Adjunctive therapies for the nonsurgical treatment of peri-implant diseases: systemic review and meta-analysis

yuhan xiao
Sichuan University West China College of Stomatology https://orcid.org/0000-0002-7636-560X
Yichun Qin
Sichuan University West China College of Stomatology
Haiyang Yu (YHYmechanics@163.com)
Sichuan University West China College of Stomatology https://orcid.org/0000-0003-0184-5278

Research article

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Abstract

Background Peri-implant diseases are caused by biofilms around the implant and may lead to implant failure. Non-surgical mechanical debridement (MD) with different adjunctive therapies has been applied in the treatment of peri-implant diseases. This systematic review aimed to deduce the optimal adjunctive therapy.

Methods Two independent authors screened the literature using MEDLINE and Cochrane Library. Only clinical randomized controlled trials (RCTs) about adjunctive therapies for non-surgical treatment of peri-implant diseases were included in this review. Studies selected were published before February 2020. The clinical outcomes were compared in this meta-analysis.

Results: A total of 31 RCTs met the inclusion criteria. The following adjunctive interventions were compared in the included studies: modification of the prosthesis; air abrasive; Er:YAG laser; diode laser; photodynamic therapy; local antibiotics; system antibiotics; probiotics; and enamel matrix derivative. Follow-up ranged from 3 months to 1 year. A statistically significant difference was observed between MD with photodynamic therapy and MD alone at 3 months follow-up ($P < 0.01$). However, such a difference was not detected between MD with chlorhexidine and MD alone at 3 months follow-up ($P = 0.61$), between MD with probiotics and MD alone ($P = 0.47$), and between systemic antibiotics and MD alone ($P = 0.96$).

Conclusion Currently, the optimal non-surgical intervention is not known. Also, among the interventions with similar efficiency, that with fewer side effects, easy to use, and cost-effective is yet to be identified. Thus, well-designed RCTs with prolonged follow-ups to assess the accurate effectiveness of therapies are imperative.

Background

Peri-implant diseases include peri-implant mucositis and peri-implantitis. Peri-implant diseases are inflammatory responses to tissues adjacent to the implant. The inflammatory response of peri-implant mucositis occurs in the mucosa adjacent to the implant without loss of bone. The inflammatory response of peri-implantitis occurs in the mucosal tissue and bone tissue adjacent to the implant, with the loss of marginal supporting bone. [1, 2]. The incidence of peri-implant diseases is high. According to a previous review, peri-implant mucositis occurred in approximately 80% of the patients, and the disease in 28–66% of the patients translated into peri-implantitis [3].

Peri-implant diseases are resulted from oral biofilms around the implant in susceptible individuals, affecting the inflammation of tissues adjacent to the implant [4]. The decontamination of the implant surface and elimination of the oral biofilms and endotoxins are the big challenges in the treatment of peri-implant diseases [5]. Mechanical debridement (MD) is recognized as indispensable, basal procedure in the non-surgical treatment. It improves the outcomes, such as clinical attachment level (CAL) gain and pocket probing depth (PPD) reduction [6]. However, some clinical studies showed recurrence of the peri-implant diseases in a significant percentage of patients several weeks after MD [7, 8]. The complete resolution of the diseases after MD is still not a frequent event.

To assist MD in treating peri-implant diseases, researchers have applied various adjunctive therapies to enhance the clinical outcomes. These adjunctive therapies include: 1) air abrasive; 2) Er:YAG laser; 3) diode laser; 4) photodynamic therapy; 4) local drug delivery (for example, chlorhexidine gel, chloramine, or probiotic); 5) systemic antibiotics; 6) matrix chips; 7) modification of the prosthesis; 8) combination of some of the above therapies. Previous studies compared these adjunctive therapies and obtained different results [9-39]. Thus, a consensus regarding the optimal protocol for non-surgical treatment of peri-implant diseases is yet lacking. A systematic comparison of different adjunctive therapies for the peri-implant diseases has not yet been undertaken. Therefore, the present systematic review aimed to deduce whether one adjunctive therapy of non-surgical decontamination was superior to any other method.

This systematic review was designed and conducted in accordance with the guidelines from the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) 2015 statement [40].

Methods

Inclusion criteria

Only clinical randomized controlled trials (RCTs) that reported adjunctive therapies for the non-surgical treatment of peri-implant diseases published before February 2020 were considered eligible for inclusion in this review. No language restrictions were applied.

Exclusion criteria

Studies requiring an additional surgical technique, such as flap surgery, guided bone regeneration, or any grafting procedure were excluded. Letters to the editor, reviews, cross-sectional studies, case reports, animal studies, *in vivo* studies and *ex vivo* studies were also excluded.

