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Nonsurgical treatment for peri-implant mucositis: a systematic review and meta-analysis

KEY WORDS
chlorhexidine, dental implants, mechanical therapy, nonsurgical treatment, probiotics, triclosan

ABSTRACT

Purpose: To assess the effectiveness of different nonsurgical protocols for the treatment of peri-implant mucositis.

Materials and methods: The identification of randomised clinical trials (RCTs) was systematically performed in three databases and supplemented by a thorough manual search of the literature in periodontics/implantology-related journals. Studies investigating the effect of mechanical and/or chemical plaque control agents aimed at preventing the development of peri-implant mucositis were excluded. When comparable trials were found, a meta-analysis was performed.

Results: Fourteen studies were included in the systematic review and three in the meta-analysis. None of the selected studies reported a complete resolution of the peri-implant mucositis lesions. A nonsurgical therapy alone showed an average reduction of: 0.57 mm (95% CI [0.30 to 0.83]) in probing pocket depth (PPD); 22.41% (95% CI [12.74 to 32.08]) in bleeding on probing (BOP); 17.28% (95% CI [3.99 to 30.58]) in the plaque index (PI); and 13.41% (95% CI [3.50 to 23.31]) in the bleeding index (BI). The meta-analysis failed to demonstrate significant improvements with the adjunct use of chlorhexidine disinfectant to nonsurgical mechanical debridement for PPD reduction (–0.07 mm; 95% CI [–0.33 to 1.15], $P = 0.62$), and relative attachment level (RAL) gain (–0.13 mm; 95% CI [–0.6 to 0.35]), $P = 0.6$).

Conclusion: Conventional nonsurgical mechanical therapy alone may be considered the standard treatment for peri-implant mucositis as there is still a lack of evidence supporting the use of additional chemical/mechanical agents for clinical and/or microbiological improvement.

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Introduction

The long-term success of dental implants has been vastly demonstrated in the literature, rendering them the gold standard procedure for treating edentulous sites[1-4]. Despite promising results of implant therapy, many factors such as peri-implant mucositis and peri-implantitis have been linked to the promotion of implant diseases[5-7]. Among them, biofilm accumulation plays a vital role as the primary aetiologic factor in the development of this inflammatory reaction[8].

The link between bacteria accumulation and peri-implant mucositis/peri-implantitis has been shown in classical articles, where undisturbed plaque accumulation around implants over a period of 3 weeks has been shown to cause inflammation in the surrounding tissues[9]. Consequently, it has

been reported that just as periodontitis follows gingivitis, peri-implant mucositis is considered the precursor of peri-implantitis, which is the inflammation of the mucosa around the dental implant in the absence of marginal bone loss beyond the initial physiologic bone settlement. Hence, similarly to what has been previously reported for gingivitis, peri-implant mucositis is a reversible condition that if properly addressed, can lead to the resolution of the inflammatory infiltration[10].

Inflammation around dental implants is not a rare event; its prevalence has been reported from 20% in compliant patients (enrolled in a periodontal maintenance program)[11], to about 50% in noncompliant patients with sporadic maintenance schedules[5]. Consequently, as for gingivitis, similar protocols aimed at limiting the progression of peri-implant mucositis have been developed and evaluated[12]. The improvement of clinical outcomes around implants after mechanical debridement alone[13,14] and with the adjunctive use of local antiseptic gels and mouthrinses[15], have been observed. Additionally, the adjunctive use of air-polishing devices has shown to be a viable alternative for maintaining peri-implant health[16].

However, which treatment remains the most effective in treating peri-implant mucositis, and to what extent, is still debatable. Thus, the aim of the present study was to assess the effectiveness of different protocols for the treatment of peri-implant mucositis, while evaluating clinical data deriving exclusively from randomised clinical trials (RCTs).

Materials and methods

Reporting format

The protocol of this review was prepared and registered prior to the commencement of the study on the PROSPERO (international prospective register of systematic reviews) database (CRD42019145646) (www.crd.york.ac.uk/PROSPERO). The summary and description of the search process was performed following the 27-item checklist of the PRISMA (preferred reporting items for systematic reviews and meta-analyses) statement[17]. To achieve a preset standard of reporting the systematic review, the AMSTAR (assessment of multiple systematic reviews) guidelines[18] were used as reference.

PI(E)CO – patient, intervention (exposure), comparison, outcome

The focused question was elaborated following the PICO[19] format, where:

P: Patient diagnosed with peri-implant mucositis around implants supported restoration;

I(E): Effect of nonsurgical therapy alone in treating peri-implant mucositis;

C: Effect of the nonsurgical therapy with the adjunctive effect of chlorhexidine, glycine powder air-polishing, probiotic bacteria and photodynamic therapy (PDT);

O: The primary outcome was improvement of clinical parameters (probing pocket depth [PPD], bleeding on probing [BOP], plaque index [PI], and bleeding index [BI]) after nonsurgical mechanical therapy. The secondary outcome was comparing the improvement of clinical outcomes after nonsurgical therapy alone versus additional therapies of mechanical debridement to treat peri-implant mucositis.

