

## Review

# Clinical efficacy of single and multiple applications of antimicrobial photodynamic therapy in periodontal maintenance: A systematic review and network meta-analysis



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## ABSTRACT

**Background:** At present the clinical efficacy of single (S) versus multiple (M) applications of antimicrobial photodynamic therapy (aPDT) is controversially discussed.

**Aim:** To systematically evaluate the clinical efficacy of adjunctive S and M applications of aPDT to subgingival debridement (SD) in the treatment of residual periodontal pockets.

**Methods:** An electronic search was carried out for randomized controlled clinical trials (RCTs) reporting on SD with the adjunctive use of S- or M-aPDT applications.

**Results:** Statistically significantly higher improvement in bleeding on probing (BOP) and probing depth (PD) reduction was found for SD + S-aPDT versus SD, with Mean difference (MD) = -16.8 (95% CI: -30.7 to -2.91;  $p = 0.02$ ) and 0.4, (95% CI: 0.02 to 0.78,  $p = 0.04$ ), respectively.

Regarding BOP, there was also a statistically significant difference when SD + M-aPDT was compared with SD alone, with a MD of -5.13 (95% CI: -7.20 to -3.07;  $p < 0.00001$ ).

For all parameters, SD + S-aPDT demonstrated the best treatment ranking of probability results, followed by SD + M-aPDT and SD alone.

**Conclusions:** Within their limits, the present data indicate that in periodontal patients enrolled in maintenance: a) single and multiple adjunctive applications of aPDT following SD resulted in statistically significant BOP reduction compared to SD alone, and b) repeated applications of aPDT did not seem to result in superior outcomes compared to single applications.

## 1. Introduction

Periodontitis is the most common chronic inflammatory non-communicable disease in humans [1]. It is clinically manifested through gingival bleeding, formation of periodontal pockets, and radiographic bone loss [2]. Untreated or inadequately treated periodontitis may ultimately lead to tooth loss [1].

A thorough subgingival debridement (SD) is the basis for treating periodontal disease and remains the gold standard for initial therapy during both nonsurgical and surgical treatment [3]. Nevertheless, this method has several limitations. In particular, bacterial biofilm cannot be efficiently eliminated from deep pockets, intrabony defects, or furcation areas. It is also dependent on the operators' manual skills and various

patient-related factors (e.g., patients' smoking status and systemic diseases) [4]. Several studies have shown that adjunctive aids to SD (e.g., local antibiotics, antiseptics, lasers) may substantially improve the clinical outcomes following nonsurgical periodontal treatment [4–7].

Upon completing active periodontal therapy, a successfully treated stable periodontitis patient should exhibit  $\leq 4$  mm of PD and  $< 10\%$  BOP [8]. Nevertheless, periodontal pockets, which are defined as “residual,” often remain after nonsurgical treatment [9]. It is well established that a residual PD of 5 mm represents a risk factor for further tooth loss [9,10]. Therefore, to maintain periodontal tissue stability after initial treatment, treated periodontitis patients should remain on maintenance and be closely monitored [11].

Considering the various treatment modalities during supportive

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periodontal therapy (SPT), the existing literature is controversial. Specifically, a recent systematic review evaluating SPT alone versus SPT with adjunctive interventions concluded that adjunctive aids (e.g., local antibiotics, photodynamic therapy) may not provide additional clinical benefits compared with mechanical debridement alone [12]. On the contrary, another systematic review found significantly higher improvements in PD and CAL values following the adjunctive use of aPDT compared with SRP alone [13].

The principle of aPDT is based on the combination of 3 compounds: a per se non-toxic molecule, the so-called photosensitizer (PS), light of a spectral range appropriate for excitation of the PS (typically from the visible to near-infrared spectrum), and molecular oxygen [14]. The conversion of energy during photoactivation process produces highly reactive singlet oxygen or other reactive oxygen species (e.g., hydroxyl radicals, superoxide anions and hydrogen peroxide) that exert the oxidative burst killing bacteria by oxidative processes depending on the singlet oxygen quantum yield of the given PS (type I vs type II process). Clinically used PS such as Methylene Blue mainly act according to type I process, thus mainly generating hydroxyl radicals, superoxide anions and hydrogen peroxide. [15].

Numerous studies have demonstrated that aPDT can be an effective adjunct in managing untreated periodontitis [14,16–19]. However, evidence of its effectiveness as an adjunct in periodontal maintenance is scarce. Therefore, the aim of the current systematic review was to evaluate the clinical efficacy of a single or multiple applications of aPDT when used adjunctively to SD, as compared with SD alone, in treating periodontal patients enrolled in regular SPT.

## 2. Materials and Methods

This systematic review reporting adhered to the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) statement [20]. The protocol for this systematic review was registered in the INPLASY database under the number INPLASY202110022.

### 2.1. Focus question

The following focus question was developed according to the population, intervention, comparison, outcome, and study design (PICOS): “In periodontal patients enrolled in maintenance, do multiple applications of aPDT adjunctive to SD additionally enhance the clinical outcomes as compared to single applications?”

**Population (P):** Systemically healthy patients, older than 18 years, included in regular SPT.

**Intervention (I):** SD + aPDT (S or M).

**Comparison (C):** SD + S-aPDT vs. SD + M-aPDT vs. SD alone.

**Outcome (O):** The primary outcome variable was BOP reduction; the secondary outcome variables included PD reduction and CAL gain.

