et al. 2012).

Risk of bias within studies

After the corresponding authors of the articles were contacted, analysis of the methodological quality of the included RCTs revealed that seven studies (Braun et al. 2008, Chondros et al. 2009, Lulic et al. 2009, Ge et al. 2011, Campos et al. 2013, Cappuyns et al. 2012, Theodoro et al. 2012) were at low risk of bias. The remaining studies (Andersen et al. 2007, Christodoulides et al. 2008, Polansky et al. 2009, Sigusch et al. 2010, Al-Zahrani & Austah 2011, Berakdar et al. 2012, Dilsiz et al. 2012) were at high risk of bias (inter-reviewer agreement, $\kappa = 1$). The most frequently unsatisfied methodological criteria were the absence of a sample size calculation (Criteria A; $n = 5$), absence of reported methods of randomization (Criteria B), absence of the specified reason for dropouts (Criteria D) and absence of masking (Criteria F). The results of the CONSORT-based quality analysis are illustrated in Table 2.

Synthesis of the results

For CAL gain, the intra-patient correlation coefficient could only be calculated from the complete raw data provided by one study (Dilsiz et al. 2012). For PD reduction, this parameter was calculated from the complete raw data reported by one study (Dilsiz et al. 2012) and from the *p*-value reported by another study (Berakdar et al. 2012). The intra-patient correlation coefficient was 0.43 for CAL gain and ranged from 0.41 to 0.45 for PD reduction. An *r*-value of 0.43 was used to estimate the SE of CAL gain for the other split-mouth studies.

Only primary outcomes could be pooled into the meta-analysis. The secondary outcomes showed a wide heterogeneity in terms of the different type of indices used, which prevented their quantitative analysis. One study (Sigusch et al. 2010) was included in the systematic review but not in the meta-analysis, because the data provided in the study were not sufficient to convert the median and interquartile ranges into mean and SD, and the authors did not agree to provide additional data.

Outcome: PD reduction

The meta-analysis failed to show a significant PD reduction between SRP + aPDT and SRP (MD 0.12, 95% CI −0.08 to 0.33, $p = 0.24$, Fig. 1a). However, a significant PD reduction was observed in the subgroup of parallel studies (MD 0.23, 95% CI 0.07–0.40, $p = 0.006$, Fig. 1a) in favour of SRP + aPDT. No significant difference was found in the split-mouth studies subgroup (MD 0.05, 95% CI −0.30 to 0.40, $p = 0.78$, Fig. 1a).

Outcome: CAL gain

The results of the pooled analysis indicated that a high and significant CAL gain was present in favour of SRP + aPDT (MD 0.27 95% CI 0.12–0.42, $p = 0.005$, Fig. 1b). A larger amount of CAL gain was observed in the parallel studies subgroup, in favour of SRP + aPDT (MD 0.32, 95% CI 0.17–0.48, $p < 0.0001$, Fig. 1b), whereas no significant differences were detected in the split-mouth studies subgroup (MD 0.15, 95% CI −0.21 to 0.50, $p = 0.43$, Fig. 1b).

Risk of bias across studies

Intra- and inter-study heterogeneities appeared relevant for PD reduction ($\chi^2 = 50.44$, $p < 0.00001$, $I^2 = 72\%$, Fig. 1a). For CAL gain, significant but moderate heterogeneity was found ($\chi^2 = 19.06$, $p = 0.09$, $I^2 = 37\%$, Fig. 1b).

Additional analyses

Sensitivity analysis

Significant heterogeneity was found for both PD reduction and CAL gain. Galbraith radial plots (Appendix S3.1) indicated that, in PD reduction, three studies (Berakdar et al. 2012, Campos et al. 2013, Theodoro et al. 2012) were outliers. When these studies were excluded, no evidence of heterogeneity was detected for PD reduction ($\chi^2 = 5.41$, $p = 0.86$, $I^2 = 0\%$, Fig. 2a); this result became significant in favour of SRP + aPDT (MD 0.19, 95% CI 0.07–0.31, $p = 0.002$, Fig. 2a). For CAL gain, one study (Theodoro et al. 2012) was identified as outlier (Appendix S3.2): after removing this study, no evidence of heterogeneity was detected ($\chi^2 = 9.02$, $p = 0.53$, $I^2 = 0\%$, Fig. 2b), and this result showed higher and significant gain in favour of SRP + aPDT (MD 0.37, 95% CI 0.26–0.47, $p < 0.0001$, Fig. 2b).

