Efficacy of alternative or additional methods to professional mechanical plaque removal during supportive periodontal therapy. A systematic review and meta-analysis.

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ABSTRACT

Aims: To systematically review the literature addressing the following focused questions: "*What is the efficacy of either (#1) alternative or (#2) additional methods to professional mechanical plaque removal (PMPR) on progression of attachment loss during supportive periodontal therapy (SPT) in periodontitis patients?*".

Methods: A systematic search for randomized clinical trials was performed. Change in clinical attachment level (CAL) from baseline was the primary outcome.

Results: Routine PMPR performed with either a combination of ultrasonic/hand instruments or Er:Yag laser showed similarly effective in preventing CAL loss. Moreover, a routine SPT regimen based on PMPR led to stability of CAL irrespective of a daily sub-antimicrobial doxycycline dose (SDD). Finally, an adjunctive photodynamic therapy (PDT) did not enhance the magnitude of CAL gain when sites with probing depth≥ 4 mm were repeatedly treated. After pooling all data, the results of the meta-analysis showed no statistical differences in CAL change from baseline: mean overall CAL change was -0.233 mm (95% confidence interval: -1.065, 0.598; p=0.351).

Conclusions: Weak evidence indicate that in treated periodontitis patients enrolled in a 3-4 month SPT based on PMPR, Er:Yag laser (as alternative), SDD and PDT (as additional) do not produce a greater clinical effect on periodontal conditions compared to PMPR.

CLINICAL RELEVANCE

Scientific background: When managing maintenance of treated periodontitis patients, limited information exists on the efficacy of alternative or adjunctive treatments for conventional professional mechanical plaque removal (PMPR).

Principal findings: Within the context of a 3-4 month SPT recall program, (i) daily supplementation with sub-antimicrobial dose of doxycycline and routine photodynamic therapy have limited to no adjunctive effect over PMPR; (ii) Er:Yag laser may maintain stable attachment levels at deep bleeding and/or suppurating pockets similarly to ultrasonic/hand instrumentation.

Practical implications: Limited evidence indicates that adjunctive treatments may not provide any additional benefit compared with mechanical PMPR in supportive periodontal therapy.

INTRODUCTION

The removal of the dental biofilm and calcified deposits from the tooth surface (here identified under the term "plaque removal") is currently considered as the essential procedure for the prevention and treatment of plaque-induced periodontal diseases (Lang, 1983; Cobb, 2002; van der Weijden & Slot, 2011).

Several systematic reviews have shown that, when encompassing professional mechanical plaque removal (PMPR) administered on a routine basis (i.e., at specific, pre-determined intervals), supportive periodontal therapy (SPT) may result in low rates of tooth loss and limited attachment level changes in both the short and long-term in patients treated for periodontitis (Heasman et al., 2002; Pastagia et al., 2006; Chambrone et al., 2010; Trombelli et al., 2015). In particular, a recent systematic review reported a weighted mean yearly rate of tooth loss of 0.15 and 0.09 for follow-up of 5 years or 12–14 years, respectively, and a mean clinical attachment loss lower than 1 mm at follow-up ranging from 5 to 12 years (Trombelli et al., 2015). In the included studies, PMPR was often combined with other procedures (e.g., reinforcement of oral hygiene instruction, additional active treatment at sites showing disease recurrence), thus making it difficult to isolate information on the magnitude of the mere effect of PMPR on tooth survival and stability of periodontal parameters. However, the results of these reviews collectively support that patients with a history of treated periodontitis can maintain their dentition with limited variations in periodontal parameters when regularly complying with a SPT regimen based on routine PMPR (Sanz et al., 2015).