**Study design (S):** Randomized controlled clinical trials (RCTs) with parallel or split-mouth designs with a minimum of 3 months of follow-up.

### 2.2. Information sources

The electronic databases MEDLINE (PubMed), EMBASE, and the Cochrane Central Register of Controlled Trials (CENTRAL) were searched for eligible clinical trials published before March 31, 2021. The search was limited to human studies and those in the English language.

### 2.3. Unpublished data and manual search

A database of unpublished studies (OpenGray [<http://www.opengrey.eu/>]) was searched. In addition, all of the included full-text studies' references were screened to find additional relevant publications. Furthermore, a manual search of the following scientific journals was performed: Journal of Periodontology, Journal of Periodontal Research,

Journal of Clinical Periodontology, International Journal of Periodontics and Restorative Dentistry, Periodontology 2000, *Journal of Photochemistry and Photobiology*, *Photomedicine and Laser Surgery*, *Lasers in Surgery and Medicine*, *Lasers in Medical Science*, and *Photodiagnosis and Photodynamic Therapy*.

### 2.3. Search

The keywords used to search the selected electronic databases included specific Medical Subject Headings (MeSH) terms and free-text words: (“periodontitis” [MeSH term] OR “chronic periodontitis” OR “periodontal disease” OR “recurrent periodontitis” OR “refractory periodontitis” OR “residual pockets” [MeSH term] AND “treatment” [MeSH term] OR “periodontal maintenance care” [MeSH term] OR “periodontal supportive care” [MeSH term] OR “therapy” [MeSH term] OR “scaling and root planing” [MeSH term] OR “subgingival debridement” [MeSH term] AND “photodynamic therapy” [MeSH term] OR “photodisinfection” OR “phototherapy” OR “lasers” [MeSH term]).

### 2.4. Selection of studies

Two independent reviewers (E.R. and A.S.) assessed the resulting articles based on the inclusion criteria. The reviewers' agreement level regarding studies' inclusion was expressed using Cohen's kappa coefficient.

### 2.5. Inclusion criteria

During the first stage of study selection, the titles and abstracts were screened and evaluated according to the following inclusion criteria:

- RCTs compared the effectiveness of aPDT to SD in patients diagnosed with residual periodontal pockets.
- Patients were enrolled in regular periodontal maintenance programs.
- Parallel and split-mouth design studies included systemically healthy patients.
- A control group receiving SD either alone or with a placebo was present.
- The test group received the same SD as a control group, plus the aPDT (S or M).
- SD was carried out by manual or sonic scaling.
- The study reported on BOP, PD, and/or CAL changes before and after treatment as mean values with standard deviations.
- Follow-up was  $\geq 3$  months.
- English language.

### 2.6. Exclusion criteria

- Studies included patients with systemic diseases.
- Patients had received initial periodontal treatment rather than SPT.
- Studies had carried out aPDT as a monotherapy.
- Studies had not reported on the clinical treatment outcomes, including changes in BOP, PD, and/or CAL.

All studies excluded at this stage and the reasons for their exclusion were recorded (Table 1).

### 2.7. Data extraction and data items

From the selected articles fulfilling the inclusion criteria, the following data were retrieved into data-extraction templates:

- Table 2 presents general information (country, study design, included patients' periodontal status, time of involvement in maintenance programs, number of participants, follow-up time, patients' gender, smoking status, and age).

**Table 1**  
Excluded studies and reasons for exclusion.

Author	Reason for exclusion
Capuyans I. et al., 2012 [35]	The same study cohort as Giannopoulou C. et al., 2012 [28]
Carvalho V.F. et al., 2015 [36]	aPDT used as monotherapy in test group
da Cruz Andrade P.V. et al., 2017 [37]	aPDT used as monotherapy in test group
Habashneh R.A. et al., 2019 [38]	Not a RCT
Kolbe M.F. et al., 2014 [39]	aPDT used as monotherapy in test group
Mongardini C. et al., 2014 [40]	Follow-up 1 week
Petelin M. et al., 2015 [41]	Multiple applications of aPDT associated with initial periodontal treatment
Rühling A. et al., 2010 [42]	aPDT used as monotherapy in test group

aPDT – antimicrobial Photodynamic therapy; RCT – randomized controlled clinical trial.

- **Table 3** presents the number of patients included in the final analysis, treatment protocols in the control and test groups, laser types, parameters, type of photosensitizers, and clinical outcomes. The mean values and standard deviations of changes in BOP reduction, PD reduction, and CAL gain following the treatment, in both the test and control groups, were extracted for data analysis and presented in **Table 3**.

## 2.8. Risk of bias assessment

The quality of all included studies was assessed during the data-extraction process, which involved evaluating the methodological elements that could influence each study's outcome (**Table 4**). The Cochrane Collaboration's two-part tool for assessing the risk of bias was

**Table 2**

Material and methods of the selected studies: country, study design, periodontal status of included patients, time of involvement into periodontal maintenance, number of patients included in the study, follow-up time, patients' gender, smoking status and age.