Table 1. Characteristics of included studies

Study Type Region	Clinical parameters	Male/Female Age (years)	Microbiological technique Microorganisms	Treatment arms	Photosensitizer Laser	Smoking SM/NSM	Laser parameters	Findings
Al-Zahrani & Austah (2011) Split-mouth Saudi Arabia	CAL, BOP, PD, PI, REC	17/0 41.6 ± 9.6	Not analysed	Test: SRP + aPDT Control: SRP	Methylene blue (Periowave, Ondine Biopharma, Vancouver, Canada) Diode laser	Only smokers included 17/0	Wavelength 670 nm	Significant differences in favour of SRP + aPDT in CAL gain and PD reduction. No significant differences in REC and BOP changes
Andersen et al. (2007) Parallel England	CAL, BOP, PD	11/22 53 (18–75)	Not analysed	Test 1: aPDT Test 2: SRP + aPDT Control: SRP	Methylene blue (Periowave) Diode laser (Periowave)	Unclear	Wavelength 670 nm Energy density 10–20 J/cm^2 Maximum power 150 mW Application time 60 s/site	Significant differences in favour of SRP + aPDT in CAL gain and PD reduction were observed
Berakdar et al. (2012) Split-mouth Germany	CAL, BOP, PD, PI, GI, REC	12/10 59.3 ± 11.7	Not analysed	Test: SRP + aPDT Control: SRP	Methylene blue 0.005% Diode laser (Periowave)	Excluded	Wavelength 670 nm Maximum power 150 mW Application time 60 s	A significant CAL gain but not PD reduction in favour of SRP + aPDT was observed
Braun et al. (2008) Split-mouth Germany	CAL, BOP, PD, REC	9/11 46.6 ± 6.1	Not analysed	Test: SRP + aPDT Control: SRP	Phenothiazine chloride (HELBO Blue Photosensitizer, HELBO Photodynamic Sys., Grieskirchen, Austria) Diode laser (Helbo Photodynamic Sys., Walldorf, Germany)	Excluded	Wavelength 660 nm Power output 100 mW Application time 10 s/site	Significant differences in favour of SRP + aPDT in CAL gain and PD reduction. No significant differences in REC changes
Campos et al. (2013) Split-mouth Brazil	CAL, BOP, PD, REC	5/8 (48.15 ± 7.53)	Not analysed	Test: SRP + aPDT Control: SRP	Methylene blue 10 mg/ml Diode laser (Thera Lase–DMC, São Paulo, SP, Brazil)	Excluded	Wavelength 660 nm Power output 60 mW Energy density 129 J/cm^2 Application time 60 s/site	Higher and significant CAL gain, PD reduction and reduction in BOP were observed; no differences in REC changes were detected
Cappuyns et al. (2012) Split-mouth Switzerland	PD, BOP, REC, PI, GI	21/8 52 (36–74)	Direct hybridization A.a., P.g., T.f., T.d.	Test 1: SRP + aPDT Test 2: SRP + DL Control: SRP	Phenothiazine chloride (HELBO Blue Photosensitizer) Diode laser (HelboPhotodynamic Sys.)	Included 12/17	Wavelength 660 nm Power output 40 mW Application time 60 s/site	No significant difference in any clinical or microbiological investigated parameter

Table 1. (Continued)