Due to its validation by decades of sound scientific evidence, supra- and sub-gingival removal of dental biofilm and calculus from the tooth surfaces with mechanical and/or manual instruments still represents the conventional method for administrating PMPR in the maintenance phase of patients actively treated for periodontitis. However, alternative or adjunctive treatments to conventional PMPR have also been evaluated. A recent systematic review (Manresa et al., 2018) considered three studies at high or unclear risk of bias compared PMPR/SPT with and without adjunctive interventions (i.e., photodynamic therapy, PDT; locally delivered antibiotics) (Lulic et al., 2009; Tonetti et al., 2012; Killeen et al., 2016). The results were judged not informative enough to draw any conclusion about the equality or superiority of different approaches to PMPR/SPT in terms of clinical efficacy (Manresa et al., 2018). Moreover, in the included studies, test and control subjects/sites underwent an identical professional maintenance protocol after the administration of the investigated interventions, with a confounding effect on the resulting efficacy of adjunctive treatments (Lulic et al., 2009; Tonetti et al., 2012), or a single site per subject was evaluated (Killeen et al., 2016). Information on alternative methods to conventional PMPR were not analyzed.

In this context, specific literature search strategy and study selection criteria were implemented to perform a systematic review addressing the two following focused questions (FQs): "What is the efficacy of either (#1) alternative or (#2) additional methods to professional mechanical plaque removal (PMPR) on progression of attachment loss during supportive periodontal therapy (SPT) in periodontitis patients?".

METHODS

Protocol development and eligibility criteria

A protocol was developed a priori to collect and summarize the evidence from randomized studies comparatively evaluating different (1) alternative or (2) additional interventions to routine PMPR. The protocol was evaluated and approved by the Scientific Committee of the XVI European Workshop on Periodontology. The manuscript was prepared according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations (Moher et al., 2009; Liberati et al., 2009).

Study selection criteria

Inclusion criteria (PICOS)

- **Population:** studies were included if conducted on > 10 patients with the following characteristics: (i) at least 18 years of age; (ii) affected by periodontitis; (iii) undergone active periodontal therapy (APT) (including non-surgical periodontal therapy with or without a corrective surgical phase); (iv) with a follow-up of at least 1 year following the first administration of intervention/control treatment during SPT;

- **Intervention**: for FQ#1, any given alternative intervention to conventional PMPR (the latter including supragingival and/or subgingival removal of plaque, calculus and debris performed with manual and/or powered instruments). For FQ#2, any given additional intervention to conventional PMPR;

- **Comparison (control group):** routine, conventional PMPR;

- **Outcome measures:** data extraction related to outcome measures was referred to baseline visit (i.e., the SPT visit where intervention/control treatment were administered for the first time) and last visit where SPT outcomes were assessed.

  The change in clinical attachment level (CAL) was considered as the primary outcome variable. As secondary outcomes, the following (based on the Parameters on Periodontal Maintenance; American Academy of Periodontology, 2000) were evaluated: tooth loss, recorded as (i) total number

of teeth lost, and (ii) total number of teeth lost due to periodontal reasons during the follow-up period; change in: probing depth (PD), bleeding on probing (BoP), suppuration, amounts of plaque and calculus, furcation lesions, gingival recession, tooth mobility, radiographic measurements of bone levels; incidence of other periodontitis-related adverse events (e.g. periodontal abscesses); patient-reported outcomes.

Only studies using the patient as statistical unit were included. Studies were excluded if the outcomes of the investigated interventions had been assessed at a single site per patient.

- **Study design:** only parallel-arm or split-mouth randomized clinical trials (RCTs) where either (i) intervention and control treatments were only administered once and patients had been followed up for a period of at least 1 year without receiving any additional treatment; or (ii) intervention and control treatments had been administered at each SPT visit for a period of at least 1 year.

Literature search

Electronic search

Electronic database searches of Medline (www.pubmed.com) were performed up to and including March 2019 using a combination of MeSH terms and free keywords. Also, Elsevier Scopus© (www.scopus.com), and the Cochrane Oral Health Group Specialty Trials' Register (www.thecochranelibrary.com) were consulted (Appendix S1). Only full text articles written in the English language were considered. Hand searching was performed of the *Journal of Clinical Periodontology*, *Journal of Periodontology*, *Journal of Periodontal Research*, the clinical supplement of the *Journal of Dental Research*, and the proceedings of the European Workshops on Periodontology that had not been published in the *Journal of Clinical Periodontology*. Also, the reference list of pertinent systematic reviews and selected publications was screened for the presence of eligible studies. Titles and abstracts from the electronic searches were managed by EndNote® v.X7 software.