Screening process

Searches were performed without language restrictions in MEDLINE (PubMed) and the Cochrane Library databases until February 1, 2020. For the PubMed library, the key terms used were as follows: (((((oral implant [MeSH Terms]) OR dental implant [MeSH Terms]) AND treatment) OR therapy) AND peri-implantitis). The key terms used for Cochrane Library were as follows: *(Title, Abstract, Keywords):* dental implant AND therapy OR treatment AND peri-implantitis. The electronic search was complemented by manual searches of the reference lists of the selected publications, including *Journal of Clinical Periodontology, Journal of Dental Research, International Journal of Periodontics and Restorative Dentistry,* and the *Journal of Periodontology*, from January 2019 to February 2020.

Two independent reviewers (YX & YQ) screened all the titles/abstracts, and the full texts of the eligible articles were retrieved by the search strategy. Subsequently, the articles that fulfilled the eligibility criteria were included in the present study. The reviewers searched the reference lists of the included articles for additional relevant publications. Any discrepancies between the two reviewers were resolved by discussion with a third reviewer (HY).

Quality assessment

The quality of the included studies (RCTs) was assessed according to the Recommendations for Systematic Reviews of Interventions of the Cochrane Collaboration [41]: random sequence generation and allocation concealment (both accounting for selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias), or other possible causes of bias.

Data extraction and statistical analysis

Two independent reviewers (YX & YQ) extracted the data. The disagreements between the two reviewers were resolved by discussion with a third reviewer (HY). A standardized data extraction form was used to collect the following parameters: 1) author, year; 2) number of patients; 3) number of implants; 4) mean age of the patients; 5) years of implant in function; 6) gender distribution; 7) smoking history; 8) history of periodontitis; 9) length of follow-up; 10) whether following the CONSORT [42]; 11) adjunctive treatments; 10) clinical outcomes, including method of assessment and time intervals..

Meta-analysis was performed using the Review Manager software (Review Manager version 5.3; The Cochrane Collaboration, Copenhagen, Denmark). The statistical heterogeneity among the RCTs selected for meta-analysis was assessed utilizing the DerSimonian–Laird estimate τ^2 for interstudy variance. Because each clinical outcome was evaluated similarly, preferring smaller values, the meta-analysis could be performed together to investigate a standardized mean difference between the clinical outcomes in the groups of adjunctive therapies and MD. Data for each group were summarized using the standardized mean difference and the standard deviation with a 95% confidence interval (CI).

Results

The initial search retrieved 1621 publications from PubMed and 1460 in the Cochrane Library. Four more publications were identified by manual search. After removing the duplicate studies, 1684 publications of potential interest were left to screen. After excluding the articles based on the titles and abstracts, 35 studies were left for full-text assessment. Following a discussion after full-text analysis, 31 studies were included for systematic review and qualitative synthesis. The process of identification of the included studies from the initial yield is described in Fig. 1. The number of patients, mean age, gender distribution, implant data, and adjunctive treatments are listed in Table 1.

Quality assessment

14/31 RCTs were designed according to CONSORT. The results of the quality assessment of RCTs are listed in Table 2, following the recommendations [41]. The difference between the assessment results was low, and the consensus was reached by discussion.

Meta-analysis

Meta-analysis was carried out, including data reporting the mean values of PPD, bleeding of probing (BOP), CAL, and plaque index (PI), comparing the outcomes of MD combined with photodynamic therapy, chlorhexidine, systemic antibiotics, or probiotics with MD alone. The follow-up time for each study was not identical, and so, only the most comprehensive results reported at 3 months were included. For meta-analysis, only the summary measures of each included study were used, because individual dataset could not be extracted from the studies. Subgroup analyses of these studies concerning different clinical outcomes were performed.

Due to different measurement methods, the standardized mean difference was investigated to compare the clinical outcomes in the groups of adjunctive therapies and MD. The standardized mean difference of clinical outcomes (BOP, CAL, PPD) of 0.60 ($CI_{95\%}$ -1.20–2.40) between the MD group with photodynamic treatment and MD group alone differed significantly from 0 ($P < 0.01$) (Fig. 2). Interestingly, the standardized mean difference of clinical outcomes (BOP, PPD) of -0.01 ($CI_{95\%}$ -0.24–0.22) between the MD group with chlorhexidine treatment and the MD group alone did not show any significant difference from 0 ($P = 0.61$) (Fig. 3). In addition, the standardized mean difference of clinical outcomes (BOP, PI, PPD) of -0.26 ($CI_{95\%}$ -0.54–0.03) between the MD group with probiotics treatment and the MD group alone did not differ significantly from 0 ($P = 0.96$) (Fig. 4). Also, the standardized mean difference of clinical outcomes (BOP, PPD) of -0.02 ($CI_{95\%}$ -0.32–0.29) between the MD group with systemic antibiotics treatment and the MD group alone showed no significant difference from 0 ($P = 0.47$) (Fig. 5).