Information sources and search strategy

Two calibrated reviewers (SB, AR) performed a literature search for articles written in English without date limit. The search was conducted in a computerised and systematic way until May 2018 using the following terms:

1. MEDLINE: (peri-implant[All Fields] AND ("mucositis"[MeSH Terms] OR "mucositis"[All Fields])) AND english[Language] AND Clinical Trial[ptyp]; (("glycine"[MeSH Terms] OR "glycine"[All Fields]) AND implant[All Fields]) AND english[Language] AND Clinical Trial[ptyp]; (("chlorhexidine"[MeSH Terms] OR "chlorhexidine"[All Fields]) AND (peri[All Fields] AND implant[All Fields] AND ("mucositis"[MeSH Terms] OR "mucositis"[All Fields]))) AND english[Language] AND Clinical

Trial[ptyp]; ((("mucositis"[MeSH Terms] OR "mucositis"[All Fields]) AND implant[All Fields]) AND ("lasers"[MeSH Terms] OR "lasers"[All Fields] OR "laser"[All Fields])) AND english[All Fields]; ("triclosan"[MeSH Terms] OR "triclosan"[All Fields]) AND english[All Fields] AND ("mucositis"[MeSH Terms] OR "mucositis"[All Fields]) AND Clinical Trial[ptyp]; ("mucositis"[MeSH Terms] OR "mucositis"[All Fields]) AND ("probiotics"[MeSH Terms] OR "probiotics"[All Fields] OR "probiotic"[All Fields]) AND Clinical Trial[ptyp].

2. EMBASE: 'mucositis' AND 'implant' AND 'randomized controlled trial'/de.
3. Cochrane Central Register of Controlled Trials: "peri-implant" AND "mucositis" AND "randomized".

In addition, periodontics/implantology-related journals and previous narrative and systematic reviews were also screened, to make sure no articles were left out of the search[20-26]. An electronic screening of the medicine Gray Literature Report (www.opengrey.eu and www.clinicaltrials.gov) was performed to check for ongoing/unpublished trials. The kappa statistic was used to assess the agreement between researchers.

Eligibility criteria

Articles were considered eligible if they met the following inclusion criteria: 1) RCT involving patients with peri-implant mucositis treated with two different methodologies; 2) articles published in peer-reviewed journals.

The exclusion criteria were: 1) case series, prospective cohort studies, retrospective studies, narrative and systematic reviews; 2) animal studies; 3) articles whose patients were treated for peri-implantitis; 4) articles without a definition for peri-implant mucositis.

Data extraction and statistical analysis

During the first stage of the search, articles were excluded based on titles and abstract screening. During the second and final stage, a predetermined data extraction form was used to include the selected articles after screening their full text. Every step was performed by two calibrated reviewers (SB, AR). The data such as patient characteristics, treatment covariates and clinical outcomes, were independently extracted by the same reviewers, and analysed by a reviewer with extensive training and experience in statistical analysis (SB). Descriptive analyses were used to display characteristics, interventions and results of the included trials. The differences between baseline and follow-up data were also calculated whenever possible. To assess the overall effect of nonsurgical treatment and debridement of peri-implant mucositis, the control treatment arms of the RCTs that used nonsurgical therapy were grouped based on the similarity between treatments, and whenever possible, inverse variance-weighted means (WM) of the PPD, BOP reduction, PI and BI reduction were computed for each group of treatment. When all studies were combined, forest plots were produced to visualise the treatment outcomes, and funnel plots were utilised to display heterogeneity.

Additionally, when comparable clinical and treatment outcomes were present in both test and control, a meta-analysis was performed to increase the sample size and the power of the conclusion. A random effects model was used (DerSimonian and Laird's method) to assess the potential for publication bias and methodological differences among studies. The WM, and weighted mean differences (WMD) were obtained with 95% confidence intervals (CI). The forest plots were produced to visualise the differences in groups, and a $P < 0.05$ was deemed significant. Heterogeneity was assessed with Chi-square (χ^2) and the I^2 statistics test. All analyses were performed with the statistical software environment Rstudio for Macintosh (Rstudio, version 1.1.383, Rstudio, Massachusetts, USA) and the metafor package[27].

Risk of bias and qualitative assessment

The assessment of the quality of the selected articles was performed by two investigators (SB and AR) using the Cochrane risk of bias tool for RCTs[28]. The articles were categorised depending