Screening methods

Two Authors (R.F. and A.P.) performed the primary search by screening independently the titles and abstracts. The same reviewers selected the full manuscript of those studies meeting the inclusion criteria. No analysis of the level of agreement between reviewers was performed. After the identification of studies to be included, the Authors resolved disagreements by discussion. If consensus was not reached, any disagreement was resolved by discussion with other two reviewers (L.T., N.W.).

Data extraction: characterization of the intervention

Two reviewers (G.F. and N.C.) extracted the data in duplicate, and resolved disagreements by discussion. Authors of studies were contacted for clarification when data were incomplete or missing. For each study included in the review, data were retrieved and recorded on specifically dedicated forms. In addition to data included in the PICOS, additional data related to the characteristics and frequency of the intervention, patient adherence to the planned frequency of the intervention, and duration of follow-up (in years) were also recorded.

Quality assessment (risk of bias in individual studies)

A quality assessment of the included RCTs was performed following the Revised Cochrane risk-of-bias tool for randomized trials (RoB 2.0) (updated October 2018; Higgins et al., 2018). Briefly, five main domains for risk of bias were assessed: randomization process, deviations from the intended interventions, missing outcomes, measurement of the outcomes, and selection of the reported result. A risk of bias judgment (among "low risk of bias", "high risk of bias" or "some concerns") was assigned to either each domain (depending on the descriptions given for each individual field) or the entire study.

Risk of bias across studies

The publication bias was evaluated using Funnel plots and the Egger's linear regression method for all outcomes. A sensitivity analysis of the meta-analysis results was also performed (Tobias & Campbell 1999).

Statistical Methods

A Mixed effects meta-analysis model was used to estimate the pooled effect of active treatment versus control for the primary outcome (CAL) and 2 secondary outcomes (PD and BoP). Study was included as a random effect and treatment was a fixed effect. Heterogeneity was assessed using both the Q statistic and I^2 index. In addition, publication bias was determined using funnel plots and Egger's linear regression methods.

For the primary outcome, CAL (mm), a Bayesian NMA model was used to indirectly compare PDT and sub-antimicrobial dose of doxycycline (SDD) using non-informative priors assumed to be normally distributed (i.e. a mean difference between PDT and SDD of 0 and a pooled variance of 10^4) and 100,000 Markov Chain Monte Carlo (MCMC) simulations.

The model structure was a random effects model of the form: Y = Study + Treatment + error, where Y is the observed difference between active intervention and control:

$$\theta_k \sim N(\mu, \tau^2)$$ which means that the observed treatment effect θ_k for each of the studies k=1,2,3 is normally distributed with a common treatment effect μ and common between study variance τ^2. The hyper parameters μ and τ^2 are assumed to be non-informative normal and gamma distributed respectively.

RESULTS

Summary of the literature search and description of the included studies

The flow of study screening and selection is shown in Figure 1. After the removal of 615 duplicates and the exclusion of 5499 records out of 6147 records identified through database search, full text papers were evaluated for eligibility for 33 records. After full text assessment, two records (Krohn-Dale et al., 2012; Carvalho et al., 2015) were included, and one additional record (Reinhardt et al., 2007) that was initially excluded due to the lack of information on mean CAL change but explicitly incorporated CAL assessment among clinical parameters could re-entered in the review after the Authors provided unpublished data on CAL change upon request. The screening and selection process resulted in the inclusion of three studies (Table 1). The list of studies excluded from this review after full text evaluation (along with the reason for exclusion) is reported in Appendix S2. The overall population (based on pooled patient samples from the three included studies) consisted of 177 randomized patients, with a weighted mean age of 55.3 years and 83.6% females. Periodontitis patients enrolled in the included studies were defined as showing generalized, moderate to advanced periodontitis (Reinhardt et al., 2007), chronic periodontitis with proximal CAL≥ 5 mm in more than 30% of teeth (Carvalho et al., 2015), or recurring chronic inflammation (Krohn-Dale et al., 2012). In all studies, a number of persistently diseased or recurring sites (as assessed at the baseline visit) over a pre-determined threshold was a criterion for patient inclusion; at least 2 bleeding sites with PD≥5 mm (Reinhardt et al., 2007), 4 teeth with PD≥ 5 mm, bleeding and/or suppuration (Krohn-Dale et al., 2012), or at least 4 sites with PD ≥4 mm (of which at least 1 site with PD≥ 5 mm) (Carvalho et al., 2015). Intervention was administered daily for 2 years (Reinhardt et al., 2007) or at each SPT visit for the entire follow-up period of 1 year (Krohn-Dale et al., 2012; Carvalho et al., 2015). The frequency of SPT visits was 3 months (Krohn-Dale et al., 2012; Carvalho et al. 2015) or 3-4 months (Reinhardt et al., 2007). Details of the protocol followed for PMPR were provided only in Krohn-Dale et al. study (2012) (Table 1). The assessment of clinical

