Lasers in Medical Science (2019) 34:855–863
https://doi.org/10.1007/s10103-018-02703-2

REVIEW ARTICLE

The effects of repeated applications of antimicrobial photodynamic therapy in the treatment of residual periodontal pockets: a systematic review

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Received: 3 September 2018 / Accepted: 3 December 2018 / Published online: 11 December 2018

Abstract

The aim of this study was to assess the effects of repeated applications of antimicrobial photodynamic therapy (aPDT) on the non-surgical periodontal treatment of residual pockets. This work was performed and reported according to the Cochrane and PRISMA recommendations, respectively, and registered at the PROSPERO registry (number CRD42017058403). An extensive search of the biomedical literature was conducted on four databases from January 1960 to August 2018, followed by hand searching. Analysis of the quality of the selected studies was based on the risk of bias. Only two randomised controlled clinical trials (RCTs) met the inclusion criteria although they had unclear risk of bias. One study showed that repeated applications of aPDT in association with conventional non-surgical treatment during periodontal maintenance improved all clinical outcomes after 6 months. The other study, which assessed the effects of repeated applications of aPDT in association with ultrasound debridement on periodontal pathogens, showed no significant reduction of the main pathogens after 3–6 months but reported reductions of probing pocket depth and C-reactive protein after 3 and 6 months, respectively, compared to mechanical therapy alone. Concluding, it was not possible to state that repeated applications of aPDT, in association with non-surgical treatment of residual pockets, have effective clinical effects in the periodontal maintenance therapy. Although one can consider that aPDT is a promising adjuvant therapy, it is still necessary to carry out more RCTs with low risk of bias in order to confirm or refute the benefits of multiple applications for residual periodontal pockets.

Keywords Photodynamic therapy · Periodontitis · Clinical outcomes · Periodontal pocket, root planing

Introduction

Periodontal diseases are highly prevalent in adults, with recent studies performed in Latin America reporting a high prevalence, reaching more than 90% of the population [1]. Periodontitis is one of the forms of periodontal diseases and has a high prevalence in the United States, affecting almost half of the population (i.e. 45.9%) older than 30 years old [2]. This form results from an inflammation of the supporting dental structures in response to chronic infections caused by various periodontal pathogens [3].

In fact, bacterial biofilm plays a key role in the aetiology of periodontitis. Specifically, these microorganisms and their virulence factors can induce the release of pro-inflammatory cytokines, provoking an inflammatory response and generating alveolar bone loss [4]. In a more advanced stage, periodontitis leads to loss of the tooth, thus reducing the quality of life of the patients and affecting their general health [5]. In general, biofilm is beneficial to the host by providing colonisation resistance against exogenous pathogens and by interacting with the immune system at a level compatible with health [3]. However, the colonisation of subgingival area results in shifts in the bacterial composition of the biofilm, introducing or enhancing the level of periodontophatic bacteria that may initiate disease [3, 4]. Subgingival microbiota is dominated by

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different kinds of gram-negative rods such as Prevotella species, *Porphyromonas gingi*valis, and *Fusobacterium nucleatum* and also including motile bacteria and spirochetes located at the external portion of the biofilm in direct relation to the pocket tissue [3, 4]. Furthermore, the majority of the bacteria are anaerobic and have a proteolytic metabolism. These are favoured by the local anaerobic conditions in the periodontal pocket rich in gingival crevicular fluid, which is a tissue exudate that contains some proteins and blood products [3]. The biofilm and the ongoing inflammation will gradually result in deepening of the periodontal pockets, degradation of the bone, and ultimately loss of teeth [4].

The main objective of the periodontal therapy is to eliminate bacterial deposits on the root surfaces of the teeth by means of mechanical treatment, that is, scaling and root planing (SRP) [6]. However, it is difficult to eliminate periodontal pathogens from the deepest areas of the periodontal pockets, or into the adjacent soft tissue, root cement, and dentinal tubules [7]. Periodontal pathogens, such as *P. gingivalis*, *Tannerella forsythia* and *Treponema denticola*, have the ability to invade gingival epithelial cells which may enable them to cause inflammation within the tissue and also protect these pathogens from mechanical removal [8]. Systemic antibiotics in conjunction with scaling and root planing (SRP) can offer an additional benefit over SRP in such situation [6]. Unfortunately, the regular use of antibiotics in periodontal treatment is not advisable [9] because they could lead to the development of antimicrobial resistance or may promote the overgrowth of new pathogens [10]. Therefore, the limitations of conventional treatment open space for new treatment approaches.