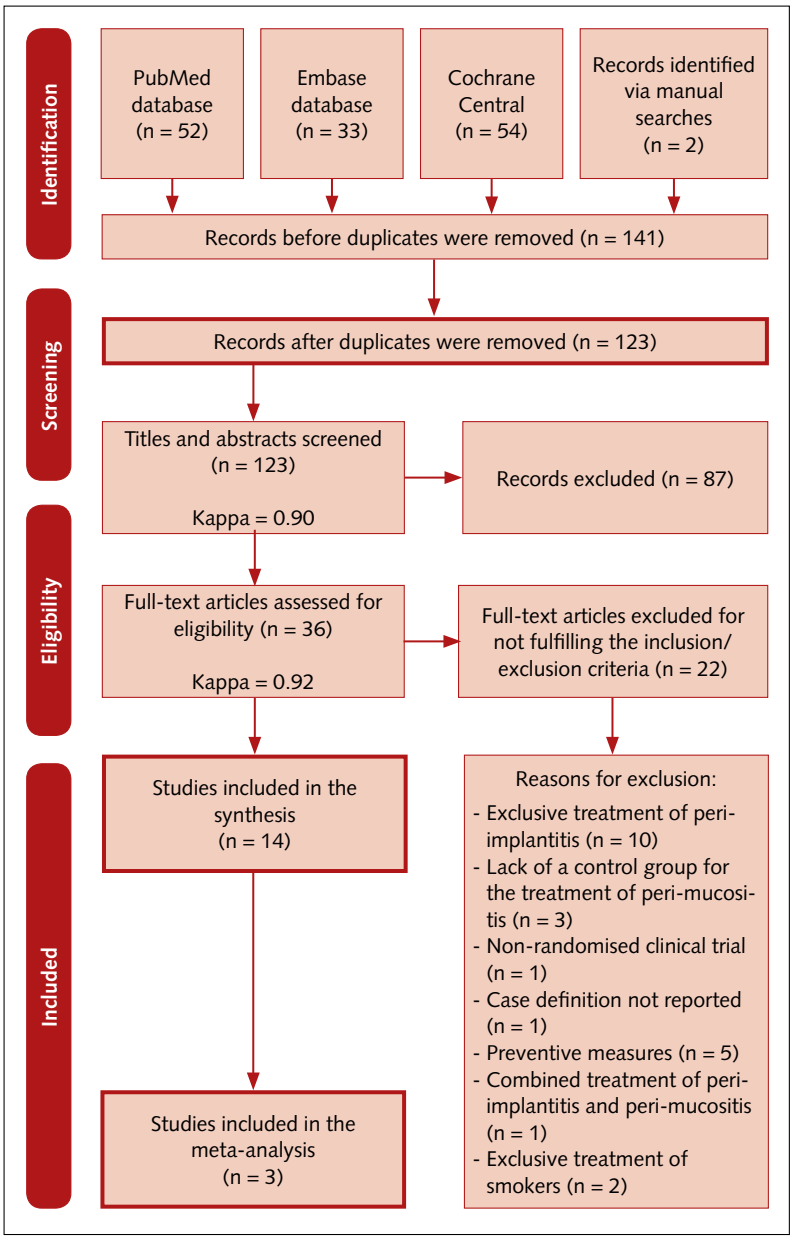

Fig 1 PRISMA flowchart of the screening process performed in different databases.

on the quality of their methodology in low, moderate or high risk of bias according to the used scale.

Results

Study selection

The total search resulted in 141 articles: 52 obtained via PubMed, 33 via EMBASE, 53 via Cochrane Central and three additional articles selected after a manual screening and cross-reference check. Following duplicate removal, 123 records remained for screening by titles and abstract. Two calibrated examiners (SB and AR) screened (in duplicate and independently) the titles and abstracts of the identified entries. Any article considered as potentially relevant was included in the next screening phase. As a result, 36 papers were selected for full-text assessment by the same reviewers. Any disagreement on the eligibility of the studies was resolved through an open debate between both reviewers until an agreement was reached or through settlement by an arbiter (HLW). After thorough evaluation, 22 articles were excluded (Supplementary Table 1), which resulted in a final group of 14 articles, which were used for the analyses (Fig 1). The K value between authors was 0.90 (titles and abstract) and 0.92 (full-text articles).

Quality assessment

The results of the bias analysis for the RCTs are described in the Supplementary Table 2. Overall, eight articles were considered as having a high risk of bias[14,16,29-34], three were categorised as showing a moderate risk of bias[35-37], and three studies demonstrated a low risk of bias[38-40].

Characteristics of the included articles

The characteristics, type of intervention, treatment outcomes and conclusion of all included trials are presented in Table 1. Factors such as the presence of BOP and absence of marginal bone loss (MBL) were common features among studies, while the reported definitions for peri-implant mucositis varied slightly (Table 2).

Effectiveness of nonsurgical mechanical therapy alone to treat peri-implant mucositis

The main treatment outcomes and interventions of all RCTs using nonsurgical mechanical treatment alone (without adjuvant) were extracted and organised in a tabular form (Supplementary