Discussion

Photodynamic therapy involves interactions between a light source and a photosensitizer in an aerobic environment. This results in the generation of free oxygen radicals that damage target cells such as bacterial cells [43]. Photodynamic therapy has also been reported to kill pathogenic microbes associated with the etiology of periodontal and peri-implant disease caused *Aggregatibacter actinomycetemcomitans (A. actinomycetemcomitans), Prevotella intermedia, and Porphyromonas gingivalis (P. gingivalis)* [44]. MD with adjunct photodynamic therapy is more effective in reducing peri-implant PPD than MD alone at 3 months following treatment (Fig. 2). However, the long-term outcomes of MD either with or without photodynamic therapy are comparable [18].

The adjunct use of diode laser did not yield any additional positive influence on the peri-implant healing as compared to MD alone at 3 months or 6 months following treatment [14, 45]. Two included RCTs described the effect of Er:YAG laser (ERL) as an adjunct in the treatment of peri-implant diseases. Studies

have indicated that non-surgical periodontal treatment with an ERL significantly improves the clinical outcomes, based on PPD reduction and gain of CAL [46, 47]. The sites treated with ERL demonstrated an alteration in the mean CAL value from 5.8 ± 1 mm at baseline to 5.1 ± 1.1 mm after 6 months. Frank et al. [12] found that ERL reduces BOP significantly at 6 months after the treatment. Thus, further studies are needed to compare the effectiveness of ERL modality to that of other adjunctive therapies.

A total of two included RCTs evaluated the effect of air abrasive as an adjunct in the treatment of peri-implant diseases [10, 11]. Both found that adjunctive air abrasive treatment seemed to have a limited beneficial effect as compared to MD alone. Air abrasive devices have been shown to be a feasible treatment option in periodontal care because of the potential to effectively erase biofilms [48]. Nonetheless, professional MD can also effectively remove the biofilms from the instrument-accessible sites; thus, the adjunctive effect of air abrasive may be limited.

Chlorhexidine is a commonly used topical drug. As shown in Fig. 3, compared to MD alone, MD with chlorhexidine has a limited beneficial effect at 3 months post-treatment. An included article reported the adjunctive effect of chloramine and found that it could not improve the clinical outcomes of peri-implant diseases [31]. The effects of probiotic *Lactobacillus reuteri* in combination with MD were evaluated in implants with peri-implantitis, and no clinical differences between probiotic and placebo treatments were observed over time [35, 36] (Fig. 4). Conversely, minocycline microspheres as an adjunct to MD treatment of incipient peri-implantitis lesions demonstrated improvements in PPD and BI and the improvements were sustained over 6 months [28, 29]. The state, concentrations, and the method of delivery of topical drugs may affect the effectiveness of the drugs. Dental water jet rinse mixed with chlorhexidine gel might supplement the response to non-surgical treatment for peri-implantitis lesions by reducing the PPD [32]. Some studies demonstrated that repeated application of chlorhexidine chips might resolve the marginal peri-implant inflammation in terms of BOP better than that by chlorhexidine gel, and the PPD was also reduced 0.65 ± 0.40 mm [30, 38]. The efficacy of a single dose is limited, but the repeated application of local drugs can prolong the effectiveness. However, the frequent use of antibiotics causes bacterial resistance in the subgingival biofilm [49]. Currently, there is no consensus on the method of delivery of topical drugs for the treatment of peri-implant diseases, thereby necessitating additional studies.

The standardized mean difference of clinical outcomes (BOP, PPD) between the MD with systemic antibiotics treatment and MD alone was not significantly different from 0 (P = 0.47) (Fig. 5). Hitherto, no evidence is available promoting the use of systemic antibiotics in the treatment of peri-implantitis [33, 34].

Tapia et al. [9] found that modifying the contour of the prostheses after MD significantly improved the clinical outcomes of peri-implant mucositis. This conclusion was correlated to the inclusion criteria of the study, which required the included patients to have at least one implant-supported restoration with an inappropriate prosthesis design or contour that made oral hygiene and access to the implant in the neck difficult. The implant-supported prosthesis design is critical to promote accessibility to oral hygiene around the implants [50], suggesting a method for the treatment of peri-implantitis.

Enamel matrix derivatives have been employed successfully in the management of periodontal diseases, especially bone loss associated with periodontitis [51]. Kashefimehr et al. [39] studied the effects of enamel matrix derivative on the non-surgical management of peri-implant mucositis and found that MD in conjunction with enamel matrix derivative, air abrasive, and 0.12% chlorhexidine mouthwash significantly improved BOP and PPD at 3 months after the treatment. In the group with enamel matrix derivative, PPD reduced from 5.40 ± 1.79 mm to 4.66 ± 1.95 mm. However, additional studies are required to prove the efficacy of enamel matrix derivative in long-terms.