Study Type Region	Clinical parameters	Male/Female Age (years)	Microbiological technique Microorganisms	Treatment arms	Photosensitizer Laser	Smoking SM/NSM	Laser parameters	Findings
Chondros et al. (2009) Parallel the Netherlands	CAL, PD, REC, BOP	10/14 Test (50.6 ± 9.2) Control (48.3 ± 7.9)	PCR technique P.g., T.f., T.d., P.i., P.n., F.n., P.m., C.r., E.n., E.c., C.s.	Test: SRP + aPDT Control: SRP	Phenothiazine chloride (HELBO Blue Photosensitizer) Diode laser (HELBO minilaser 2075 F)	Included 7/17	Wavelength 670 nm Output power density 75 mW/cm^2 Application time 60 s/tooth	A significant reduction in BOP in favour of SRP + aPDT was found. No other significant difference in clinical parameters was detected. A significant reduction in the levels of T.d., E.c. and C.s. was found in favour of SRP + aPDT
Christodoulides et al. (2008) Parallel the Netherlands	CAL, PD, REC	11/13 45 ± 8.11	PCR technique P.g., T.f., T.d., P.i., P.n., F.n., P.m., C.r., E.n., E.c., C.s.	Test: SRP + aPDT Control: SRP	Phenothiazine chloride (HELBO Blue Photosensitizer) Diode laser (HELBO TheraLite Laser)	Included 3/21	Wavelength 670 nm Output power 75 mW Application time 60 s/tooth	No significant difference in any clinical or microbiological investigated parameter
Dilsiz et al. (2012) Split-mouth Turkey	CAL, PD, BOP, PI, GI	10/14 40.7 ± 7.3	Not analysed	Test 1: SRP + aPDT Test 2: SRP + KTPL Control: SRP	Methylene blue 1% (Onur Kimya Ltd., Istanbul, Turkey) Diode laser (Doctor Smile diode, Lambda Scientifica S.r.l., Vicenza, Italy)	Excluded	Wavelength 808 nm Output power 100 mW Application time 60 s/site Dose 6 J Fibre tip diameter 300 μm	No significant difference in investigated parameter
Ge et al. (2011) Parallel China	CAL, PD, BOP	30/28 43 ± 10	Not analysed	Test 1: SRP + aPDT (a) Test 2: SRP + aPDT (b) Control: SRP	Methylene blue 0.01% Diode laser (Periowave)	Included 9/49	Wavelength 670 nm Output power 140 mW Dose 6 J Energy density 21 J/cm^2 Application time 60 s/site	No significant differences in any investigated parameter
Lulic et al. (2009) Parallel Switzerland	CAL, BOP, PD, PI	7/3 54 (40–74)	Not analysed	Test: SRP + aPDT Control: SRP + placebo aPDT	Phenothiazine chloride (HELBO Blue Photosensitizer) Diode laser (HELBO minilaser 2075 F)	Included 2/8	Wavelength 670 nm Output power density 75 mW/cm^2 Application time 60 s/site	Higher and significant CAL gain and PD reduction were detected. No significant difference in BOP changes was observed

Table 1. (Continued)

Study Type Region	Clinical parameters	Male/Female Age (years)	Microbiological technique Microorganisms	Treatment arms	Photosensitizer Laser	Smoking SM/NSM	Laser parameters	Findings
Polansky et al. (2009) Parallel Austria	CAL, BOP, PD	22/36 48.7 (25–67)	PCR technique P.g., T.f., T.d.	Test: SRP + aPDT Control: SRP	Phenothiazine chloride (HELBO Blue Photosensitizer) Diode laser (HELBO minilaser 2075 F)	Included 7/51	Wavelength 680 nm Output power 75 mW Application time 60 s/site	No significant difference in any clinical parameter. Higher and significant reduction in P.g. levels in favour of SRP + aPDT
Sigusch et al. (2010) Parallel Germany	CAL, PD, BOP, REC, PI	7/17 range 32–58	PCR technique F.n., A.a., P.g., T.f., T.d.	Test: SRP + aPDT Control: SRP	Phenothiazine chloride (HELBO Blue Photosensitizer) Diode laser (HELBO TheraLite Laser)	Excluded	Wavelength 660 nm Power density 60 mW/cm^2 Application time 10 s/site	Significant differences in favour of SRP + aPDT in CAL gain, PD reduction and reduction in BOP were observed. Significant differences in F.n. levels in favour of SRP + aPDT
Theodoro et al. (2012) Split-mouth Brazil	CAL, PD, BOP, REC, VPI, BGI	12/21 43.12 ± 8.2	PCR technique A.a., P.g., P.i., T.f., P.n.	Test 1: SRP + aPDT (a) Test 2 1: SRP + placebo aPDT (b) Control 2: SRP	Phenothiazine 100 μg/ml (Sigma Chemical Co., St Louis, MO, USA) Diode laser (BioWave GaAlAs LLLT laser; Kondortech Equipment,São Carlos, SP, Brazil)	Excluded	Wavelength 660 nm Power output 30 mW Spot size 0.07 cm^2 Power intensity 0.4 W/cm^2 Energy density 64.28 J/cm^2 Application time 150 s/site	No significant difference in any clinical parameter. Significant differences in all investigated microbiological parameters in favour of SRP + aPDT if compared to SRP alone. Significant differences in P.i and T.f. levels, in favour of SRP + placebo aPDT, when compared to SRP + aPDT

SM, smokers; NSM, non-smokers; DL, diode laser; KTPL, potassium-titanyl-phosphate laser; CAL, clinical attachment level; BOP, bleeding on probing; PD, pocket depth; PI, plaque index; REC, gingival recession; VPI, visual plaque index; BGI, bleeding gingival index; PCR, polymerase chain reaction; SRP, scaling root planing; aPDT, antimicrobial photodynamic therapy; pt., patients; *A.a.*, *Aggregatibacter actinomycetemcomitans*; *C.r.*, *Campylobacter rectus*; *C.s.*, *Capnocytophaga spp.*; *E.c.*, *Eikenella corrodens*; *E.n.*, *Eubacterium nodatum*; *F.n.*, *Fusobacterium nucleatum*; *P.g.*, *Porphyromonas gingivalis*; *P.i.*, *Prevotella intermedia*; *P.m.*, *Parvimonas micra*; *T.d.*, *Treponema denticola*; *T.f.*, *Tannerella forsythia*.