Antimicrobial photodynamic therapy (aPDT) is a proposal for treatment of periodontitis, which involves the use of low-power laser or LED in association with a non-toxic photosensibiliser (FS) to reduce the amount of periodontal pathogens. aPDT uses a laser light with an appropriate wavelength, in the presence of oxygen, to activate the photosensitizer (PS) [7]. Free radicals of singlet oxygen are formed by changing the energy status of PS molecules, which destroy the membrane, the mitochondria or the nuclei of cells [11]. In addition to bactericidal effects of aPDT, the diode laser application added benefits to periodontal healing because of its biostimulative effects [7]. The PS excited triplet can undergo two types of reactions: it can react directly with a substrate, like the cell membrane or a molecule, and transfer a proton or an electron to form a radical anion or radical cation, respectively [12]. These radicals may further react with oxygen to produce reactive oxygen species (type 1 reaction). Alternatively, in a type 2 reaction, the triplet PS can transfer its energy directly to molecular oxygen to form excited-state singlet oxygen. Both reactions can occur in the same time, and the success of these processes depends on the type of PS used, the concentrations of substrate and oxygen [12].

Some studies investigated the effect of a single application of aPDT in the treatment of periodontitis, showing conflicting results [13–15]. Compared to SRP alone, the association of a single application of aPDT resulted in greater reductions of bleeding on probing (BoP) rates [13]. On the other hand, some studies found no additional improvement in the reduction of clinical parameters [14, 15].

More recently, patients with periodontitis undergoing support periodontal therapy have been treated with non-surgical subgingival debridement in association with 2, 3 or 5 applications of aPDT [7, 9, 11]. However, up to now, no systematic reviews demonstrating whether repeated applications of aPDT provide additional benefits to the non-surgical periodontal treatment of residual pockets have been published.

The aim of this study was to assess the effects of repeated applications of aPDT on the non-surgical periodontal treatment of residual pockets.

Material and methods

This systematic review was conducted according to the criteria established by Cochrane [16] and reported following the PRISMA guidelines [17]. It was registered at the PROSPERO registry under the number CRD42017058403. The following question was developed with PICO format [18]: "Do repeated applications of aPDT in association with non-surgical periodontal treatment have superior effects on residual pockets compared to non-surgical treatment of CP alone?"

Search strategy

An extensive search of the biomedical literature was performed on the databases MEDLINE (PubMed), LILACS, Cochrane Central Register of Controlled Trials (CENTRAL) and Elsevier (Science Direct) by using appropriate keywords and titles related to photodynamic therapy and non-surgical periodontal therapy. Combinations of Boolean operators "OR" and "AND" were used for searching the following terms: Photodynamic therapy; Antimicrobial Photodynamic therapy; Photo-chemotherapy; Periodontal Disease; Periodontitis; Chronic Periodontitis; Residual Pockets; Root Planing; Scaling and Root Planing; Non-surgical periodontal therapy and supportive periodontal therapy, from January 1960 to August 2018.

Other related studies were identified by hand searching reference lists of studies. This strategy was shown to be effective for identification of clinical studies which sometimes are not found on electronic databases [19]. Moreover, each theme was manually sought from the major journals of periodontology and laser therapy published in the last 15 years, namely: "Journal of Clinical Periodontology", "Journal of

Periodontology", "Journal of Periodontal Research", "Clinical Oral Investigations", "Journal of Dental Research, Laser Medical Science", "Journal of Dental Lasers", "International Journal of Laser Dentistry", "Journal of Laser Dentistry", "The Journal of Oral Laser Applications, Laser in Dentistry and Lasers in Dental Science".

Study design

This systematic review included only original randomised controlled clinical trials with at least a 6-month follow-up. Articles were excluded according to the following criteria: duplicate study, no control group or no publication in journals. The reasons for rejecting the study during selection were recorded.

Participants

Patients diagnosed with Periodontitis according to a classification system [20] and without age restriction were included. Exclusion criteria were: diabetes or other systemic diseases and no presence of residual pockets.

Intervention

Repeated applications of aPDT (2 or more) in association with non-surgical periodontal treatment of residual pockets.

Comparison/control

Non-surgical periodontal treatment (scaling and root planing performed manually or ultrasonic debridement).