After comparing different adjunctive therapies, we found that the use of ERL or repeated minocycline microspheres as an adjunct to MD treatment for peri-implantitis is better than chlorhexidine gel [12, 28]. The adjunct use of photodynamic therapy was as effective as one unit-dosage of minocycline microspheres or diode laser after 6 months of follow-up [15, 21, 22]. The efficacy of probiotics as an adjunct to the MD treatment was better than that of systemic antibiotics in reducing PPD and mBI (modified bleeding index). Nonetheless, further studies are needed to compare the effectiveness of different adjunctive therapies.

Conclusion

In summary, the current study compared several therapies as adjuncts to the non-surgical MD treatment of peri-implantitis lesions. The results showed that ERL, repeated minocycline microspheres, photodynamic therapy, and modification of prosthesis had significant effects in the short-term (3 months), while air abrasive, chlorhexidine gel, probiotics, and system antibiotics had limited effects. Conversely, ERL and photodynamic therapy did not show any significant long-term effectiveness. These results should be interpreted with caution because only a limited number of studies are included. At present, we do not know which non-surgical intervention is superior, and for the interventions with similar effectiveness, we do not know the one with fewer side effects, ease of use, and cost-efficiency. Thus, it is necessary to conduct well-designed RCTs with longer follow-ups to assess the accuracy and effectiveness of the therapies.

List Of Abbreviations

RCTs: Randomized controlled trials

MD: Mechanical debridement

CAL: Clinical attachment level

PPD: Pocket probing depth

BOP: Bleeding of probing

PI: Plaque index

ERL: Er:YAG laser

Declarations

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

Availability of data and materials

All data generated during this system review are included in this article. The data supporting our findings can be found in articles included in this systemic review.

Competing interests

The authors declare that they have no competing interests

Funding

Not applicable

Authors' contributions

YX had made substantial contributions to the design of the system review, the acquisition and interpretation of data, and the revision of the article.

YQ had made substantial contributions to the design of the work, the acquisition of data, and the revision of the article.

HY (corresponding author) had: (*i*) ensured that original data, figures and materials upon which the submission is based were preserved following best practices in the field so that they are retrievable for reanalysis; (*ii*) confirmed that data, figures and materials presentation accurately reflects the original; and (*iii*) foreseen and minimized obstacles to the sharing of data and materials described in the work. The corresponding author should be responsible for managing these requirements across the author group and ensuring that the entire author group is fully aware of and in compliance with best practices in the discipline of publication.

All authors have read and approved the manuscript.

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Tables

Author, year	Patients (n)	Gender (M/F)	Age (mean/SD, years)		Implants (n)		Years of implant in function (mean/SD)		Current smokers		Follow-up (months)	Follow the CONSORT	A
			T	C	T	C	T	C	T	C			
Tapia et al. 2019	45	23/22	60.9/9.9	61.2/12.9	73	72	10.2/5.4	9.1/4.8	1	1	6 m	Y	T C
Ji et al. 2012	24	10/14	46.2	41.3	17	16	-	-	0	0	3 m	NR	T C
Persson et al. 2011	42	12/29	68.5/6.4	68.9/12.5	55	45	-	-	-	-	6 m	Y	T C
Schwarz et al. 2003	20	12/8	48	51	16	16	4.1	4.3	-	-	6 m	NR	T C d
Arısan et al. 2015	10	3/7	-	-	24	24	-	-	-	-	6 m	Y	T C
Aimetti et al. 2018	220	71/149	58.1/10.1	56.8/10.2	110	110	6.8/3.6	7.4/4.4	14	20	4 m	NR	T C
Birang et al. 2017	20	10/10	-	-	20	20	-	-	-	-	3 m	NR	T C
Rifaiy et al. 2017	38	38/0	33.6/2.8	35.4/2.1	38	27	4.06	4.36	20	18	3 m	Y	T C
Karimi et al. 2016	10	2/8	-	-	15	15	-	-	-	-	3 m	NR	T C
Javed et al. 2016	166	120/46	41.1	39.4	127	122	4.1	4.9	41	43	12 m	NR	T C
Javed et al. 2017	54	54/0	50.6/0.8	52.2 ± 0.5	28	26	-	-	28	26	3 m	NR	T C
Wang et al. 2019	131	48/53	44.1/9.8	42.6 ± 13.0	66	65	-	-	13	21	6 m	Y	T C
Bassetti et al. 2014	40	20/20	59	57	20	20	7.3	7.2	-	-	12 m	NR	T P C M
Schar et al. 2012	40	20/20	59	57	20	20	7.3	7.2	-	-	6 m	NR	T P C M
Heitz et al. 2011	29	-	57	53	14	15	-	-	2	2	3 m	NR	T C
Menezes et al. 2016	37	6/31	57.4/9.1	57.4/13.0	61	58	-	-	-	-	6 m	NR	T G C
Pulcini et al. 2019	46	21/25	61.3/8.9	61.0/12.0	22	24	-	-	2	4	12 m	Y	T C C C
Porras et al. 2002	16	-	-	-	16	12	-	-	-	-	3 m	NR	T & C
Pena et al. 2019	50	21/29	56.0/10.8	61.2/10.6	25	25	-	-	0	1	4.5 m	Y	T L C
Renvert et al. 2008	32	10/22	60.8/12.7	62.4/7.7	57	38	-	-	2	5	12 m	NR	T C
Renvert et al. 2006	30	12/18	65.6/8.6	61.1/8.6	16	14	-	-	5	3	12 m	NR	T C
Sahrmann et al. 2019	32	16/16	60.0	57.5	17	15	5.6/1.6	5.5/1.8	1	3	6 m	NR	T C
Roos et al. 2017	16	-	-	-	16	16	-	-	-	-	3 m	Y	T C