measurements was performed at all posterior interproximal sites (Reinhardt et al., 2007), at the two deepest, non-adjacent, bleeding or suppurating pockets at each jaw quadrant where investigated treatments had been administered (Krohn-Dale et al., 2012), or at all sites with PD≥ 4mm where investigated treatments had been administered (Carvalho et al., 2015).

FQ#1

For FQ#1, one split-mouth study evaluating Er:YAG laser as a solo, alternative intervention to conventional PMPR was selected (Krohn-Dale et al., 2012). When Er.Yag laser and PMPR were compared (Krohn-Dale et al., 2012), CAL levels remained stable during follow-up in both treatment groups (CAL change of 0 ± 1.20 mm in laser group, CAL gain of 0.2 ± 1.20 mm in control group, with no statistically significant differences between groups (p=0.533).

FQ#2

For FQ#2, two parallel-arm studies evaluating the efficacy of a daily sub-antimicrobial dose (20 mg b.i.d.) of doxycycline (SDD) (Reinhardt et al., 2007) or photodynamic therapy (PDT) with a methylene blue 0.01% photosensitizer and a diode laser with wavelength of 660 nm (Carvalho et al., 2015) as adjunctive intervention to routine PMPR were analyzed. In the Reinhardt study (unpublished data), CAL change was 0.12 ± 0.79 mm and 0.04 ± 0.82 mm at 12 months, and 0.12 ± 0.85 mm and 0.06 ± 0.83 mm at 24 months for SDD and placebo, respectively. A similar CAL gain was reported for PMPR with (0.96 mm) and without (1.54 mm) additional PDT (Carvalho et al., 2015).

Meta-analysis of primary and secondary outcomes

Since the longest observation interval was 12 months in 2 studies (Krohn-Dale et al., 2012; Carvalho et al., 2015) and 24 months in one study (Reinhardt et al., 2007), and the latter included also an assessment of study parameters at 12 months, only the 12-month follow-up was considered for the present analysis. A summary of primary and secondary outcomes from the included studies is given in Table 2.

After pooling all data, the results of the meta-analysis (Table 3, Figure 2) showed an overall mean difference in CAL change from baseline of -0.233 mm (95% confidence interval (CI): -1.065, 0.598; p= 0.351), with no statistically significant differences in CAL change between intervention and control. Similarly, there were no statistically significant differences in changes for PD (overall mean difference in PD change: 0.050 mm; 95%

CI: -1.077, 1.177; p= 0.8662) and BoP (overall mean difference in BoP change: 9.08%; 95% CI: -2.54, 20.71; p= 0.0639).

Tests of heterogeneity and risk of publication bias
No statistically significant heterogeneity or publication bias was detected for any of the outcomes (Table 3). Egger Regression tests were p=0.5032, p=0.8662 and p=0.605 for CAL, PD and BoP respectively. Funnel plot p-values were also not statistically significant with p-values in the same order as those for the Egger regression tests. The value of I^2 for each of the outcomes was zero, suggesting all variability in observed effects sizes was due to sampling error within studies and not heterogeneity. Consequently, funnel plots were not generated due to limited number of studies. However, since the number of studies were small, the power of these tests was likely to be low to detect heterogeneity and publication bias.

Indirect comparisons between PDT and SDD
Results of the indirect comparison between PDT vs SDD showed a posterior mean CAL of 0.660 mm in favour of SDD with a posterior 95% credible interval (C_rI) of 0.31 to 0.99 : thus, there is a 95% probability that the true difference in mean CAL between PDT and SDD (in favour of SDD) lies between 0.31 to 0.99 mm. The 95% C_rI excludes the value of 0 and, therefore, the equivalent p-value would be <0.001: changes in CAL with SDD are significantly higher than PDT.