Outcomes

The primary outcome of interest was the change in the clinical attachment level (CAL), whereas reductions of probing pocket depth (PPD), BoP, levels of periodontal pathogens and biological markers were secondary outcomes.

Data selection and extraction

During the selection process, two independent reviewers obtained data on population, interventions, outcomes and follow-up periods of the studies. Attempts to get in contact with the authors were made in order to verify still-open questions.

Of the chosen articles, the complete ones were analysed before consensual decision-making on their inclusion or exclusion.

Assessment of the risk of bias

Assessment of the risk of bias in the included studies was based on the Cochrane criteria [16] as follows: (1) random sequence generation; (2) allocation concealment, (3) blinding of participants and personnel, (4) blinding of outcome assessment, (5) incomplete outcome data, (6) selective reporting and (7) other bias.

After collecting these items, the studies were classified as of "low risk" (i.e. low risk of bias for all major points), "high risk" (i.e. high risk of bias for one or more points) and "unclear risk" (i.e. unclear risk of bias for one or more major points).

Data were summarised in a flowchart and tables in order to facilitate the description of the analyses performed.

Results

Electronic search resulted in the identification of a total of 632 titles and abstracts. Only one article was found after hand searching. A total of 250 studies remained after exclusion of duplicates. By using titles and abstracts, 60 studies were selected after applying the inclusion criteria, and of these, 17 were complete studies which were selected for eligibility. Fifteen studies were excluded after being fully read, and the reasons for exclusion are listed in Table 1. Therefore, only two studies were selected for qualitative analysis. Figure 1 describes the flowchart of the studies identified, selected and evaluated for review according to the eligibility criteria.

A general view of the articles excluded and the reasons for their rejection are listed in Table 1.

Two studies were included in the qualitative analysis [9, 11]. Due to a reduced number of studies selected, it was not possible to perform a meta-analysis.

The study by Muller Campanile et al. [9] was classified as of "unclear risk of bias" because the blinding of the patients was not clear. However, the method used for generating and concealing the assignment sequence was cited and the examiner and practitioners were blinded to the results and to the treatments provided, respectively. There were no missing outcome data. All patients but one completed the study (Fig. 2).

The study by Lulic et al. [11] was also classified as of "unclear risk of bias" because the blinding of outcome assessment was not mentioned. On the other hand, randomisation and assignment of patients were cited and the description of these procedures was included. Patients, researchers and oral hygienist were all blinded to the energy configuration and activation or not of the laser point used in the aPDT after intense training. There were no missing outcome data. All patients completed the study (Fig. 2).

Table 1 Studies excluded and the reasons for exclusion

Studies	Reason for exclusion
Petelin et al. [7]	Multiple applications of aPDT associate to the initial treatment
Carvalho et al. [21]	aPDT alone
Andrade et al. [22]	aPDT alone
Bassir et al. [23]	Use of LED
Sreedhar et al. [24]	PS – curcumin
Franco et al. [25]	No presence of residual pockets; 3 months of follow-up only
Ge L et al. [26]	No presence of residual pockets; 3 months of follow-up only
Ge LH et al. [27]	Comparison with high-power laser
Giannelli et al. [28]	Comparison with high-power laser
Correa et al. [29]	Single application of aPDT
Kolbe MF et al. [30]	Single application of aPDT
Campos et al. [31]	Single application of aPDT
Cappuyns et al. [32]	Single application of aPDT
Chondros et al. [33]	Single application of aPDT
Goh EX et al. [34]	Single application of aPDT

aPDT, antimicrobial photodynamic therapy; *PS*, photo-sensibiliser; *LED*, light emission diode

Finally, none of the included studies were registered in ClinicalTrials.gov which hampered the evaluation of Selective Reporting criteria.

The risk of bias of the included studies is listed in Fig. 2

The characteristics and results of the selected studies are listed in Tables 2 and 3.