Study	Country	Study design	Level of residual/ persistent disease (at the baseline visit of SPT)	Time in periodontal maintenance care	Participants (control/ test) at the beginning of the study	Follow-up	Gender (M/F)	Smokers	Mean age (range)
Grzech-Lesniak K. et al., 2019 [31]	Poland	Parallel RCT	PD $\geq$ 5 mm at single-rooted teeth	NR	40; 20/20	6 months	15M/ 25F	Excluded	50.3 $\pm$ 11.6; (32–79)
Goh E.X. et al., 2017 [32]	Singapore	Split-mouth RCT	At least two residual pockets of $\geq$ 5 mm in different quadrants, with or without BOP	NR	27	3 months	11M/ 16F	Included	55.5 $\pm$ 7.9 (44–70)
Corrêa M.G. et al., 2016 [25]	Brazil	Split-mouth RCT	At least two contra- lateral single-rooted teeth with residual PD $\geq$ 5 mm and BOP	In SPT for three months, after cause-related therapy	20	3 months	55.6% M/ 44.44F	Excluded	48.1 $\pm$ 7.5
Müller Campanile V.S. et al., 2015 [30]	Switzerland	Split-mouth three-arm RCT	At least one site in each of three dentition quadrants with a probing pocket depth (PD) $>$ 4 mm, clinical attachment loss (CAL) $>$ 1 mm, and BOP+	After completion of comprehensive periodontal therapy since 3 to 12 months	28	6 months	15M/ 13F	Included	62.8; (37–77)
Campos G.N. et al., 2013 [26]	Brazil	Split-mouth RCT	At least two contralateral single-rooted teeth with residual PD $\geq$ 5 (BOP)	At least 3 months after completion of basic periodontal therapy	15	3 months	55.6M/ 44.44F	Excluded	48.15 $\pm$ 7.53
Giannopoulou C. et al., 2012 [28]	Switzerland	Split-mouth 3-arm RCT	Presence of $\geq$ 1 site in each of three quadrants with a PD $\geq$ 5 mm, CAL loss $\geq$ 2 mm, and BOP	From 3 to 24 months after completion of comprehensive periodontal therapy	32	6 months	32 (23M, 9 F)	NR	52 (36–74)
Chondros P. et al., 2009 [27]	Holland	Parallel-arm RCT	At least one site per quadrant with PD $\geq$ 4 mm with BOP	NR	24; 12/12	6 months	10M/ 14F	Included	49.45 $\pm$ 8.62
Lulic M. et al., 2009 [29]	Switzerland	Split-mouth RCT	PD $\geq$ 5 mm with/without concomitant BOP	Patients in maintenance care for a mean of 11.3 years	10	12 months	3M/7F	Included	54 (40–74)

BOP – bleeding on probing, CAL – clinical attachment level, F- female, M- male, NR – not reported, PD- pocket probing depth.

used to assess bias across the studies and to identify papers with intrinsic methodological and design flaws [21]. The following items were evaluated as posing a low, high, or unclear risk of bias: random sequence generation, concealing allocations, blinded participants/personnel, incomplete outcome data, selective reporting outcomes, and other potential risks of bias. The degree of bias was categorized as low risk if all criteria were met, moderate risk when 1 criterion was missing, and high risk if 2 or more criteria were missing.

## 2.9. Statistical analysis

First, a traditional pairwise meta-analysis was performed. The random-effect model was utilized, incorporating the assumption that various studies were evaluated differently but had related treatment effects. The included studies' continuous variables (BOP [%], PD [mm] and CAL [mm]) were categorized in groups and analyzed using the Review Manager software (version 5.2.8, Copenhagen, Denmark, 2014). The intervention effects' estimates were expressed as mean difference (MD) with 95% confidence intervals (CIs). Chi-squared tests evaluated the heterogeneity, which was considered low for values  $\leq$  25%, moderate for values between 25% and 50%, and high for values  $>$  50% [22].

Second, a random-effect network using Bayesian-framework Markov-chain Monte Carlo methods was created using ADDIS 1.16 (<https://gemtc.drugis.org>). The continuous data of each parameter (BOP, PD, and CAL) were evaluated in a network specifying the relationship between the studies' MDs and combining direct and indirect comparisons of the various treatment types. The data were considered statistically significant when  $P <$  0.05, with a 95% CI.

The probability of the best clinical effect for each type of treatment modality was assessed by calculating each treatment group's MD, comparing them to arbitrary standard controls, and counting the proportion of iterations of the Markov chain of the MD ranking for

**Table 3**  
Treatment protocols, laser type, parameters, types of photosensitizers and changes in PD and CAL in test and control groups.