M: male; F: female; T: test group; C: control group; Y: yes; NR: not report.

Author, year	Patients (n)	Gender (M/F)	Age (mean/SD, years)		Implants (n)		Years of implant in function (mean/SD)		Current smokers		Follow-up (months)	Follow the CONSORT	A
			T	C	T	C	T	C	T	C			
Levin et al. 2015	37	19/20	-	-	18	19	-	-	-	-	3 m	NR	T w C
Shibli et al. 2019	40	11/29	-	-	20	20	-	-	-	-	12 m	NR	T C
Hallstrom et al. 2012	43	-	54.6/18.2	54.6/19.8	22	21	10.9/4.6	10.0/5.2	-	-	6 m	Y	T C
Galofre et al. 2018	44	23/21	61.6/12.5	58.4/13.3	22	22	-	-	-		3 m	Y	T L C
Laleman et al. 2020	19	9/10	64/11	69/9	9	10	-	-	0	0	6 m	Y	T L C
Tada et al. 2018	30	8/22	68.8/7.5	65.9/8.8	15	15	8.3/4.2	6.0/2.8	3	1	6 m	Y	T L & C
Machtei et al. 2012	60	25/35	60.95/7.9	57.4/10.5	37	40	-	-	5	5	6 m	Y	T g C c
Kashefimehr et al. 2016	41	21/20	50.0/2.9	45.6/2.9	74	63	2.0/0.2	2.2/0.2	-	-	3 m	Y	T c C c e

M: male; F: female; T: test group; C: control group; Y: yes; NR: not report.

Table 1: Description of Included Studies

author, year	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)
Tapia et al. 2019	Low	High	Low	Low	Low	Low
Ji et al. 2012	Low	Low	Unclear	High	Low	Low
Persson et al. 2011	Low	Low	Unclear	Low	Low	Low
Schwarz et al. 2003	Low	Low	Low	Unclear	Low	Low
Arısan et al. 2015	Low	Unclear	Low	Low	High	Low
Aimetti et al. 2018	Low	Unclear	Unclear	Unclear	Low	Low
Birang et al. 2017	Low	Unclear	Unclear	Low	High	Low
Rifaiy et al. 2017	Low	Low	Low	Unclear	Low	Low
Karimi et al. 2016	Low	Low	Low	Unclear	Low	Low
Javed et al. 2016	Low	Low	Unclear	Unclear	High	Unclear
Javed et al. 2017	Low	Low	Unclear	Unclear	Low	Low
Wang et al. 2019	Low	Low	Low	Unclear	Low	Low
Bassetti et al. 2014	Low	Unclear	Low	Unclear	Low	Low
Schar et al. 2012	Low	Low	Low	Low	Low	Low
Heitz et al. 2011	Low	Low	Low	Low	Low	Low
Menezes et al. 2016	Low	High	Unclear	Unclear	Low	Low
Pulcini et al. 2019	Low	Low	Low	Low	Low	Low
Porras et al. 2002	High	High	High	Unclear	Low	Low
Pena et al. 2019	Low	Low	Low	Low	Low	Low
Renvert et al. 2008	Low	High	Low	Unclear	Low	Low
Renvert et al. 2006	Unclear	Unclear	Low	Low	Low	Low
Sahrmann et al. 2019	Low	Low	Low	Unclear	Low	Low
Roos et al. 2017	Low	Low	Unclear	Low	High	Low
Levin et al. 2015	Low	Low	Unclear	Low	High	Low
Shibli et al. 2019	Low	Low	Low	Unclear	High	Low
Hallstrom et al. 2012	Low	Low	Low	Unclear	Low	Low
Galofre et al. 2018	Low	Unclear	Unclear	Low	Low	Low

author, year	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)
Laleman et al. 2020	Low	Unclear	Low	Low	Low	Low
Tada et al. 2018	Low	Low	Unclear	Low	Low	Low
Machtei et al. 2012	Low	Low	Low	Unclear	Low	Low
Kashefimehr et al. 2016	Low	Low	Unclear	Low	Low	Low

Table 2
Results of the quality assessment of RCTs.