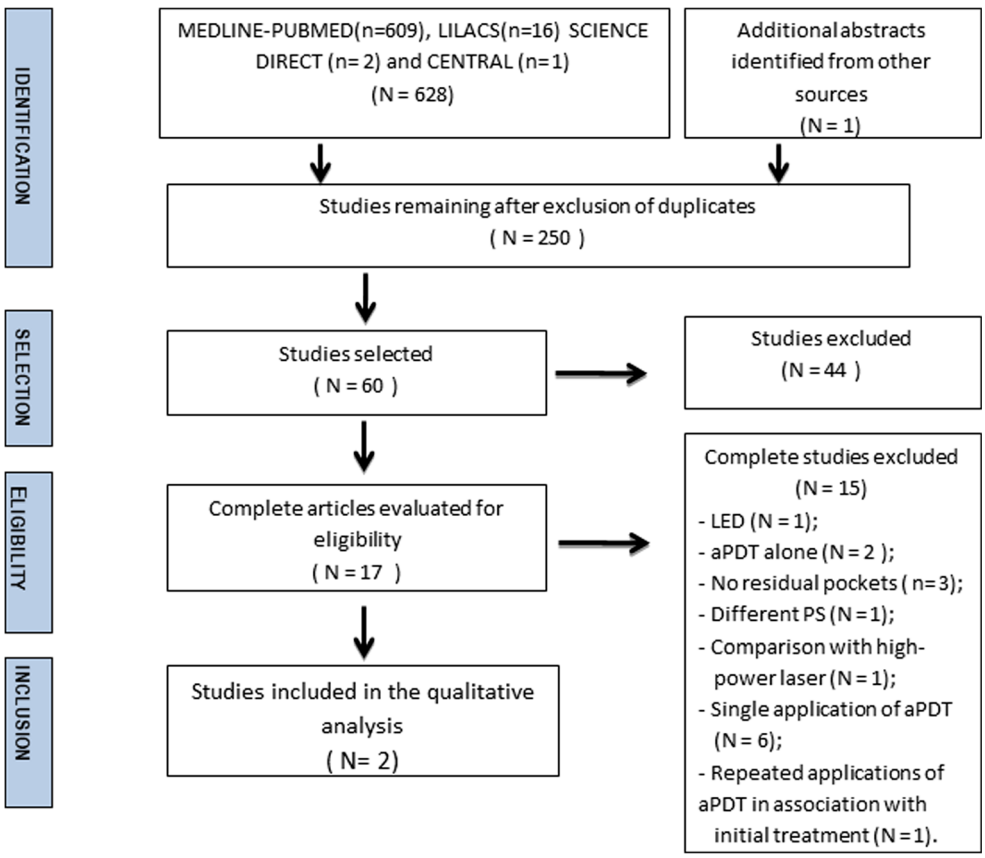

Fig. 1 Flowchart of the process of identification and selection of the studies (PRISMA) [17]

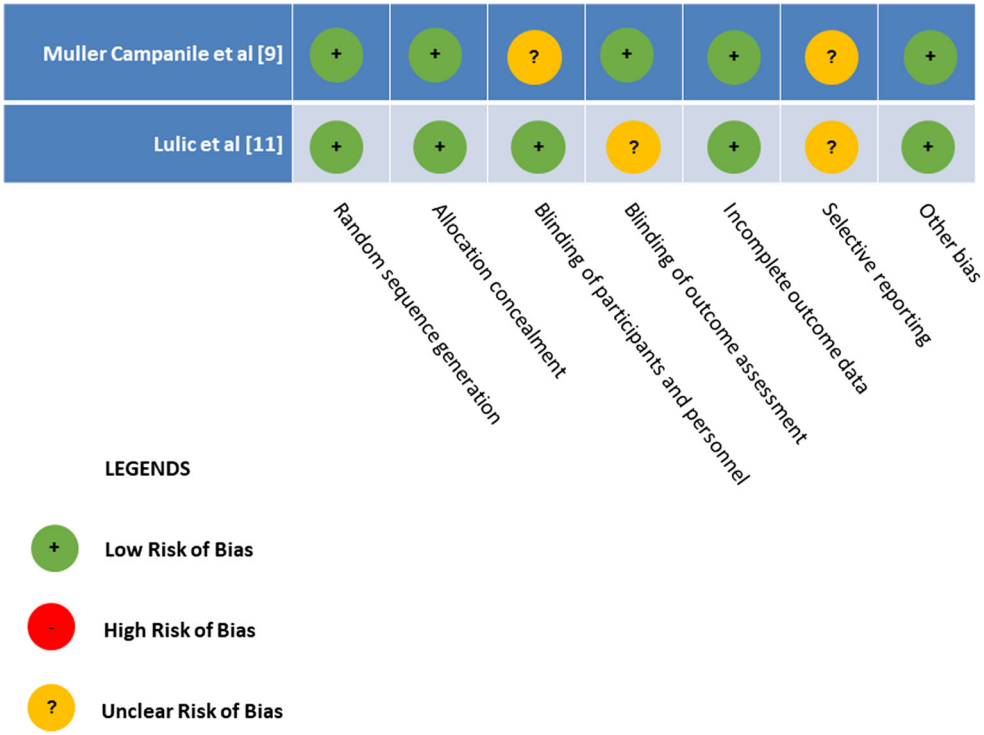

Fig. 2 Risk of bias in the studies selected (Cochrane) [16]

Discussion

The objective of this study was to describe the additional effects of repeated applications of aPDT in association with non-surgical periodontal treatment of residual pockets.