Author, year	Number of patients that completed the study (Test/Control)	Treatment protocol in control group	Treatment protocol in test group	Laser type	Laser parameters	Photosensitizer	Change in PD (mm)	Change in CAL (mm)	Change in BOP (%)	Comments
Grzech-Lesniak K. et al., 2019 [31]	40; 20/20	SRP	SRP + aPDT (3 irradiations - baseline, 7 and 14 days after baseline)	Diode laser	Wavelength: 635nm; Power output: 200 mW; Energy density: 117.64 J/mm <sup>2</sup> ; Working time: 30 s/tooth	Toluidine blue	<u>Control</u> : 0.29 ± 0.66; <u>Test</u> : 0.32 ± 0.69	-	<u>Control</u> : 16.3 ± 1.85; <u>Test</u> : 10.4 ± 4.8	NS
Goh E.X. et al., 2017 [32]	27	SRP	SRP + aPDT (baseline)	Diode laser	Wavelength: 630nm; Power density: 2000-4000 mW/cm <sup>2</sup> ; Working time: 40 s/tooth	Toluidine blue	<u>Control</u> : 0.56 ± 0.15; <u>Test</u> : 0.82 ± 0.18	<u>Control</u> : 0.6 ± 0.22; <u>Test</u> : 0.65 ± 0.25	<u>Control</u> : 52.8 ± 12.9; <u>Test</u> : 52.8 ± 12.9	NS
Corrêa M.G. et al., 2016 [25]	15	SRP + photosensitizer, the laser was positioned but not activated	SRP + aPDT (baseline)	Diode Laser	Wavelength: 660 nm; Power output: 60mW; Energy density: 129J/cm <sup>2</sup> ; Working time: 60 s/tooth	Toluidine blue	<u>Control</u> : 1.0 ± 0.8; <u>Test</u> : 2.3 ± 0.8	<u>Control</u> : 0.3 ± 0.7; <u>Test</u> : 1.3 ± 1.6	<u>Control</u> : 40 ± 12.5; <u>Test</u> : 20 ± 2.5	Significant reduction in PD and CAL in test group compared to control (p<0.05)
Müller Campanile V. S. et al., 2015 [30]	27	UD + non-activated laser	<u>Test 1</u> : UD+aPDT (1 irradiation); <u>Test 2</u> : UD+aPDT (2 irradiations-baseline and 1 week after)	Diode laser	Wavelength: 670nm; Power output: 260 mW; Working time: 60 s/tooth	Methylene blue	<u>Control</u> : 2.9 ± 1.5; <u>Test 1 (1 irradiation)</u> : 3.4 ± 1.6; <u>Test 2 (2irradiations)</u> : 2.8 ± 0.95	<u>Control</u> : 3.0 ± 2.1; <u>Test 1 (1 irradiation)</u> : 3.7 ± 2.6; <u>Test 2 (2irradiations)</u> : 2.9 ± 1.6	<u>Control</u> : 8.0 ± 9.5; <u>Test 1 (1 irradiation)</u> : 9.0 ± 9.0; <u>Test 2 (2irradiations)</u> : 7.0 ± 10	NS
Campos G.N. et al., 2013 [26]	13	SRP	SRP + aPDT (baseline)	Diode laser	Waveklength: 660 nm; Power output: 60mW; Energy density: 129J/cm <sup>2</sup> ; Working time: 60 s/tooth	Methylene blue	<u>Control</u> : 1.14 ± 1.53; <u>Test</u> : 2.17 ± 0.91	<u>Control</u> : 0.51 ± 0.76; <u>Test</u> : 1.43 ± 1.61	<u>Control</u> : 60 ± 23.5; <u>Test</u> : 20.2 ± 3.6	Significant reduction in PD and CAL in test group compared to control (p<0.05)
Giannopoulou C. et al., 2012 [28]	29	SRP	UD + aPDT (baseline)	Diode laser	Wavelength: 660nm; Power output: 100 mW; Energy density: 3J/cm <sup>2</sup> ; Working time: 60 s/tooth	Phenothiazine chloride	<u>Control</u> : 1.9 ± 0.3; <u>Test</u> : 1.8 ± 1.2	-	NR	NS
Chondros P. et al., 2009 [27]	24; 12/12	Sonic scaler	Sonic scaler + aPDT (baseline)	Diode laser	Wavelength: 670nm; Energy density: 75J/cm <sup>2</sup> ; Working time: 60 s/tooth;	Phenothiazine chloride	<u>Control</u> : 0.9 ± 0.8; <u>Test</u> : 0.8 ± 0.5	<u>Control</u> : 0.5 ± 0.6; <u>Test</u> : 0.7 ± 0.7	<u>Control</u> : 48 ± 18; <u>Test</u> : 19 ± 3.5	NS
Lulic M. et al., 2009 [29]	10	SRP + non-activated laser	SRP + aPDT (5 irradiations – baseline, 1, 2, 7, and 14 days after baseline)	Diode laser	Wavelength: 670nm; Power density: 75mW/cm <sup>2</sup> ; Working time: 60 s/tooth	Phenothiazine chloride	<u>Control</u> : 0.07 ± 0.61; <u>Test</u> : 0.27 ± 0.43	<u>Control</u> : 0.2 ± 0.61; <u>Test</u> : 0.09 ± 0.61	<u>Control</u> : 87 ± 41; <u>Test</u> : 77 ± 36	NS

aPDT - antimicrobial photodynamic therapy; CAL - clinical attachment level; NR – not reported; NS – no statistically significant differences between test and control groups; PD - probing depth; SRP - scaling and root planing; UD – ultrasonic debridement.

**Table 4**  
Assessment of the risk of bias.

Author, year	Random sequence generation	Allocation concealment	Blinding	Incomplete outcome data	Selective reporting	Other bias
Grzech-Lesniak K. et al., 2019 [31]	+	?	-	+	?	+
Goh E.X. et al., 2017 [32]	-	+	?	+	+	+
Corrêa M.G. et al., 2016 [25]	+	?	+	+	+	+
Müller Campanile V.S. et al., 2015 [30]	+	+	?	+	+	+
Campos G.N. et al., 2013 [26]	+	?	+	+	+	+
Giannopoulou C. et al., [28]	+	+	?	+	+	+
Chondros P. et al., 2009 [27]	?	+	+	+	+	+
Lulic M. et al., 2009 [29]	+	+	+	+	?	+

+ = Low risk ? = Unclear risk - = High risk.

treatments [23].

Inconsistency between direct and indirect comparisons was assessed through the node-splitting model.