Table 2. Quality assessment of selected studies prior to and after contact (parentheses) with corresponding authors

Study	A (0–2)	B (0–2)	C (0–1)	D (0–1)	E (0–2)	F (0–2)	G (0–2)	Estimated risk of bias
Al-Zahrani & Austah (2011)	0	2	1	0	2	2	2	High
Andersen et al. (2007)	0 (0)	2 (2)	1 (1)	1 (1)	2 (2)	0 (0)	1 (1)	High (High)
Berakdar et al. (2012)	0	2	1	1	2	2	2	High
Braun et al. (2008)	0 (2)	2 (2)	1 (1)	0 (1)	2 (2)	2 (2)	2 (2)	High (Low)
Campos et al. (2013)	2 (2)	2 (2)	1 (1)	1 (1)	2 (2)	2 (2)	2 (2)	Low (Low)
Cappuyns et al. (2012)	2 (2)	2 (2)	1 (1)	1 (1)	2 (2)	2 (2)	2 (2)	Low (Low)
Chondros et al. (2009)	2 (2)	2 (2)	1 (1)	1 (1)	2 (2)	2 (2)	2 (2)	Low (Low)
Christodoulides et al. (2008)	2 (2)	0 (0)	1 (1)	1 (1)	2 (2)	2 (2)	2 (2)	High (High)
Dilsiz et al. (2012)	0	2	1	1	2	2	2	High
Ge et al. (2011)	0 (2)	2 (2)	1 (1)	1 (1)	2 (2)	2 (2)	2 (2)	Moderate (Low)
Lulic et al. (2009)	2 (2)	2 (2)	1 (1)	1 (1)	2 (2)	2 (2)	2 (2)	Low (Low)
Polansky et al. (2009)	2 (2)	2 (2)	1 (1)	1 (1)	2 (2)	0 (0)	2 (2)	High (High)
Sigusch et al. (2010)	0	2	1	0	2	2	2	High
Theodoro et al. (2012)	2 (2)	2 (2)	1 (1)	1 (1)	2 (2)	2 (2)	2 (2)	Low (Low)

Letters refer to categories of quality assessment: A, Sample size calculation, estimating the minimum number of participants required to detect a significant difference among compared groups (0 = did not exist/not mentioned/not clear, 1 = was reported, but not confirmed, 2 = reported and confirmed); B, Randomization and allocation concealment methods 0 = clearly inadequate, 1 = possibly adequate, 2 = clearly adequate); C, Clear definition of inclusion and/or exclusion criteria (0 = no, 1 = yes); D, Completeness of follow-up (specified reasons for withdrawals and dropouts in each study group) (0 = no/not mentioned/not clear, 1 = yes/no withdrawals or dropouts occurred); E, Experimental and control groups comparable at study baseline for important prognostic factors(0 = no, 1 = unclear/possibly not comparable for one or more important prognostic factors, 2 = clearly adequate; F, Presence of masking (0 = no, 1 = unclear/not complete, 2 = yes); G, Appropriate statistical analysis (0 = no, 1 = unclear/possibly not the best method applied, 2 = yes).

Subgroup analysis

When analysing PD reduction at 3 months, a significant difference was detected in favour of SRP + aPDT (MD 0.21, 95% CI 0.06–0.35, $p = 0.005$, Appendix S4.1). The split-mouth studies subgroup did not reveal a significant difference between SRP and SRP + aPDT (MD 0.17, 95% CI −0.13 to 0.548, $p = 0.27$, Appendix S4.1) and showed high and significant intra- and inter-study heterogeneity results ($\chi^2 = 12.92$, $p = 0.01$, $I^2 = 69\%$, Appendix S4.1). The parallel studies subgroup did not reveal evidence of heterogeneity ($\chi^2 = 6.93$, $p = 0.33$, $I^2 = 13\%$, Appendix S4.1). A high and significant CAL gain in the SRP + aPDT group was observed at 3 months (MD 0.25, 95% CI 0.11–0.39, $p = 0.0004$, Appendix S4.2). At 6 months, no significant differences were observed in PD reduction (MD −0.01, 95% CI −0.36 to 0.33, $p = 0.94$, Appendix S4.3) and there was high heterogeneity ($\chi^2 = 45.29$, $p < 0.00001$, $I^2 = 85\%$, Appendix S4.2). These outcomes were similar in parallel and split-mouth studies. CAL gain was not significant at 6 months (MD 0.11, 95% CI −0.20 to 0.42, $p = 0.49$, Appendix S4.4).