Figures

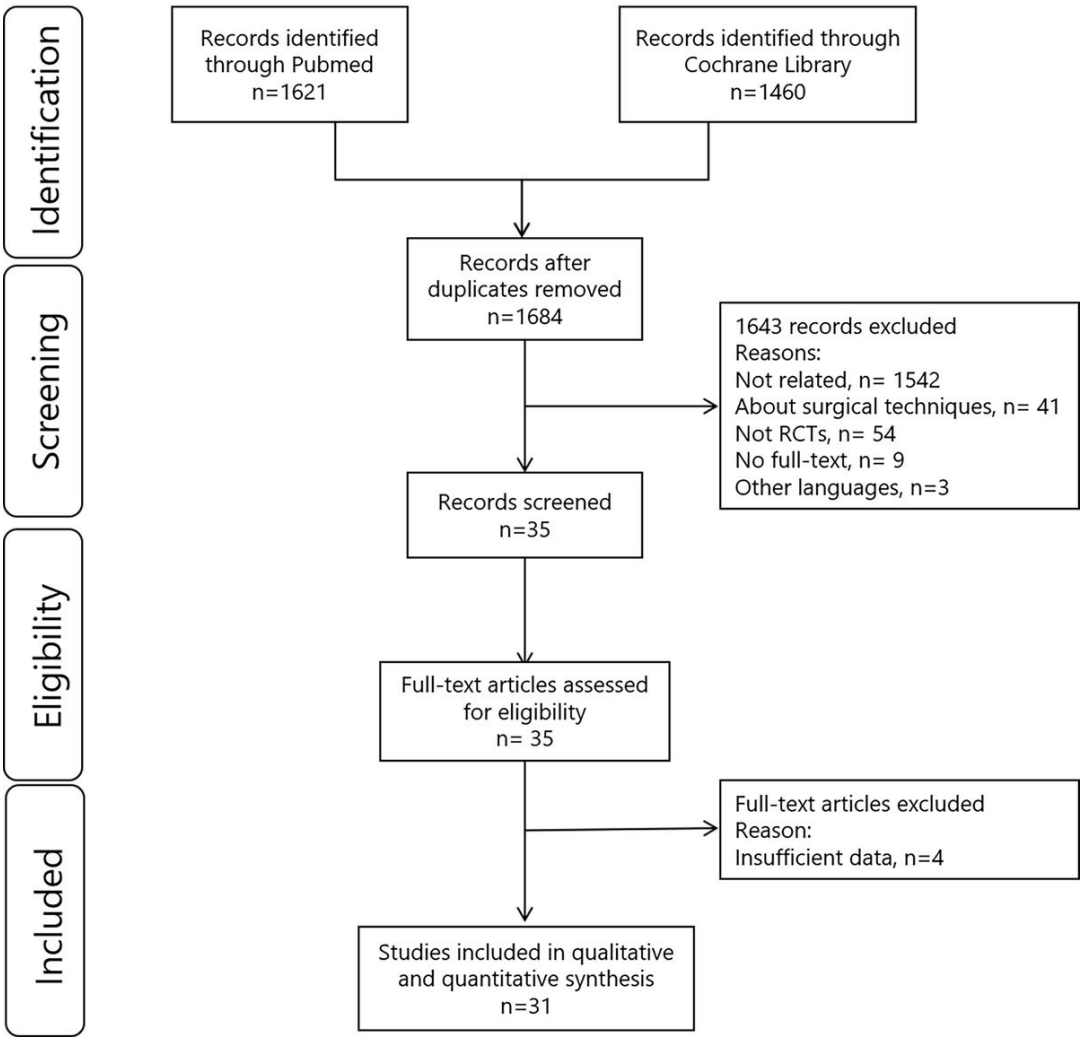

Figure 1

Flow chart of manuscripts screened throughout the review process.