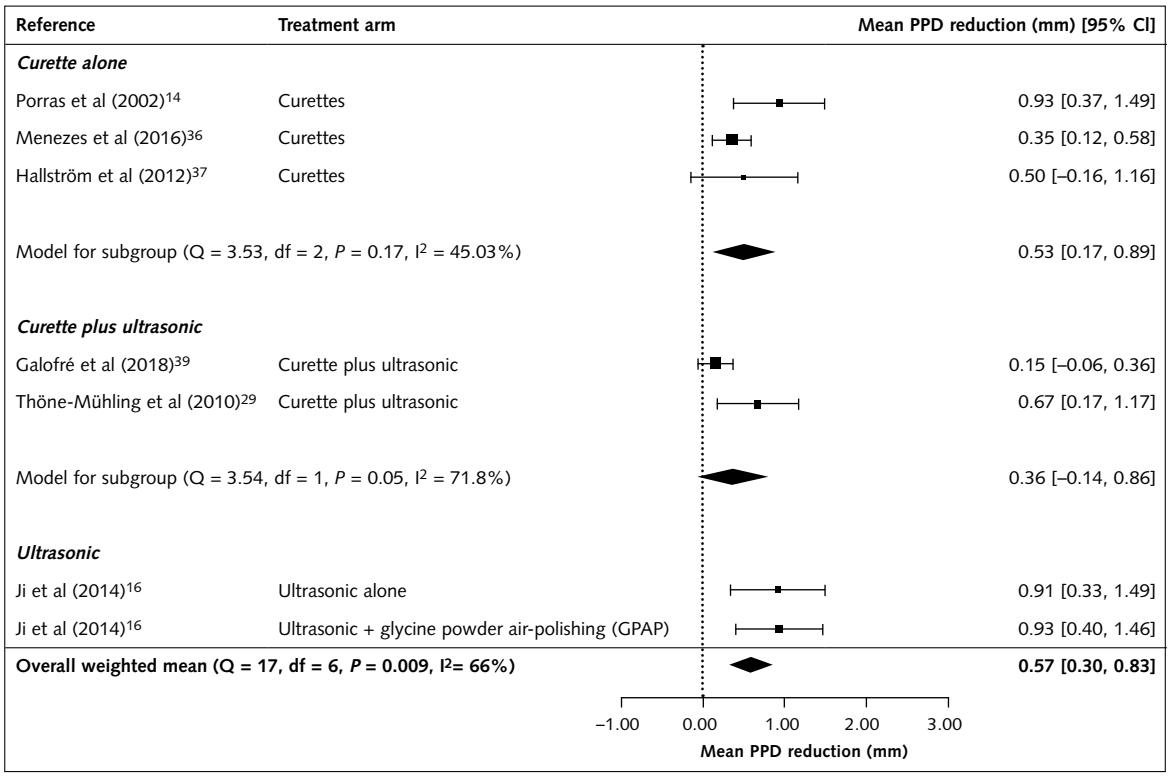

Fig 2 Forest plots showing the WM value for probing pocket depth (PPD) reduction in eight treatment groups, and subgroup analysis for the use of 'curettes alone', and 'curettes + ultrasonic' devices.

Table 3). Based on the treatment similarities, the studies were categorised into three groups: 1) curettes alone; 2) curettes plus ultrasonic devices; 3) ultrasonic. The average WMs for PPD, BOP, PI and BI reduction were calculated for each group and for the group as a whole.

PPD reduction

In three studies[14,36,37] where 'curettes alone' were used in the control treatment arm, an average WM of 0.53 mm (95% CI [0.17 to 0.89]) was found. Furthermore, two studies[29,39] utilising both curettes and ultrasonic devices reported an average of 0.36 mm (95% CI [–0.14 to 0.86]). Therefore, a computed reduction of 0.57 mm (95% CI [0.30 to 0.83]) was observed when all the six articles were analysed together[14,16,29,36,37,39] (Fig 2). As shown by the funnel plots, a considerable heterogeneity was present among the treatment arms (I^2 = 66%, P = 0.009) (Supplementary Fig 1a).

BOP reduction

The percentage of BOP reduction varied among treatment groups that utilised nonsurgical therapies. For the mechanical therapy with curettes alone[36,37], an average reduction of 26.21% (95% CI [15.69 to 36.73]) was observed, while a mean reduction of 13.3% (95% CI [–0.24 to 26.85]) was estimated when curettes were used together with ultrasonic[29,39]. Lastly, an overall reduction of 22.41% (95% CI [12.74 to 32.08]) was noted when all treatment groups using nonsurgical mechanical treatments were combined[29,30,36,37,39] (Fig 3). Considerable heterogeneity was observed among these results (I^2 = 44.13%, P = 0.13) (Supplementary Fig 1b).

PI reduction

An average PI reduction of 22.03% (95% CI [–11.51 to 55.57]) was estimated when only curettes were used[36,37], while a mean value of 9.05% (95% CI [6.69 to 11.4]) reduction was observed when curettes were used together with

Table 1 Characteristics, interventions and outcomes of the included randomised clinical trials for the nonsurgical treatment of peri-implant mucositis