With regard to CAL gain, studies with low risk of bias showed significant CAL gain in favour of SRP + aPDT (MD 0.27, 95% CI 0.04 –0.49, $p = 0.02$, Appendix S4.5). Studies with low risk of bias failed to show significant differences in PD reduction (MD 0.00, 95% CI −0.34 to 0.35, $p = 0.98$, Appendix 4.6), but high and significant heterogeneity was detected ($\chi^2 = 36.95$, $p < 0.0001$, $I^2 = 78\%$, Appendix S4.6). Conversely, studies with high risk of bias reported significant PD reduction for adjunctive aPDT (MD 0.29, 95% CI 0.15–0.43, $p = 0.0001$, Appendix S4.7) without heterogeneity ($\chi^2 = 3.42$, $p < 0.0001$, $I^2 = 0\%$, Appendix S4.7). Studies with high risk of bias showed a significant gain in CAL (MD 0.24, 95% CI 0.05–0.43, $p = 0.01$, Appendix S4.8 respectively).

With regard to the time of application of photosensitizer, studies that reported a mean time of 10s showed a non-significant PD reduction (MD 0.15, 95% CI −0.04 to 0.34, $p = 0.013$, Appendix S4.9), with non-significant heterogeneity ($\chi^2 = 1$, $p = 0.61$, $I^2 = 0\%$, Appendix S4.9); those with an application time of 60 s per site showed a significant reduction in PD (MD 0.25, 95% CI 0.06–0.43, $p = 0.009$, Appendix 4.6) and no evidence of heterogeneity ($\chi^2 = 8.39$, $p = 0.3$, $I^2 = 17\%$, Appendix S4.9). For CAL gain, studies with an application of 10 s or 60 s per site showed significant difference in favour of SRP + aPDT (MD 0.36, 95% CI 0.20 –0.52, $p < 0.0001$, and MD 0.35, 95% CI 0.17–0.53, $p = 0.0001$, respectively, Appendix S4.10) with no evidence of heterogeneity ($\chi^2 = 2.31$, $p = 0.32$, $I^2 = 13\%$, and $\chi^2 = 6.5$, $p = 0.37$, $I^2 = 8\%$, respectively, Appendix S4.10).

Publication bias

An inspection of the funnel plot for overall PD reduction (Appendix S5.1) suggested a slight asymmetry. This finding was confirmed by the trim-and-fill analysis, which showed that five studies were missing (Appendix S5.2). The trim-and-fill analysis indicated a consistent difference between the original (MD 0.12, 95% CI −0.08 to 0.33, Table 3) and adjusted MD (MD −0.06, 95% CI −0.27 to 0.15). However, the Egger regression asymmetry test showed that this difference was not significant. For overall CAL gain, no evidence of publication bias was detected by visual inspection or quantitative analysis (Table 3).

Discussion

Summary of evidence

In general, the results of this systematic review indicated that the adjunctive use of aPDT to SRP could provide