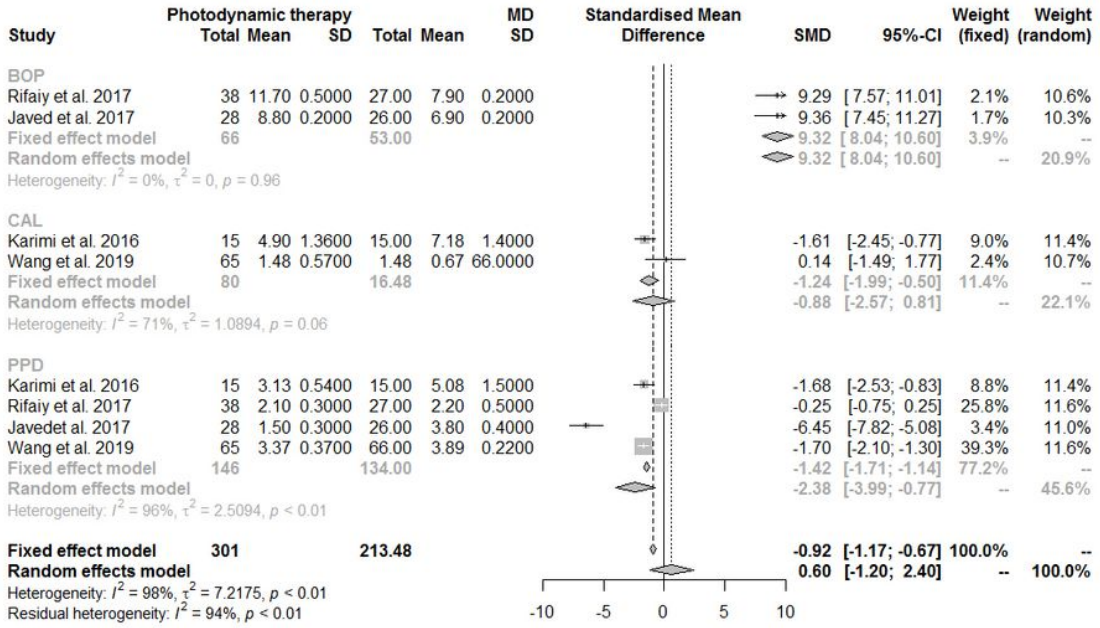

Figure 2

Meta-analysis compares the clinical outcomes of MD with photodynamic treatment versus MD alone after 3 months follow-up.

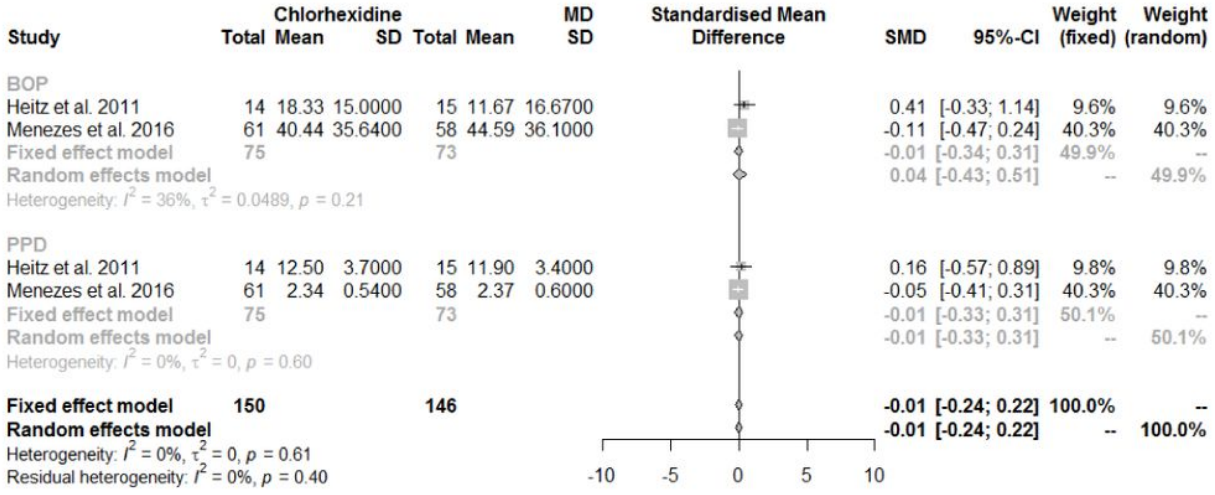

Figure 3

Meta-analysis compares the clinical outcomes of MD with chlorhexidine versus MD alone after 3 months follow-up.