In the past decade, several clinical studies assessed the effects of aPDT in the periodontal therapy [7, 9, 11, 13–15, 21–34]. The fact is that the reestablishment of a subgingival environment compatible to periodontal health is essential for preventing both recolonisation by putative periodontal pathogens and recurrence of the disease [35].

Nevertheless, the anatomical difficulties found during SRP suggest the need to use other therapeutic modalities aiming at microbial control. As aPDT has been associated with diode laser for photo-biomodulation of tissues, this approach might further benefit patients with systemic impairment [24]. Moreover, anti-inflammatory and bio-modulating properties of low-power laser can facilitate both the process of proliferation and the healing of inflamed periodontal tissues [7], thus contributing to the treatment of residual pockets.

Some authors showed statistically significant results for aPDT in association with SRP, which increased CAL and reduced BoP after 3 months of treatment [36, 37]. However, Balata et al. [38] reported no additional clinical benefits when a single application of aPDT in the initial periodontal therapy was tested in comparison to ultrasound. In the treatment of residual pockets, the improvement seems to only occur for decreasing BoP in already-treated sites in maintenance patients [7, 33, 39–41].

In addition to clinical studies, some systematic reviews and meta-analyses assessed the effect of a single application of aPDT alone or in conjunction with treatment of chronic periodontitis, showing inconclusive controversial results regarding the clinical advantages of their use [42–44]. A recent systematic review concluded that the use of a single application of aPDT in association with SRP improves clinical parameters in the maintenance of residual pockets [42] but there is no evidence yet supporting its effectiveness in the medium and long terms [43]. Another review concluded that a single application of aPDT is not superior to SRP alone as an alternative therapy [44].

These controversial results seem to suggest that a single application of aPDT may not be enough to promote an additional benefit to SRP. Some authors have suggested that repeated applications of aPDT, associated with non-surgical periodontal treatment, can be a more advantageous approach in the treatment of residual pockets [9, 11]. The present study was carried out to assess whether this hypothesis can be confirmed.

Initially, up to now, there is no systematic review describing the effects of multiple applications of aPDT associated with non-surgical periodontal treatment of residual pockets. Literature search was conducted after defining the objective of the study, followed by selection of articles, acquisition of data, evaluation of methodology quality and synthesis of data. After this process, two articles were included for discussion.

The study conducted by Lulic et al. [11] demonstrated that SRP promoted a great reduction in PPD, significant increase

Table 2 General characteristics of the included studies

	Study design	Num. of patients (M/F)	Mean age variation	Study groups		Smoker/non-smoker	Residual pockets (PPD)	No use of antibiotic
				Test	Control			
Muller Campanile et al [9]	RCT Parallel group Double blind?	$N = 27$ (14/13)	62.8 years (37–77)	US + 2 X aPDT US+ 1 X aPDT (1 week)	US + non-active laser	8 smokers (> 20 cigarettes/day) 14 non-smokers 1 ex-smoker (< 10 cigarettes/day)	≥ 5 mm	2 months
Lulic et al [11]	RCT Parallel group Double blind	$N = 10$ (7/3)	54 years (40–70)	SRP + 5 X aPDT (2 weeks)	SRP+ non-active laser	2 smokers 8 non-smokers	≥ 5 mm	3 months

	Follow-up	Photosensibiliser (PS)	Laser parameters	Clinical outcomes	Biological data	Microbiological data
Muller Campanile et al [9]	6 months	Phenothiazine chloride (methylene blue) pre-irradiation time (1 min)	Diode laser (PERIOWAVE™ System) (670 nm, 280 mW) $T = 60$ s optical fibre	Primary PPD, BoP Secondary CAL, microorganisms	Bioplex test 20 markers from the gingival sulcus fluid	Aa, Tf, Pg, Td, Pi and Pm
Lulic et al [11]	12 months	Phenothiazine chloride (HELBO-Blue) Pre-irradiation time (3 min)	Diode laser (HELBO Minilaser 2075) (670 nm, 75 mW/cm^2) $T = 60$ s optical fibre	Primary PPD Secondary CAL, BoP	Not informed	Not informed