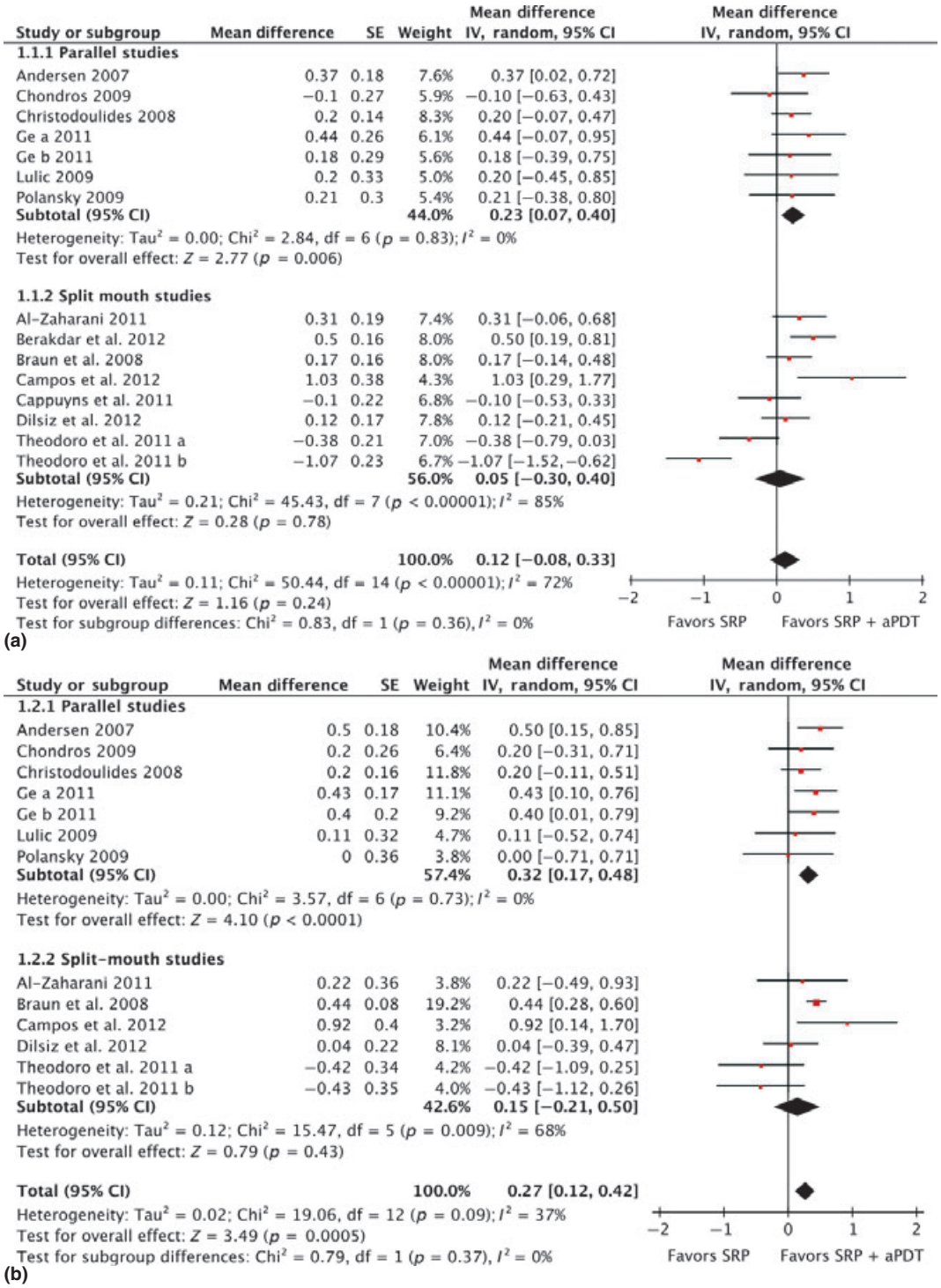

Fig. 1. Forest plots of (a) overall PD reduction and (b) overall CAL gain.

additional benefits, when compared with SRP alone, in terms of PD reduction and CAL gain. Although the initial analysis indicated contradictory results (Fig. 1a,b) with significant heterogeneity, after the identified outlier studies were removed, the results were homogenous ($I^2 = 0\%$) and indicated a significant positive effect (PD reduction: MD 0.19, 95% CI 0.07–0.31, $p = 0.002$, Fig. 2a; CAL gain MD 0.37, 95% CI 0.26–0.47, $p < 0.0001$, Fig. 2b). However, these clinical improvements, although statistically significant, appeared to be of little clinical relevance. Furthermore, they were observed only at the 3-month follow-up time-point (Appendix S4.1, S4.2), whereas no significant differences were observed at 6 months (Appendix S4.3, S4.4). However, this finding could be related to the small number of included studies that reported a follow-up time of 6 months.