Protocol used	Study characteristics		Inclusion of smokers	Intervention	Patients/ implants (n)	Treatment outcomes* BOP reduction (SD), *P* value	
	Reference	Follow-up time, study design					
Chlorhexidine	Porras et al (2002)[14]	3-month single-blinded RCT	No	Mechanical cleansing + OHI.	N.A./12	NSSD between baseline, and other time points ($P > 0.05$)†	
				Mechanical cleansing (rubber cups, polishing paste, plastic scalers) + OHI + local irrigation with 0.12% CHX using a plastic syringe + topical application of 0.12% CHX gel. Prescription of 0.12% CHX mouthrinse twice a day for 10 days.	N.A./16		
	Thöne-Mühling et al (2010)[29]	8-month RCT	Yes	One-session SRP with curettes and ultrasonic.	5/14	21% (32%)	
				One-session SRP with curettes and ultrasonic + one application of 1% CHX gel subgingivally + 1 minute brushing of the dorsum of the tongue with 1% CHX + 0.2% CHX spray on tonsils once daily for 14 days + 1 minute rinse with 0.2% CHX solution for 14 days.	6/22	8% (19%)	
	Heitz-Mayfield et al (2011)[35]	3-month RCT	Yes	One-time debridement with curettes and polishing pastes + OHI twice a day with placebo gel around implant (for 4 weeks).	14/14	Significant in 1 and 3 months for both groups, without intergroup differences†	
				One-time debridement with curettes and polishing pastes + OHI twice a day with 0.5% CHX gel around implant (for 4 weeks).	15/15		
	De Siena et al (2013)[31]	3-month RCT	Yes	Mechanical therapy + OHI + 0.2% CHX mouthwash twice daily for 10 days.	13/13	N.A.	
				Mechanical therapy + OHI + 0.1% CHX gel for self-administration in pockets twice daily for 10 days.	10/10		
	Menezes et al (2016)[36]	6-month double masked RCT	No	Full mouth SRP + OHI + placebo mouthwash + prescription of twice daily mouthrinse for 14 days.	15/58	22.95% (50.38%)‡, ($P < 0.001$)	
				Full mouth SRP + OHI + 0.12% CHX mouthwash + prescription of twice daily mouthrinse for 14 days.	22/61	35.35% (49.74%)‡, ($P < 0.001$)	
	Hallström et al (2017)[34]	3-month double-blind RCT	Yes	OHI + mechanical debridement (titanium curettes and rubber cup) + once a day brushing with a full brush of placebo gel for 12 weeks.	19/19	4% ($P < 0.05$)	
				OHI + mechanical debridement (titanium curettes and rubber cup) + once a day brushing with a full brush 0.2% CHX gel for 12 weeks.	19/19	4% ($P < 0.05$)	
Glycine powder air-polishing (GPAP)	Ji et al (2014)[16]	3-month single-blinded RCT	No	OHI + nonsurgical debridement (ultrasonic)	12/16	N.A.	
				OHI + nonsurgical debridement (ultrasonic) + GPAP.	12/17		

	Treatment outcomes*					Microbiological results	Conclusion
	PPD reduction (mm)/(SD), *P* value	Bleeding index reduction (SD), *P* value	Plaque index/modified plaque index reduction (SD), *P* value	Keratinised mucosa gain (mm) (SD), *P* value	Relative attachment level gain (mm) (SD), *P* value		
	0.93 (0.99)‡, ($P < 0.01$)	NSSD in either groups at any evaluation point ($P > 0.05$)†	NSSD distribution of plaque scores in different time points among either groups ($P > 0.05$)†	N.A.	1.07 (1.87)‡, ($P < 0.01$)	A marked improvement in all microbial samples at 3 months.	Mechanical cleansing alone may be sufficient for treatment of peri-implant mucositis. Adjunct CHX did not enhance the outcomes.
	0.56 (1.11)‡				0.33 (2.285)‡		
	0.58 (0.21), ($P < 0.01$)	18% (60%)	19% (23%)	N.A.	0.57 (0.29), ($P < 0.01$)	A temporary reduction in bacterial count 24 hours after treatment, without significant differences at 8 months between groups.	One-session nonsurgical treatment of peri-implant mucositis was effective with or without CHX. Addition of CHX did not display any significant differences.
	0.65 (0.55), ($P < 0.01$)	16% (25%)	1% (3%)		0.5 (0.92)		
	Main reduction in the first month, no intergroup differences†	N.A.	N.A.	N.A.	N.A.	The major reduction in mean DNA counts was during the first month, without significant differences between 1 and 3 months, and among groups.	Nonsurgical treatment and oral hygiene was effective with and without adjunct CHX gel, while successful therapy did not always result in complete resolution of the inflammation.
	Decreased with every visit except the last follow-up. More significant in the mouthwash group and during the first month	Significant reduction for both groups compared with baseline. Lacking significant intergroup differences	Significant reduction in both groups after 10 days. Less plaque accumulation in the gel group at the last follow-up ($P < 0.05$)	N.A.	N.A.	N.A.	Both treatments were equally effective. Patients preferred gel over mouthwash, even though it was more difficult to use.
	0.35 (0.91)‡, ($P < 0.001$)	18.53% (36.01%)‡, ($P < 0.001$)	38.36% (41.65%)‡, ($P < 0.001$)	–0.06 (2.26)‡, ($P = 0.4$)	N.A.	N.A.	Nonsurgical mechanical therapy reduces peri-implant mucositis, however the use of CHX was not more effective than placebo.
	0.51 (0.81)‡, ($P < 0.001$)	26.64% (39.65%)‡, ($P < 0.001$)	28.28% (39.91%)‡, ($P < 0.001$)	0.32 (2.47)‡, ($P = 0.4$)			
	15% reduction in sites with ≥ 4 mm PPD	N/A	0% decrease ($P > 0.05$)	N.A.	N.A.	N.A.	If used once a day, oral care brush-on gel (0.2% CHX) can be a beneficial adjunct to mechanical debridement.
	35% reduction in sites with ≥ 4 mm PPD ($P < 0.05$)		7% decrease ($P < 0.05$)				
	0.91 (1.18)‡, ($P < 0.001$)	0.8 (1.53)‡, ($P < 0.001$)	0.2 (0.89)‡, ($P = 0.01$)	N.A.	N.A.	N.A.	Nonsurgical mechanical therapy alone could effectively control peri-implant mucositis, adjunctive GPAP treatment had limited beneficial effects compared with mechanical therapy alone.
	0.93 (1.11)‡, ($P < 0.001$)	0.6 (1.36)‡, ($P = 0.002$)	1 (1.23)‡, ($P < 0.001$)				