M, male; *F*, female; *US*, ultrasonic debridement; *SRP*, scaling and root planing; *aPDT*, antimicrobial photodynamic therapy; *RCT*, randomised controlled clinical trial; CAL, clinical attachment level; *PPD*, probing pocket depth; *BoP*, bleeding on probing

in CAL and decrease in BoP after five applications of aPDT associated to SRP for a period of 2 weeks (days 0, 1, 2, 7, 14) compared to SRP alone. The results in the experimental groups were statistically significant after 6 months, improving the clinical outcomes for residual pockets (≥ 5 mm) during periodontal maintenance. After 3 months, only percentages of BoP decreased. Clinical advantages were also observed as all the parameters improved after 12 months of follow-up, suggesting that the use of multiple applications of aPDT in association with SRP should be recommended for treatment of residual pockets.

In the study by Muller Campanile et al. [9], three therapeutic modalities were compared between groups A, B and C. In the groups receiving two (A) and one (B) application of aPDT during 1-week period, statistically significant differences were reported in the reduction of PPD after 3 months compared to the non-irradiated group (C). After 6 months, however, the differences were non-significant regarding all the clinical outcomes, differently from the results found in the study by Lulic et al. [11]. As for the microbiological effects, there was no reduction of six periodontal pathogenic microorganisms (*P. gingivalis*, *Aggregatibacter actinomycetemcomitans*, *T. forsythia*, *T. denticola*, *Prevotella intermedia*, *Parvimonas micra*), which were evaluated by means of DNA probe and PCR-based assays in three groups analysed after 3 and 6 months.

The risk of bias assessed in the studies by Muller Campanile et al. [9] and Lulic et al. [11] were classified according to the Cochrane criteria [16]. After assessment of all points regarding the quality of the methodology applied in each of the studies, both were considered as of unclear risk of bias. Lulic et al. [11] showed clearly that researchers, patients and oral hygienist were blinded to the use of laser. However, such a finding was contrary to Muller Campanile et al. [9], who reported only the blinding of researchers and examiner of the results. However, the blinding of outcome assessment was not found in Lulic et al. [11]. Furthermore, none of the studies were registered in *ClinicalTrials.gov*. So, it was not possible to identify if there was selective report or not.

In the two studies included in the present systematic review, both smokers and non-smokers participated in the experimental and control groups. Lulic et al. [11] found greater clinical advantages in their sample of ten patients, of whom eight were non-smokers. On the other hand, Muller Campanile et al. [9] used a much larger sample consisting of 27 patients, of whom one was ex-smoker and 14 were non-smokers. The fact that the study by Lulic et al. [11] used a sample, although small, with a majority of non-smokers suggests that the improvement in all clinical parameters after 6 months may also be related to the non-smoking habit.

Muller Campanile et al. [9] assessed the effect of one and two applications of aPDT plus US on the reduction of pathogenic microbiota, reporting no positive results compared to

Table 3 Main outcomes of the included studies

	Clinical	Microbiological	Biological
Muller Campanile et al [9]	< PPD (Three groups: A – US + 2 aPDT, B – US + 1 aPDT, C – US + placebo); < PPD (A vs C): (− 0.6 mm)/*p = 0.04; (B vs C): (− 0.7 mm)/*p = 0.03/3 months;	No reduction in MO (A, B, C) *3 and 6 months	< CRP; (A)/*p < 0.05/6 months
	PPD: non-significant differences (A, B, C)/6 months		
Lulic et al [11]	< PPD (test and control groups); < PPD: (− 0.67 mm)/*p = 0.01/6 months; > CAL: (+ 0.52 mm)/*p = 0.01/6 months;	Not informed	Not informed
	< BoP: (97–64%)/*p < 0.002/3 months; (67%)/*p < 0.001/6 months; (77%)/*p < 0.03/12 months		

CAL, clinical attachment level; *PPD*, probing pocket depth; *BoP*, bleeding on probing; *US*, ultrasonic debridement; *MO*, microorganisms; *CRP*, C-reactive protein; *Statistically significative

US alone. This also suggests that the presence of smoker patients can contribute to the maintenance of residual pockets, resulting in non-effective outcomes. Other clinical studies have shown a great clinical improvement of the patients, with aPDT plus SRP reducing periodontal pathogens in non-smoker patients compared to the use of SRP alone [7]. This finding was reiterated by a long-term study conducted by Matuliene et al. [44], who concluded that residual pockets were related to the smoking habit. Similarly, Rieder et al. [45] confirmed the dose-dependent relationship between smoking habit and presence of residual pockets in periodontal patients undergoing support therapy.