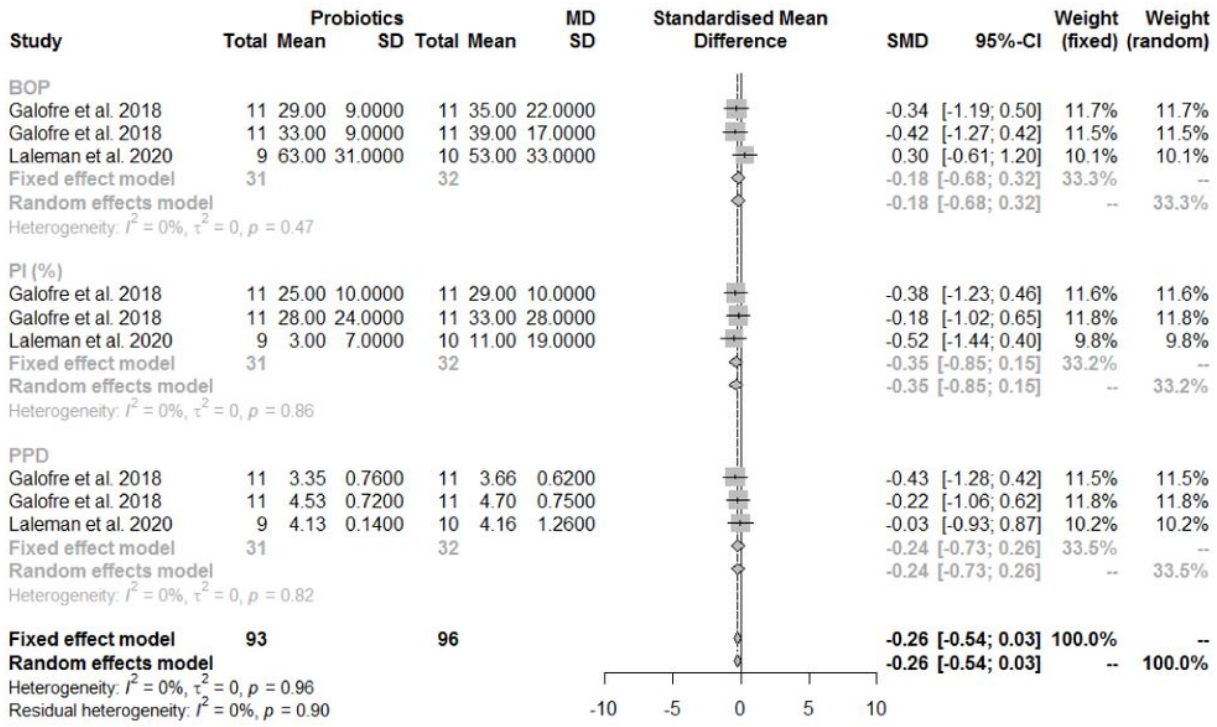

Figure 4

Meta-analysis compares the clinical outcomes of MD with probiotics versus MD alone after 3 months follow-up.

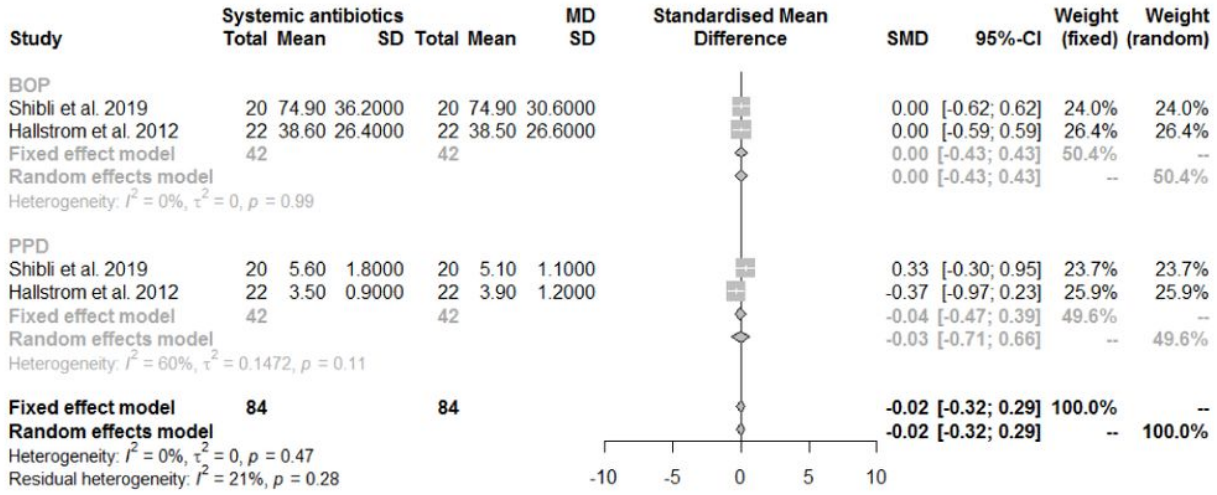

Figure 5

Meta-analysis compares the clinical outcomes of MD with systemic antibiotics versus MD alone after 3 months follow-up.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- PRISMA2009checklist.doc