Protocol used	Study characteristics Reference	Follow-up time, study design	Inclusion of smokers	Intervention	(n) (patients/ implants)	Treatment outcomes* BOP reduction (SD), *P* value	
Glycine powder air-polishing (GPAP)	Riben-Grundstrom et al (2015)[30]	12-month single-blinded RCT	Yes	OHI + three times treatment with Ultrasonic device throughout the entire follow-up (at baseline, 3 and 6 months).	18/18	35.1% (44.71%)‡, ($P < 0.001$)	
				OHI + three times treatment with GPAP throughout the entire follow-up (at baseline, 3 and 6 months).	19/19	31.8% (36.75%)‡, ($P < 0.001$)	
Triclosan toothpastes	Ramberg et al (2009)[33]	6-month double-blind RCT	Yes	OHI + brushing with a dentifrice containing 0.243% sodium fluoride (6 months).	29 patients (mean 3.5 implants per patient)	–6.5% (36.21%)‡, ($P > 0.05$)	
				OHI + brushing with a dentifrice containing 0.3% triclosan (6 months).	30 patients (mean 3.5 implants per patient)	24.7% (24.36%)‡, ($P < 0.001$)	
Adjunct antimicrobials	Schenk et al (1997)[32]	3-month split mouth RCT	N/R	OHI + supra- and sub-gingival scaling + 0.2% CHX mouthrinse twice daily for 10 days.	8 patients, 12 implants each group	–15% (37%)	
				OHI + supra- and sub-gingival scaling + placement of tetracycline HCL fibres around implants for 10 days and 0.2% CHX mouthrinse twice daily for 10 days.		17% (25%)	
	Hallström et al (2012)[37]	6-month RCT	N/R	OHI + mechanical debridement (curettes and rubber cups).	21 patients	32.5% (42.11%)‡, ($P < 0.02$)	
				OHI + mechanical debridement (curettes and rubber cups) + systemic Azithromycin: 500 mg day 1, 250 mg day 2 to 4.	22 patients	55.3% (31.71%)‡, ($P < 0.02$)	
Probiotics	Mongardini et al (2017)[38]	6-week cross-over double blind RCT	No	OHI + professionally administered plaque removal and PDT + placebo medication for 14 days.	20/20	The number of BOP positive sites was significantly reduced in both groups. (significantly more in the probiotics group)†	
				OHI + professionally administered plaque removal and PDT + systemic and local probiotic (*Lactobacillus plantarum* and *L. brevis*) administration for 14 days.	20/20		
	Galofré et al (2018)[39]	3-month triple-blind RCT	No	Supra-gingival prophylaxis + 30 (placebo) tablets to be dissolved in the oral cavity once daily (30 days).	11/11	7.1% (24%), ($P = 0.377$)	
				Supra-gingival prophylaxis + 30 probiotic tablets (*L. reuteri*) to be dissolved in the oral cavity once daily (30 days).	11/11	32% (24%), ($P < 0.001$)	

Positive changes for BOP reduction and PPD reduction indicate a decrease from the start (baseline) to the end of the study, while negative changes are indicative of an increase in the values. Positive and negative changes for other outcomes indicate an increase in the values at the end of the study, and a decrease at the end of the study, respectively.

*Reported treatment outcomes represent the data at the last follow-up recall compared with baseline; †Exact numbers not specified for numeric and/or statistical comparison among groups; ‡Calculated by the authors based on reported values in the article; §Values expressed in logarithms. BOP, bleeding on probing, CAL, clinical attachment level; CHX, chlorhexidine; mPI, modified plaque index; n, number; N.A., not available; N/R, not reported; NSSD, no statistically significant differences; OHI, oral hygiene instructions; PPD, probing pocket depth; PDT, photodynamic therapy; RCT, randomised clinical trial; SD, standard deviation; SRP, scaling and root planing.