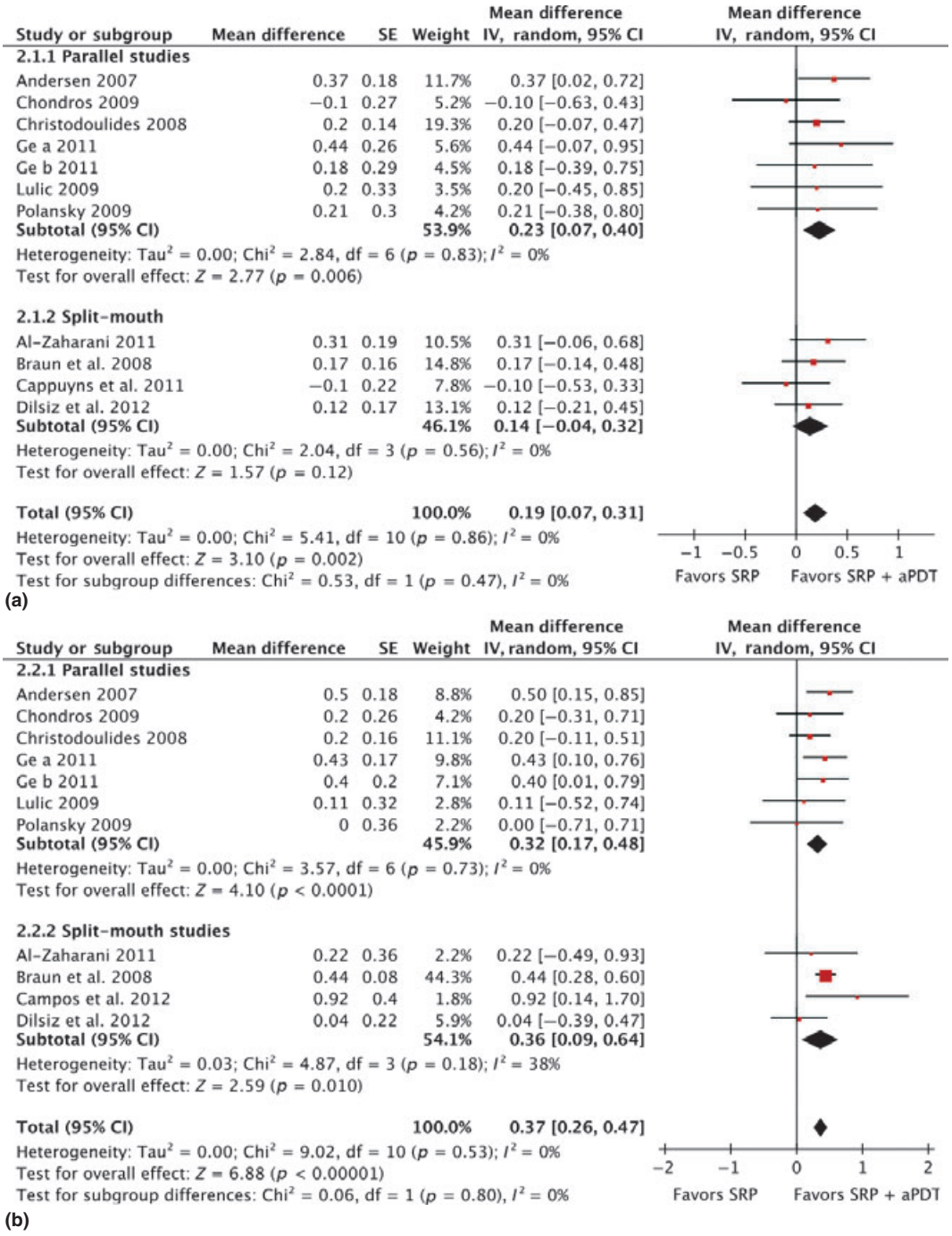

Fig. 2. Forest plots without outlier studies for (a) PD reduction and (b) CAL gain.

Subgroup analysis revealed that low risk of bias studies showed significant differences in CAL gain (Appendix S4.5) but not for PD reduction (Appendix S4.6), with significant heterogeneity. High risk of bias studies showed significant differences in favour of SRP + aPDT for both PD reduction and CAL gain, with no evidence of intra- and inter-study heterogeneities (Appendix S4.7, S4.8). However, after outliers were removed, both the low and high risk of bias groups showed significant differences for PD reduction and CAL gain, with no evidence of heterogeneity. Therefore, the quality of the studies did not seem to influence the results of the meta-analysis. Interestingly, subgroup analysis revealed that studies adopting a time of application of 60 s showed an higher and significant PD reduction and CAL gain; unfortunately, no subgroup analysis could be performed to assess the influence of the concentration of photosensitizers on clinical parameters, due to the very low number of studies that reported this information: however, it should be noted that

Table 3. Quantitative analysis for publication bias assessments

	Original meta-analysis		Trim-and-Fill analysis		
Outcome	MD (95% CI)	*p*	MD (95% CI)	Studies trimmed/ Total studies	Egger regression *p*
CAL gain	0.27 (0.12 to 0.42)	0.0005	0.26 (0.11 to 0.41)	0/13	0.05
PD reduction	0.12 (−0.08 to 0.33)	0.24	−0.06 (−0.27 to 0.15)	5/19	0.80

one study (Theodoro et al. 2012), that reported the worst clinical results, used a very low concentration of photosensitizer (0.0001%) and an high time of application (150 s/site). Nevertheless, it is difficult to state whether such differences could influence clinical outcomes, since no comparative data are available to define the most effective concentration and time of application of photosensitizer, as well as optimal laser settings.