Risk of bias in included studies
The risk of bias for the selected papers are illustrated in Table 4. While the study by Carvalho et al. (2015) was judged at a low risk, the remaining two studies (Reinhardt et al., 2007; Krohn-Dale et al., 2012) presented some concerns due to deviations from the intended interventions.

DISCUSSION
Summary of main results
The present systematic review aimed at evaluating the efficacy of different therapeutic protocols other than PMPR during SPT. RCTs of at least 1-year duration assessing the clinical outcomes of different procedures, used either as an alternative or in addition to supra- and subgingival dental biofilm removal, were considered. CAL change from the first administration of intervention or control treatment was the primary variable. Three studies were selected for data extraction, one addressing FQ#1 (Krohn-Dale et al., 2012) and two addressing FQ#2 (Reinhardt et al., 2007 published and unpublished data; Carvalho et al., 2015). After pooling all data,

the results of the meta-analysis show no statistically significant differences in primary (CAL change) and secondary (PD and BoP reduction) outcomes of the investigated interventions to PMPR. In particular, PMPR session performed with a 3-month frequency with either a combination of ultrasonic/hand instruments or Er:Yag laser showed similarly effective in preventing CAL loss and reducing PD at pockets ≥ 5 mm with persisting or recurring gingival inflammation. Moreover, a routine SPT regimen (i.e. 3-4 month yearly recalls) based on PMPR led to stability of CAL irrespective of a daily SDD. Finally, an adjunctive PDT did not enhance the magnitude of CAL gain when sites with PD≥ 4 mm were repeatedly treated.

Overall completeness and applicability of evidence

Three studies met the eligibility criteria for this review, all of which had small sample sizes and featured diverse designs, interventions and outcome reporting, any inferences made from this review must be guarded.

The similarity in clinical effectiveness between Er:Yag laser monotherapy and mechanical instruments when used to perform PMPR during SPT is consistent with previous studies where similar intra-group improvement in clinical parameters was reported during maintenance of periodontitis patients (Tomasi et al., 2006; Ratka-Krüger et al., 2012). Data also suggested that the intensity of pain sensations are lower following use of Er:YAG laser compared to sonic scaler instrumentation during SPT sessions (Braun et al., 2010). Collectively, these results seem to indicate that Er:Yag laser may represent an alternative method to PMPR with ultrasonic/hand instruments in SPT. However, the level of evidence is low (based on a single, split-mouth RCT of 15 patients) and thus the strength of recommendation should be carefully evaluated. It should also be considered that, while the favorable cost-benefit ratio of PMPR performed with mechanical and hand instruments is well supported by the existing literature (Gaunt et al., 2008; Pennington et al., 2011), no cost-benefit or cost-effective analyses are currently available for the application of Er:Yag laser in periodontal maintenance.

SDD, 20 mg twice daily for 2 weeks, significantly reduced collagenase activity in the gingival crevicular fluid and gingival tissues of patients with adult periodontitis (Golub et al., 1990). Evidence indicates that SDD also contributes to decreased connective tissue breakdown by downregulating the expression of proinflammatory mediators and cytokines (Golub et al., 2001). A systematic review (Moreno Villagrana & Gómez Clavel, 2012) reported that the host modulating agent was effective in improving CAL and reducing PD when administered as an adjuvant in the non-surgical treatment of chronic and aggressive periodontitis. However,

our study showed that PMPR either alone or associated with daily adjunctive administration of SDD resulted in stable CAL level after 2-year SPT in post-menopausal women.