**2.10. Risk of bias across studies**

The publication bias analysis was analyzed for each outcome of interest through visual analysis of the funnel plot [24]. The analyses were conducted using the Review Manager software (version 5.2.8, Copenhagen, Denmark, 2014).

**3. Results**

**3.1. Study selection**

The initial electronic search resulted in 461 total titles from the MEDLINE (PubMed), EMBASE, and Cochrane Central Register of Controlled Trials (CENTRAL) databases. Two additional articles were identified through the manual search. After eliminating duplicate and irrelevant titles, a total of 17 articles were considered for possible inclusion ( $\kappa = 0.94$ ). After applying the inclusion and exclusion criteria, 9

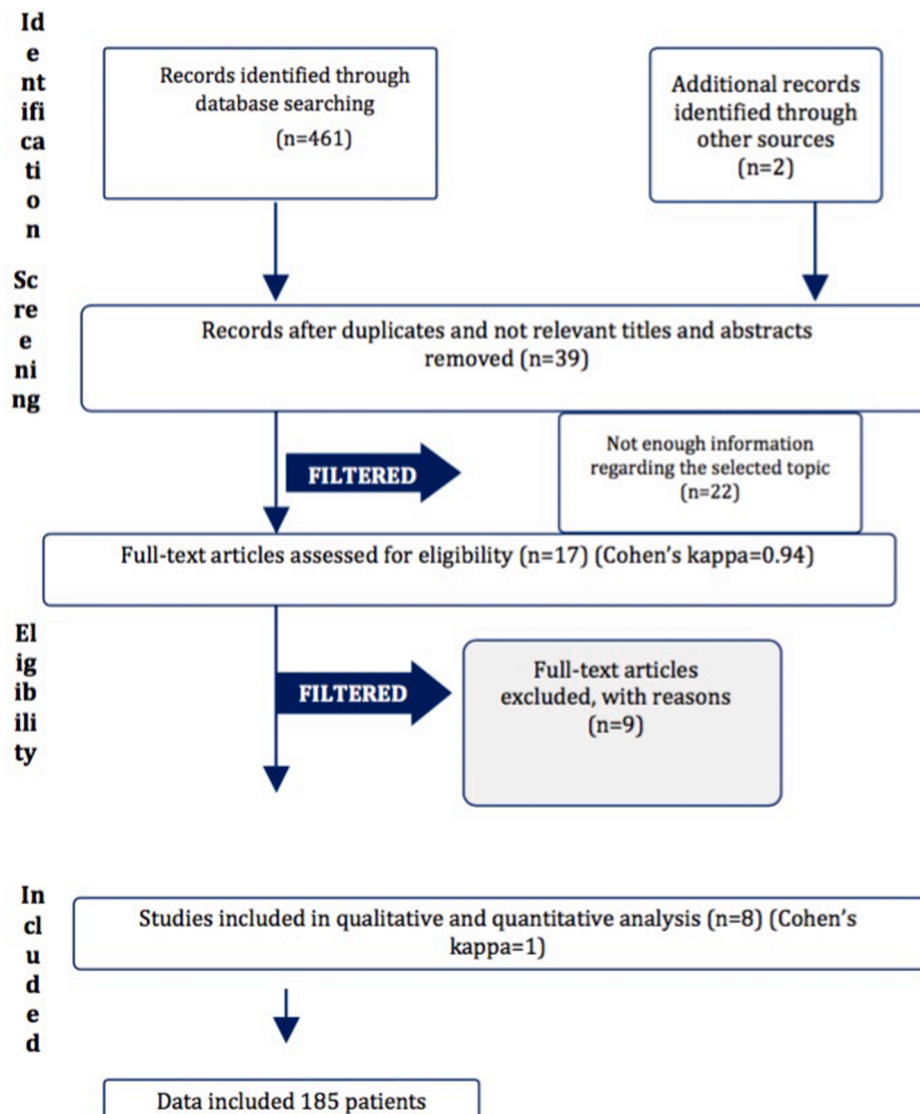


Figure 1. PRISMA flow diagram

articles were excluded from the final analysis (Table 1), resulting in a final selection of 8 studies ( $\kappa = 1$ ). Figure 1 illustrates the study selection process.

### 3.2. Quality assessment

Six studies were classified as having moderate risk of bias (for 1 key domain) [25–30], and 2 studies were judged to have a high risk of bias [31,32] (Table 4).

### 3.3. Characteristics of included studies

Table 2 depicts the included studies. Two studies used a parallel arms design [27,31], whereas the remaining 6 investigations had a split-mouth design [25,26,28–30,32]. Two studies included 1 control and 2 experimental groups [28,30], while the remaining 6 articles included 1 control and 1 experimental group. The follow-up time ranged from 3 [25,26,32] to 12 months [29].

In total, 196 patients were included in the current investigation, of whom 185 (94.4%) completed the studies. Sample sizes varied from 10 [29] to 40 [31] patients, and the power calculation was described in all studies, except for 1 [31]. The mean age of the included patients ranged from 32 [31] to 79 [31] years, and the ratio of the included males and females ranged from 0.4 [29] to 2.6 [28]. Smokers were included in 4 studies [27,29,30,32]. In 3 studies [25,26,31], smoking was an exclusion criterion, whereas 1 study did not report patients' smoking status [28].

The length of time that patients were involved in periodontal maintenance ranged from 3 months [25,26] to 11.3 years [25,26], whereas this period was not reported in 3 of the studies [27,31,32].