To highlight the possible presence of a carry-across effect (Hujoel & De Rouen 1992), we reported each analysis by separating the parallel from split-mouth studies. Interestingly, after adjusting for outlier studies, we did not observe an influence of the type of design on the results of the meta-analysis. Nevertheless, all of the studies that were identified as outliers (Berakdar et al. 2012, Campos et al. 2013, Theodoro et al. 2012) were split-mouth studies.

Agreement and disagreement with previous systematic review and studies

The results of this study are partially consistent with those of a previous meta-analysis (Atieh 2010), which revealed significant CAL gain when aPDT was used but did not show significant PD reduction. However, that previous meta-analysis had important methodological issues, such as a low number of included studies and high heterogeneity among studies, which may not be conducive to achieving reliable and unbiased results. A meta-analysis by Azarpazhooh et al. (2010) showed no significant effects of SRP + aPDT; however, that study had several limitations, such as the inclusion of different types of periodontitis and a low number of studies that were of low quality, which made the results unreliable. The present results are in agreement with a previous meta-analysis (Sgolastra et al. 2013) that found a positive but modest effect of adjunctive aPDT. However, that systematic review did not include split-mouth studies and was performed on a small number of studies; thus, the results were potentially biased (Lesaffre et al. 2009).

Quality of evidence

The CONSORT-based quality analysis revealed that seven studies (Braun et al. 2008, Chondros et al. 2009, Lulic et al. 2009, Ge et al. 2011, Campos et al. 2013, Cappuyns et al. 2012, Theodoro et al. 2012) were at low risk of bias, whereas the remaining seven (Andersen et al. 2007, Christodoulides et al. 2008, Polansky et al. 2009, Sigusch et al. 2010, Al-Zahrani & Austah 2011, Berakdar et al. 2012, Dilsiz et al. 2012) were at high risk of bias. The most frequently unsatisfied criterion was the calculation of sample size (Criterion A), which could have contributed to the low statistical power of the studies with high risk of bias (Table 2).

The present meta-analysis included rigorous inclusion/exclusion criteria and used a wide search strategy with no language restrictions. An analysis of publication bias was also performed. Although the inspection of the funnel plot for PD reduction (Appendix S5.1) revealed the presence of asymmetry, and the trim-and-fill analysis indicated that five studies were missing in the meta-analysis, the Egger regression test revealed that these differences were not significant. Therefore, we may assume that the possibility of publication bias can be excluded.

Implications for research

Future RCTs focused on the clinical medium/long-term efficacy of adjunctive aPDT are needed. Such studies should adopt high methodological quality, possibly CONSORT-based (Pihlstrom et al. 2012), and should have a parallel rather than split-mouth design. The effect of adjunctive aPDT on main periodontal pathogens has been poorly evaluated and should be further considered. Future studies should also address the role of potential confounders, such as the effects of smoking and laser settings.

Implications for clinical practice

An evidence-based assessment of current literature suggested that the adjunctive use of aPDT could provide additional short-term benefits to SRP; however, these beneficial effects seemed to be modest and not stable over the time. Therefore, until the remaining issues are clarified, no clinical recommendation can be given.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Appendix S1. (online supplemental material). Abstracts retrieved by electronic, manual and reference searching.

Appendix S2. Studies excluded and reason for exclusion.

Appendix S3. (online supplemental material). Galbraith radial plot for CAL gain and PD reduction.
Appendix S4. (online supplemental material). Forest plots of subgroup analysis for PD reduction and CAL gain.
Appendix S5. (online supplemental material). Funnel plots for PD reduction.

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Clinical Relevance

Scientific rationale for the study: Studies conducted on humans reported contrasting results when analysing the clinical efficacy of antimicrobial photodynamic treatment (aPDT) as an adjunctive therapy to non-surgical periodontal treatment. Therefore, there was a need to systematically assess the scientific literature on that topic.
Principal findings: Evidence is available to support the short-term use of aPDT, while there is not enough evidence to support the medium-term use of adjunctive aPDT.
Practical implications: Adjunctive aPDT could provide short-term improvement in clinical parameters, albeit to a clinically not significant degree. However, medium-term clinical and microbiological improvements should be addressed in future randomized clinical trials.