The antibacterial effect of PDT involves the interaction between a photoactivable compound (such as toluidine blue, methylene blue or indocyanine green), which is taken up preferentially by bacteria, and low energy laser light in the presence of oxygen molecules. The conversion of energy during photoactivation process produces highly reactive singlet oxygen and free radicals which exert cytotoxic effect on bacteria, including periodontal pathogens, and their products which were shown of clinical benefit in non-surgical treatment of periodontitis patients (Sgolastra et al., 2013). In our material, the selected study failed to show any additional benefit on CAL gain as well as PD and BoP reduction for repeated applications of additional PDT to PMPR during maintenance. These findings contrast with those by a recent secondary analysis of 4 RCTs addressing the potential efficacy of PDT as an adjunct to PMPR in the treatment of residual pockets during SPT which indicated a significant improvement (as PD reduction and CAL gain) in favor of the combined therapy (Xue & Zhao, 2017). Differences may be partly explained by more stringent inclusion criteria used in the present study in terms of sample size (Lulic et al., 2009) or duration of the follow-up (Chondros et al., 2009; Campos et al., 2013; Corrêa et al., 2016).

Limitations

Due to the area of research under investigation, and although a broad literature search strategy (including split-mouth studies) was used, the paucity of studies fulfilling search criteria is regrettable. It must therefore be recognized that strong conclusions cannot be drawn from the data. Also, there was no analysis of the level of agreement between reviewers, and studies assessing just one site were excluded from the systematic review.

Study inclusion was restricted to sufficiently powered RCTs in terms of sample size that had been conducted on adult periodontitis patients with a follow-up of at least 1 year following the first administration of intervention/control treatment during SPT. A limitation of the method of this meta-analysis, despite all trials being RCTs, relates to the differences in procedures, visits, dosing and exposure of interventions. Also, two study designs were considered for inclusion: 1) trials where patients had undergone intervention or control treatment and had been followed up for a period of at least 1 year without receiving any other treatment, and 2) trials where patients had received intervention or control treatment at each SPT visit for a period of 1 year or more. In contrast, studies where patients receiving a single intervention or control treatment had then been

entered an identical SPT protocol were excluded from the review. Although these criteria may have limited the number of included studies with a potential impact on the level of evidence and strength of recommendations, stringent criteria for study inclusion have resulted in the isolation of a group of studies where the true effect of either a single administration or multiple sessions of the investigated treatments could be clearly extrapolated. When considering that in all included studies PMPR was homogeneously administered every 3-4 months as suggested by the existing evidence (Trombelli et al., 2019), data from the present review may be of clinical relevance when evaluating the efficacy of a stringent, effective SPT regimen based on different PMPR protocols in the secondary prevention of periodontitis.

All selected studies were conducted on cohorts of actively treated periodontitis patients who had entered SPT with a pre-determined number of residual pockets. According to the World Workshop for the Classification of Periodontal and Peri-implant Diseases and Conditions, the presence of at least one site with PD≥ 5 mm excludes the possibility to qualify these patients as cases of stable periodontitis (Chapple et al., 2018). Moreover, in two over three studies the efficacy of interventions was limitedly assessed to diseased/unstable sites (i.e., sites with PD≥ 5 mm with or without bleeding or pus upon probing) (Krohn-Dale et al., 2012; Carvalho et al., 2015). Although it may have emphasized the effect of the investigated SPT protocols on the stability or improvement of periodontal conditions at recurrent or persistently diseased sites following APT, this evaluation prevents the possibility to generalize the efficacy of such protocols when applied in either stable periodontitis patients or sites. Available data suggest that the amount/proportion of residual diseased sites (intended as pockets or bleeding pockets) (Ramseier et al., 2019; Trombelli et al., 2019) or the individual risk profile (Lang et al., 2015; Trombelli et al., 2017) may be of value for establishing the maintenance regimen. Interestingly, in none of the studies the investigated intervention has been tailored on disease severity or a risk assessment tool at the beginning of experimental phase. Whether an SPT regimen, based on 3-month sessions, should be simply based on conventional PMPR rather than alternative or additional interventions in patients/sites with different periodontal conditions remains still undetermined.

Conclusions

Collectively, pooled data from a limited number of studies (with a risk of bias ranging from low to some concerns) indicate that, in treated periodontitis patients enrolled in a 3-4 month SPT, alternative (Er:Yag laser) or additional (SDD or PDT) treatments do not produce added clinical benefits to PMPR on the progression of attachment loss during SPT in periodontitis patients.