The biological effects were also assessed, but only by Muller Campanile et al. [9], who showed very significant results in the reduction of important biological biomarkers. A significant decrease of C-reactive protein (CRP), amyloid A, fibrinogen, procalcitonin and alpha-2 macroglobulin was demonstrated in this study after 6 months of treatment. When the authors assessed the groups separately, PCR was lower only in the group with two applications of aPDT (A). The effects of aPDT on inflammatory mediators involved in the pathogenesis of periodontal disease are not yet well understood and there are currently a few studies assessing these aspects [46]. Significant reductions in the levels of inflammatory cytokines in the gingival sulcus fluid following non-surgical periodontal treatment with aPDT were demonstrated elsewhere, thus indicating a significant clinical improvement of the periodontal tissues [30, 46]. In contrast, Pourabas et al. [15] assessed the effects of a single application of aPDT associated with SRP and concluded that there were no additional benefits in the clinical parameters or inflammatory markers TNF-α, Interleucina1-β and metalloprotein matrix after 3 months of treatment.

With regard to the action of the photosensibiliser (PS), the phenothiazine dye (i.e. methylene blue) was used at a concentration of 10 mg/ml in the two studies analysed [9, 11] regarding the periodontal pockets. In addition to being the most used currently, this approach has been shown by other clinical studies to have better bactericidal and bacteriostatic effects. Both methylene blue (MB) and toluidine blue (TB) are phenothiazine compounds available at concentrations of 10 mg/ml or 100 mg/ml, which are effective for inactivating periodontal pathogenic Gram-positive and Gram-negative bacteria, thus making PS the treatment of choice for periodontitis [47]. Phenothiazine dyes are naturally cationic and have been widely used in aPDT for inactivating a great variety of Gram-positive microorganisms, Gram-negative bacteria and also fungi cells [48]. The pre-irradiation time, after application of the dye to periodontal pockets, was different in the two studies as Lulic et al. [11] used a pre-irradiation time of 3 min, whereas Muller Campanile et al. [9] used 1 min only. Although the microbiological effects have not been assessed in the study by Lulic et al. [11], the longer pre-irradiation time may explain the better clinical results. On the other hand, the study by Muller Campanile et al. [9] showed no significant microbiological results and used a shorter time of pre-irradiation (i.e. 1 min), differently from a study assessing the microbiological effects of aPDT plus SRP by using a pre-irradiation time of 3 min, reporting positive results [7]. The longer time of pre-irradiation time seems to represent more positive clinical outcomes compared to a shorter one [25, 28]. After the pre-irradiation time, optical fibres were adapted to the laser points and then inserted into the residual pockets. Lasers were activated and the pockets irradiated. In the two studies, low-power diode lasers were used in the red light spectrum with wavelength of 670 nm and irradiation time of 60 s. It should be also emphasised that laser potencies (75 mW and 280 mW) and energy densities were different in both studies, perhaps explaining the differences in the results reported [9, 11]. The possible correlation between laser energy density and reduction of periodontal pathogens by using aPDT needs to be better determined.

In conclusion, the two studies included in this review were found to be very heterogeneous due to their clear differences related to the eligibility criteria, outcomes assessed and evaluation of the results reported. Thus, it is suggested that similar

clinical protocols should be tested in a larger number of patients by means of randomised clinical trials with better methodological quality in order to confirm the clinical, microbiological and anti-inflammatory benefits of the multiple applications of aPDT associated with non-surgical mechanical treatment of residual periodontal pockets.

Conclusion

From the studies included in the present systematic review, it was not possible to state that repeated applications of aPDT, in association with non-surgical treatment of residual pockets, have effective clinical effects in the periodontal maintenance therapy. Although one can consider that aPDT is a promising adjuvant therapy, it is still necessary to carry out more RCTs with low risk of bias in order to confirm or refute the benefits of multiple applications for residual periodontal pockets.

Compliance with ethical standards

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

Ethical approval Not applicable (systematic review).

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