	Treatment outcomes*					Microbiological results	Conclusion
	PPD reduction (mm)/(SD), *P* value	Bleeding index reduction (SD), *P* value	Plaque index/modified plaque index reduction (SD), *P* value	Keratinised mucosa gain (mm) (SD), *P* value	Relative attachment level gain (mm) (SD), *P* value		
	14% reduction in sites with ≥ 4 mm PPD‡, ($P < 0.001$)	7.4% (12.8%)‡, ($P < 0.05$)	16.7% (40.44%)‡, ($P < 0.05$)	N.A.	N.A.	N.A.	Both devices were equally reliable instruments for maintaining implant health, and were effective in reducing inflammation and the number of peri-implant pockets subject to patient compliance.
	17% reduction in sites with ≥ 4 mm PPD‡, ($P < 0.001$)	5.8% (13.12%)‡	19.9% (35.7%)‡, ($P < 0.05$)	N.A.	N.A.	N.A.	
	–0.1 (0.4), ($P > 0.05$)	N.A.	6.4% (23.14%)‡, ($P > 0.05$)	N/A	N/A	N/A	Clinical signs of peri-implant inflammation in the mucosa may have reduced with adjunct use of a dentifrice containing 0.3% triclosan.
	0.3 (0.7), ($P < 0.01$)		1.7% (29.31%)‡, ($P > 0.05$)				
	N.A.	N.A.	–0.01 (0.53)	N.A.	N.A.	N.A.	From the resultant trend towards a reduction in BOP scores in the SRP + tetracycline HCL group, it was concluded that beneficial effects on peri-implant mucositis and hyperplasia may occur from the adjunct application of tetracycline.
			–0.11 (0.15)				
	0.5 (1.54)‡, ($P < 0.01$)	5.8% (24.86)‡, ($P < 0.01$)	4.1% (42.21%)‡, ($P < 0.01$)	N.A.	N.A.	NSSD between study groups, in bacterial counts for all bacterial species, and in changes from baseline to 3, or 6 months	No short-term (6 month) clinical improvements could be attributed to the adjunct use of systemic antibiotics. Oral hygiene may have been the main contributing factor to the improved clinical outcomes.
	0.9 (1.53)‡, ($P < 0.01$)	18.1% (22.36%)‡, ($P < 0.01$)	26.9% (38.73%)‡, ($P < 0.01$)				
	N.A.	N.A.	Reduction of baseline to 0.17 (median mPI), ($P < 0.001$)	N.A.	N.A.	N.A.	The combination of professionally administered plaque removal (PAPR) and PDT was effective in reducing the BOP positive sites in experimentally induced per-mucositis at 2, and 6 weeks. The adjunct use of probiotics did not significantly enhance the clinical outcomes of PAPR + PDT.
			Reduction of baseline to 0 (median mPI), ($P < 0.001$)				
	0.15 (0.36), ($P = 0.187$)	N.A.	9% (4%), ($P < 0.001$)	N.A.	N.A.	0.36 (1.01) increase in total bacterial load in 3 months§	The probiotic *L. reuteri*, combined with the mechanical therapy produced an overall additional improvement, while having very limited effects on the peri-implant microbiota.
	0.48 (0.5), ($P = 0.009$)		16% (17%), ($P = 0.012$)			0.12 (0.88) decrease in total bacterial load in 3 months§	

Table 2 Definition and diagnostic criteria of peri-implant mucositis of the selected studies in chronological order

Reference	Peri-implant mucositis definition
Schenk et al (1997)[32]	PPD ≥ 4 mm, BOP in at least one site per implant, without detectable peri-implant bone loss
Porras et al (2002)[14]	Lesions with supra- and sub-gingival plaque, a PPD ≤ 5 mm, with evidence of inflammation (measured by modified sulcus bleeding index)
Ramberg et al (2009)[33]	According to the definitions by Zitzmann and Berglundh (2008)[50]; Heitz-Mayfield (2008)[5]; Lindhe and Meyle (2008)[15] (i.e., predominantly BOP, redness and swelling of soft tissues)
Thöne-Mühling et al (2010)[29]	BOP with/without a gingival index ≥ 1 at least on one site at baseline and the absence of peri-implant bone loss during the last 2 years before baseline
Heitz-Mayfield et al (2011)[35]	Bleeding on light probing without loss of supporting bone
Hallström et al (2012)[37]	PPD ≥ 4 mm combined with BOP, and/or pus on probing with a 0.2 N probing force
De Siena et al (2013)[31]	BOP or spontaneous bleeding and local swelling with plaque accumulation at the implant-abutment level, without peri-implant bone resorption of > 3 mm (from definitive prosthesis placement)
Ji et al (2014)[16]	At least one implant site with PPD ≥ 4 mm and BOP positive, without detectable loss of supporting bone (compared with radiographs immediately after restoration)
Riben-Grundstrom et al (2015)[30]	Presence of at least one site with PPD ≥ 4 mm (0.2 N) combined with BOP with or without suppuration, with bone loss of ≤ 2 mm (from the implant shoulder due to bone remodelling during initial healing)
Menezes et al (2016)[36]	Implant with PPD ≤ 5 mm and BOP without radiographic evidence of bone loss beyond the first two threads of the implant (according to Mombelli et al [1999][51])
Hallström et al (2017)[34]	PPD ≥ 4 mm, combined with BOP and/or pus with a probing force of 0.2 N, excluding bone loss of more than 2 mm (compared with radiographs at prosthetic delivery
Mongardini et al (2017)[38]	Peri-implant PPD ≥ 4 mm, distance between the peri-implant bone crest and the implant shoulder < 2 mm, negative to BOP
Galofré et al (2018)[39]	An implant with an inflamed mucosa with BOP and/or suppuration, with no evidence of radiographic bone loss (criteria by the VIII European Workshop on Periodontology, Atieh et al [2013][52], and the American Academy of Periodontology [2013][53] for a definition of mucositis)