Implication for practice

Evidence included in the present systematic review supports the following clinical recommendations for oral care providers:

- an SPT program based on 3-4 month recall intervals, each including a session of PMPR performed with ultrasonic and hand instrumentation, is effective in maintaining stable CAL levels in unstable periodontitis patients. Also, sites with residual or persisting diseased characteristics (e.g., deep pockets) may benefit in terms of PD reduction;

- Although data from one study indicate Er:Yag laser as a valid alternative to mechanical/manual instrumentation in SPT, the true benefit from Er:Yag laser monotherapy should be considered with caution since cost-benefit or cost-effective analyses are not currently available;

- Available level of evidence does not indicate the general use of additional SDD to PMPR in order to maintain long-term stable periodontal conditions;

- Additional PDT seems of limited benefit in adjunct to PMPR at residual/persisting pockets during maintenance.

Implication for research

- When planning an RCT on the effect of treatment protocols for SPT, studies should be designed to provide clear information on the true efficacy of either single or multiple administrations of the investigated treatments;

- Studies should include patients and sites with different periodontal conditions and varying level of risk for disease progression at completion of APT to enhance the generalizability of the treatment effect;

- Comparisons among intervention protocols encompassing different frequency and methods of PMPR should include long-term clinical efficacy as well as cost-benefit and cost-effective analysis.

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TABLES

Table 1. Characteristics and main findings of the included studies.

Table 2. Summary of primary and secondary outcomes.

Table 3. Summary of meta-analyses results.

Table 4. Consensus results of the risk of bias assessment.

FIGURE LEGEND

Figure 1. Flow chart of study selection and inclusion.

Figure 2. Forest plots of primary and secondary outcomes.

SUPPLEMENTARY MATERIAL (ONLINE ONLY)

Appendix 1 (S1). MEDLINE search strategy.

Appendix 2 (S2). List of studies excluded from this review after full text evaluation and reasons for exclusion.

Table 1. Characteristics and main findings of the included studies.

Type of study in relation to the investigated intervention	First author (year)	Source of funding	Study population (diagnosis)	Level of residual/persisting disease (as assessed at the baseline visit during SPT)	Study design	Control treatment (n)	Intervention (n)	Frequency of administration of the intervention	Frequency of administration of PMPR during SPT	Duration of follow-up (from the first administration of intervention to last SPT visit)	Main findings
Intervention evaluated as adjunct therapy to routine, conventional PMPR	Reinhardt (2007, unpublished data)	public (National Institute of Dental & Craniofacial Research)	generalized, moderate to advanced periodontitis	≥ 2 bleeding sites with PD≥5 mm	parallel-arm RCT	Mechanical PMPR plus placebo (n= 64)	sub-antimicrobial dose (20 mg b.i.d.) of doxycycline (SDD) (n= 64)	daily	3-4 months	2 years	Conventional PMPR either implemented with daily SDD similarly resulted in stable attachment level (i.e., median relative CAL change= 0 in both groups).
	Carvalho (2015)	public (Sao Paulo	chronic periodontitis with proximal	≥ 4 sites with PD ≥4 mm (of which at least 1 site with PD≥ 5 mm)	parallel-arm RCT	Mechanical PMPR plus pocket	photodynamic therapy (methylene blue	3 months (within each SPT visit)	3 months	1 year	Conventional PMPR either

		State Research Foundati on)		CAL≥ 5 mm in more than 30% of teeth			irrigation with saline solution and application of inactivated laser light (n= 16)	0.01% photosensitizer; diode laser with wavelength of 660 nm) (PDT) (n= 18)				combined or not with PDT similarly resulted in a significant reduction of CAL, PD, BoP and PII at sites with PD≥ 4 mm
Intervention evaluated as alternative to routine, conventional PMPR	Krohn-Dale (2012)	public (Tissue Engineeri ng Research Group, Universit y of Bergen)	patients with recurring chronic inflammation	4 teeth with PD≥ 5 mm, bleeding and/or suppuration	split-mouth RCT	PMPR administered with ultrasonic and hand (curettes) instrumentation (n= 15)	Er:YAG laser (n= 15)	3 months (within each SPT visit)	3 months	1 year	Conventiona l PMPR and Er:Yag laser were similarly effective in maintaining stable CAL and reducing PD at the two deepest, non-adjacent, bleeding or suppurating pockets

Table legend

BoP: bleeding on probing; CAL: clinical attachment level; PD: probing depth; PDT: photodynamic therapy; PMPR: professional mechanical plaque removal; RCT: randomized controlled trial; SD: standard deviation; SDD: sub-antimicrobial dose of doxycycline; SPT: supportive periodontal therapy.