Table 3 outlines the treatment protocols in the control and test groups. All of the included patients had been previously treated and included in regular periodontal maintenance programs. SD in the control and test groups was accomplished with Gracey curettes and ultrasonics in 6 of the studies [25,26,28,29,31,32], and in the remaining 2 investigations, SD was performed solely by ultrasonics [27,30]. A diode laser was used in test groups in all of the included studies [25–32]. Three of the studies used toluidine blue as the photosensitizer [25,31,32], 3 used phenothiazine chloride [27–29], and the other 2 used methylene blue [26,30].

Regarding the frequency of applying aPDT in test groups, aPDT was applied once at the study's baseline in 6 of the investigations [25–28,30,32], 2 times (baseline and 7 days after) in 1 study [30], 3 times (baseline, 7 days after, and 14 days after) in 1 study [31], and 5 times (baseline and 1, 2, 7, and 14 days after) in the remaining study [29]. One of the studies [30] had 2 test groups with 1 and 2 irradiations [30].

### 3.4. Synthesis of results

#### 3.4.1. Pairwise meta-analysis

The aPDT groups (S and M) could be directly analyzed through pairwise meta-analysis for the BOP, PD, and CAL parameters.

Regarding BOP reduction, due to methodological heterogeneity, one of the studies [28] could not be included in the analysis. There was a significant difference favoring SD + S-aPDT when compared with SD alone, with a MD of -16.8 (95% CI: -30.7 to -2.91;  $p = 0.02$ ). In addition, there was a significant difference when SD + M-aPDT was compared with SD alone, with a MD of -5.13 (95% CI: -7.20 to -3.07;  $p < 0.00001$ ).

For PD reduction, there was a significant difference favoring SD + S-aPDT when compared with SD alone, with a MD of 0.40 (95% CI: 0.02 to 0.78;  $p = 0.04$ ). However, there was no significant difference when SD + M-aPDT was compared with SD alone, with a MD of 0.04 (95% CI: -0.27 to 0.35;  $p = 0.80$ ).

For the CAL, no significant difference was found between SD + S-aPDT and SD + M-aPDT compared with SD alone (MD = 0.37, 95% CI:

-0.02 to 0.76;  $p = 0.06$  and MD = -0.11, 95% CI: -0.71 to 0.50;  $P = 0.73$ , respectively).

All of the pairwise meta-analyses performed can be found in the Supplementary Appendix (S1).

#### 3.4.2. Network meta-analysis

Figure 2 shows the network comparisons. Table 5 summarizes the results of the network meta-analysis for each treatment analyzed. When SD alone was compared indirectly with SD + S-aPDT and SD + M-aPDT, using SD + S-aPDT showed the best clinical effect for BOP, PD, and CAL parameters (Figures 3A, 3B, and 3C).

#### 3.4.3. Rank probabilities

Table 6 shows the treatment ranking of the probability results.

According to the network comparisons for BOP, the cumulative probabilities of being the most efficient treatments were 0.74% for SD + S-aPDT, followed by 0.24% for SD + M-aPDT, and 0.01% for SD alone. For PD reduction, the cumulative probabilities of being the most efficient treatments were 0.87% for SD + S-aPDT, followed by 0.11% for SD + M-aPDT, and 0.02% for SD alone. For the CAL parameter, the cumulative probabilities of being the most efficient treatments were 0.86% for SD + S-aPDT, followed by 0.10% for SD + M-aPDT, and 0.03% for SD alone. The rank probabilities can be found in Table 6.

### 3.5. Risk of bias across studies

One study [32] showed slight asymmetry (the study was outside the confidence interval) in relation to the SD + S-aPDT, which is analyzed in the Supplementary Appendix (S2)."

## 4. Discussion

The present study aimed to investigate the potential beneficial clinical effects of adjunctive aPDT to SD for treating residual periodontal pockets in patients undergoing periodontal maintenance. To the best of our knowledge, this is the first systematic review analyzing the clinical efficacy of single versus multiple applications of aPDT following SD.

The meta-analysis was based on data extracted from 8 RCTs [25–32]. With regard to the mode in which aPDT was applied, the investigated studies were subgrouped into 2 categories: studies with a S-aPDT application [25–28,30,32] and studies with M-aPDT applications [29–31].

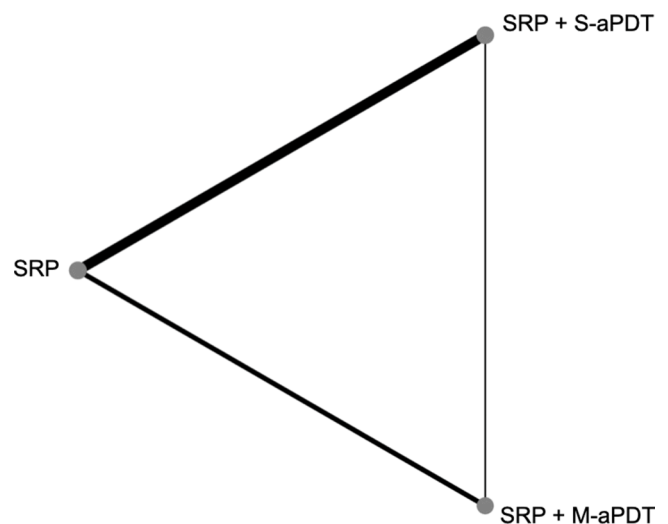


Figure 2. Network comparing the effect of the multiple-treatment meta-analysis. The width of the lines is proportional to the number of trials comparing each pair of treatments and the size of each node is proportional to the number of participants.