Table 2. Summary of Primary and Secondary Outcomes.

Article	Treatment	Primary outcome CAL gain (mm)		Secondary outcomes PD reduction (mm)		Reduction in BoP score (%)	
		mean	SD	mean	SD	mean	SD
Carvalho (2015)	PMPR + PDT	0.96	n/a	1.24	n/a	34.72	n/a
Carvalho (2015)	PMPR	1.54	n/a	1.64	n/a	26.55	n/a
Reinhardt (2007)	PMPR + SDD	0.12	0.79	0.18	n/a	n/a	n/a
Reinhardt (2007)	PMPR + placebo	0.04	0.82	0.13	n/a	n/a	n/a
Krohn-Dale (2012)	Er:Yag laser	0	1.20	1.90	0.9	14.00	n/a
Krohn-Dale (2012)	PMPR	0.20	1.20	1.40	1.50	4.00	n/a

Table legend

BoP: bleeding on probing; CAL: clinical attachment level; n/a: missing or not provided in article; PD: probing depth; PDT: photodynamic therapy; PMPR: professional mechanical plaque removal; SD: standard deviation; SDD: sub-antimicrobial dose of doxycycline.

Table 3: Summary of meta-analyses results.

Outcome	Intervention Mean (SE)	Control Mean (SE)	Overall Mean Difference (SE) [95% CI]	Test for Homogeneity	Publication Bias (Egger Regression)	Number of studies
CAL gain (mm)	0.795 (0.381)	1.029 (0.381)	-0.233 (0.193) (-1.065, 0.598; p=0.351)	P=0.4433	P=0.5032	3
PD reduction (mm)	1.163 (0.4003)	1.121 (0.4003)	0.050 (0.262) (-1.077, 1.177; p=0.8662)	P=0.2064	P=0.8662	3
Reduction in BOP score (%)	32.99 (6.52)	23.91 (6.527)	9.08 (-2.54, 20.71; p=0.0639)	P=0.3396	P=0.605	2

Table legend

BoP: bleeding on probing; CAL: clinical attachment level; PD: probing depth; SE: standard error.

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Table 4. Consensus results of the risk of bias assessment.

	Krohn-Dale at al. (2012)	Carvalho et al. (2015)	Reinhardt et al. (2007)
Risk of bias arising from the randomisation process	Low	Low	Low
Risk of bias due to deviations from the intended interventions – effect of assignment to intervention	Low	Low	Low
Risk of bias due to deviations from the intended interventions – effect of adhering to intervention	Some concerns	Low	Some concerns
Missing outcome data	Low	Low	Low
Risk of bias in measurement of the outcome	Low	Low	Low
Risk of bias in selection of the reported result	Low	Low	Low
Overall risk of bias	Some concerns	Low	Some concerns

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a Forest plot for CAL change (mm)
Mean difference in change and 95%CI

	Mean difference	Low 95%	Upp 95%	Weight
Reinhardt (2007) (n= 128)	0.080			1.2
Krohn-Dale (2012) (n= 15)	-0.200			0.15
Carvalho (2015) (n= 34)	-0.580			0.225
OVERALL (n= 177)	-0.233	-1.065	0.598	

favors control / favors intervention

b Forest plot for PD change (mm)
Mean difference in change and 95%CI

	Mean difference	Low 95%	Upp 95%	Weight
Reinhardt (2007) (n= 128)	0.050			1.25
Krohn-Dale (2012) (n= 15)	0.500			0.075
Carvalho (2015) (n= 34)	-0.400			0.15
OVERALL (n= 177)	0.050	-1.077	1.177	

favors control / favors intervention

c Forest plot for BoP change (%)
Mean difference in change and 95%CI

	Mean difference	Low 95%	Upp 95%	Weight
Krohn-Dale (2012) (n= 15)	10.00			0.05
Carvalho (2015) (n= 34)	8.170			0.125
OVERALL (n= 49)	9.080	-2.54	20.71	

favors control / favors intervention