**Table 5**

Comparison of the interventions: mean difference (95% CI). Each cell gives the effect of the column-defining intervention relative to the row-defining intervention. The values are expressed in mm for PD and CAL and % for BOP.

BOP		
SRP	8.327 (-15.488, 31.169)	16.341 (-1.076, 35.412)
SRP + M-aPDT		8.208 (-18.441, 35.942)
SRP + S-aPDT		
PD		
SRP	-0.016 (-0.708, 0.655)	-0.413 (-0.950, 0.044)
SRP + M-aPDT		-0.393 (-1.194, 0.336)
SRP + S-aPDT		
CAL		
SRP	0.163 (-0.669, 0.998)	-0.348 (-0.980, 0.059)
SRP + M-aPDT		-0.514 (-1.529, 0.321)
SRP + S-aPDT		

BOP- bleeding on probing; CAL - clinical attachment level; M-aPDT – multiple applications of antimicrobial photodynamic therapy; PD - probing depth; S-aPDT - single application of antimicrobial photodynamic therapy; SRP - scaling and root planing.

The primary outcome variable in patients enrolled in maintenance is the reduction in inflammation (i.e., in BOP). According to the results of the current investigation, a statistically significant PD and BOP reduction was found for the adjunctive S-aPDT application, compared with SD alone ([MD = 0.4, 95% CI: 0.02 to 0.78,  $p = 0.04$ ] and [MD = -16.8, 95% CI: -30.7 to -2.91;  $p = 0.02$ ], respectively). This finding corroborates those obtained in previous systematic reviews investigating the effects of adjunctive aPDT to SD in periodontal supportive care [13,33,34]. In particular, higher improvements in PD were found following the adjunctive use of aPDT, compared with SD alone (0.44 mm [33], 0.9 mm [13], and 0.69 mm [34]). Regarding BOP, only 1 out of 3 aforementioned studies investigated the changes of this parameter and found no statistically significant changes for adjunctive aPDT compared to SD alone ( $p = 0.3895$ ) [13]. However, it should be noted that in all of the aforementioned systematic reviews [13,33,34], the final analysis pooled both S-aPDT and M-aPDT.

Upon further analysis of the present data set, statistically significant changes were found for BOP when SD + M-aPDT was compared with SD alone, with a MD of -5.13 (95% CI: -7.20 to -3.07;  $p < 0.00001$ ); however, no statistically significant differences were found for PD reduction (MD = 0.04, 95% CI: -0.27 to 0.35,  $p = 0.8$ ) or CAL gain (MD = -0.11, 95% CI: -0.71 to 0.50,  $p = 0.73$ ).

As stated above, both of the investigated treatment modalities (SD +

S-aPDT and SD + M-aPDT) significantly reduced BOP scores, whereas significant PD reduction was observed only for SD + S-aPDT compared to SD alone. Furthermore, none of the examined test groups showed superiority over SD alone in significantly changing CAL. This observation goes in line with the results of a recent review indicating that, in patients enrolled in periodontal maintenance, the main effect of the additional use of aPDT to SD is on the reduction of inflammation, as evidenced by statistically significantly higher reduction of BOP scores following SRP + aPDT when compared to SD alone, and not necessarily on PD reduction [43].

No direct comparison was feasible in clarifying whether SD + M-aPDT would have an advantage in improving the investigated clinical outcomes over SD + S-aPDT or vice versa, as all of the included studies compared SD + S-aPDT with SD or SRP + M-aPDT with SD. Thus, the only way to compare multiple and single applications of adjunctive aPDT was through indirect comparisons (network meta-analysis).

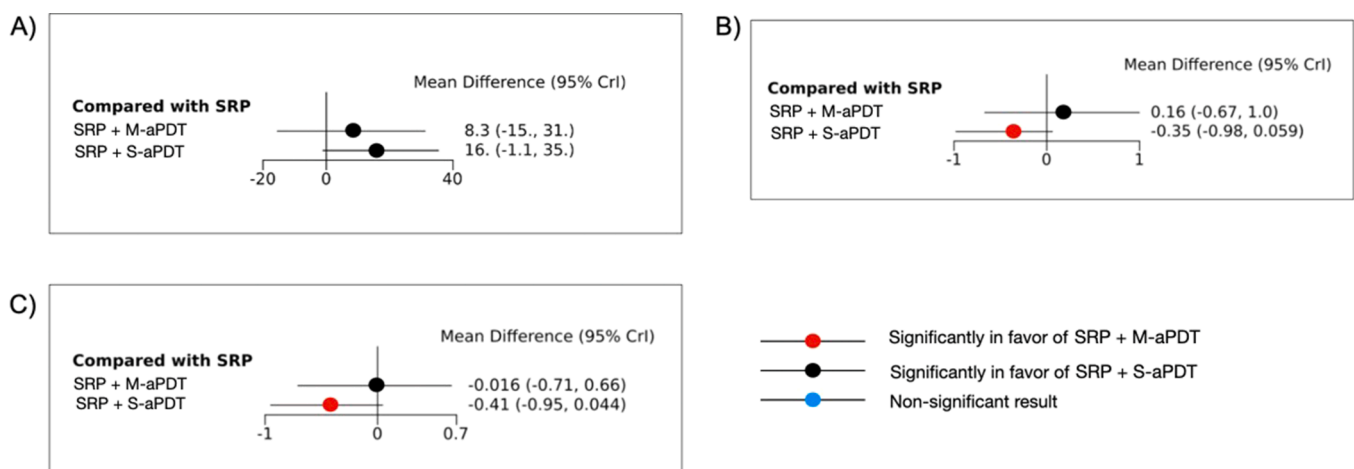
Accordingly, based on the network comparisons for BOP, PD, and CAL parameters, the highest cumulative probabilities of being the most efficient treatments were for SD + S-aPDT (0.74%; 0.87% and 0.86%, respectively), followed by SD + M-aPDT (0.24%; 0.1% and 0.10%, respectively) and SD alone (0.01%; 0.02% and 0.03%, respectively). These findings basically align with the results of a pairwise meta-

**Table 6**

Rank probabilities of each treatment modality for BOP, PD and CAL.

Rank probabilities table for BOP			
	Rank 1	Rank 2	Rank 3
SRP	0.763	0.225	0.013
SRP + M-aPDT	0.215	0.546	0.240
SRP + S-aPDT	0.022	0.230	0.748
Rank probabilities table for PD			
	Rank 1	Rank 2	Rank 3
SRP	0.508	0.473	0.020
SRP + M-aPDT	0.474	0.416	0.110
SRP + S-aPDT	0.019	0.111	0.871
Rank probabilities table for CAL			
	Rank 1	Rank 2	Rank 3
SRP	0.316	0.652	0.033
SRP + M-aPDT	0.669	0.229	0.102
SRP + S-aPDT	0.016	0.119	0.865

BOP- bleeding on probing; CAL – clinical attachment level; M-aPDT – multiple applications of antimicrobial photodynamic therapy; PD – probing depth; S-aPDT – single application of antimicrobial photodynamic therapy; SRP – scaling and root planing.



**Figure 3.** Forest plot for the relative effect between the analyzed treatments when compared with SRP alone. When circles deviate to the left of the central line (neutrality), they favor of the respective treatment, while when they deviate to the right they favor to SRP + PDT (SA) or SRP + PDT (MA). A) PD parameter, B) CAL parameter C) BOP parameter.

analysis suggesting that a repeated application of aPDT might not result in superior outcomes compared with its single application. Nonetheless, this outcome might have been influenced by the limited number of RCTs included in the subgroup of SRP + aPDT (MA) (3 RCTs) with a relatively small number of patients ( $n = 57$ ), compared with the subgroup of SRP + aPDT (SA) (6 RCTs,  $n = 123$  patients).

In interpreting these results, it must be mentioned that 2 studies were performed with a parallel arm design and that the other 6 employed a split-mouth design. Therefore, in order to compensate for the heterogeneity between the studies, all analyses in network comparison were conducted using the random effect model. The random effects model considers that the effect observed in a given study is an estimate of its real effect and that the effects of all studies follow a general distribution. Thus, the summary measure has a broader confidence interval, and smaller studies gain greater weight than they did in a fixed effects model.

High heterogeneity was detected among the studies in the subgroup of S-aPDT application, which might be at least partly attributed to the various definitions used for residual periodontal pockets in the included studies. In particular, a threshold of 4 mm of PD was an inclusion criterion in 2 of the included studies [27,30], whereas the criterion of including a patient in the study was 5 mm of PD in the remaining 4 investigations [25,26,28,32]. Furthermore, a potential wash-over effect could possibly not be controlled when applying aPDT in studies with a split-mouth design, probably biasing the outcomes. In addition, smokers were included in 3 studies [27,30,32], which might have in turn affected the treatment outcomes. Ultimately, various subgingival instrumentation protocols (ultrasonics vs. ultrasonics plus gracey curettes), pre-irradiation times, frequencies of adjunctive aPDT applications in the M-aPDT group, output power parameters, and the duration of exposure might have also contributed to the heterogeneity among the included studies.

Another important aspect that must be acknowledged is the fact that the wavelengths in all of the included studies were in the red spectrum of electromagnetic irradiation (635, 660, and 670 nm). Therefore, the present results are valid only for these wavelengths and not, for instance, 810 nm, which is the wavelength for indocyanine green.

Furthermore, the absorption coefficient by the bacteria depends not only on the specific laser wavelength but also the photosensitizer and can have various effects on the periodontal tissues [17]. Phenothiazine compounds were utilized as PSs in the included studies. They show strong absorption in the red spectrum ( $\approx 600\text{--}680$  nm), which is advantageous for their application as PS due to the better tissue penetration of light from longer wavelengths [14].

Aspects such as short follow-up periods, heterogeneity of aPDT protocols, and the lack of clinical studies directly comparing single versus multiple aPDT applications might have influenced the outcomes of the present analysis.

In the light of the previously discussed results and limitations of this study, there is a need for future well-designed RCTs with medium to long follow-up periods directly comparing single and multiple applications of aPDT for establishing optimal protocols of its use in periodontal maintenance.

## 5. Conclusion

Within their limits, the present data indicate that in periodontal patients enrolled in maintenance: a) single and multiple adjunctive applications of aPDT following SD resulted in statistically significant BOP reduction compared to SD alone, and b) repeated applications of aPDT did not seem to result in superior outcomes compared to single applications.

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## Supplementary materials

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