BOP, bleeding on probing; PPD, probing pocket depth.

ultrasonic devices[29,39]. Finally, an overall average of 17.28% (95% CI [3.99 to 30.58]) was estimated for all treatment groups that used nonsurgical mechanical therapies (Fig 4). A low heterogeneity was observed among the subgroup 'curettes plus ultrasonic' ($I^2 = 0\%$, $P = 0.63$), whereas considerable heterogeneity was noted in the subgroup 'curettes alone' ($I^2 = 90.12\%$, $P = 0.005$), and the overall WM average ($I^2 = 82.52\%$, $P < 0.001$) (Supplementary Fig 1c).

BI reduction

BI outcomes were not commonly reported among trials, being reported only in four articles[29,30,36,37], which allowed us to include them in the analysis. A small subgroup analysis of two studies[36,37] where 'curettes alone' were used to treat peri-implant mucositis showed an estimated average WM for BI reduction of 12.44% (95% CI [–0.02 to 24.91]). Overall, the BI reduction was 13.41% (95% CI [3.50 to 23.31]) (Fig 5). A moderate amount of heterogeneity was observed for both analyses ($I^2 = 68.04\%$, $P = 0.07$ for the subgroup 'curettes alone'; $I^2 = 70.75\%$, $P = 0.02$ for the overall estimation) (Supplementary Fig 1d).

Adjuvant treatment to the mechanical nonsurgical therapy

Chlorhexidine

Six RCTs studied the efficacy of chlorhexidine as an adjunctive factor for the treatment of peri-implant

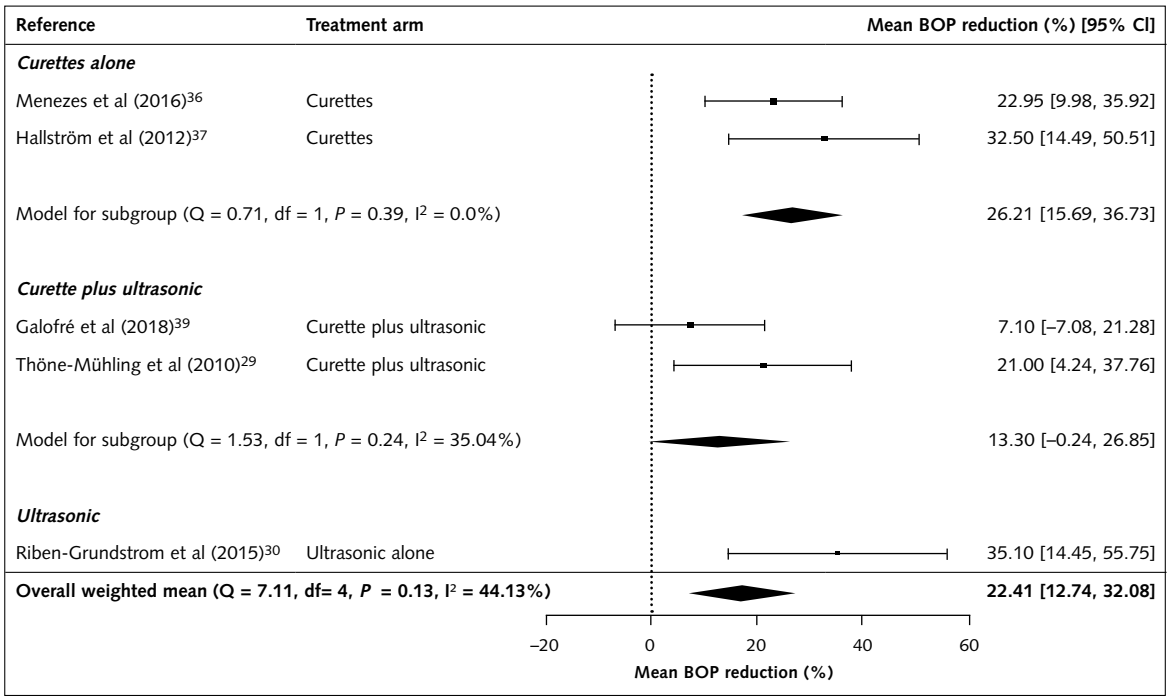

Fig 3 Forest plots showing the WM value for bleeding on probing (BOP) reduction for eight treatment groups, and subgroup analysis for the use of 'curettes alone', and 'curettes + ultrasonic' devices.

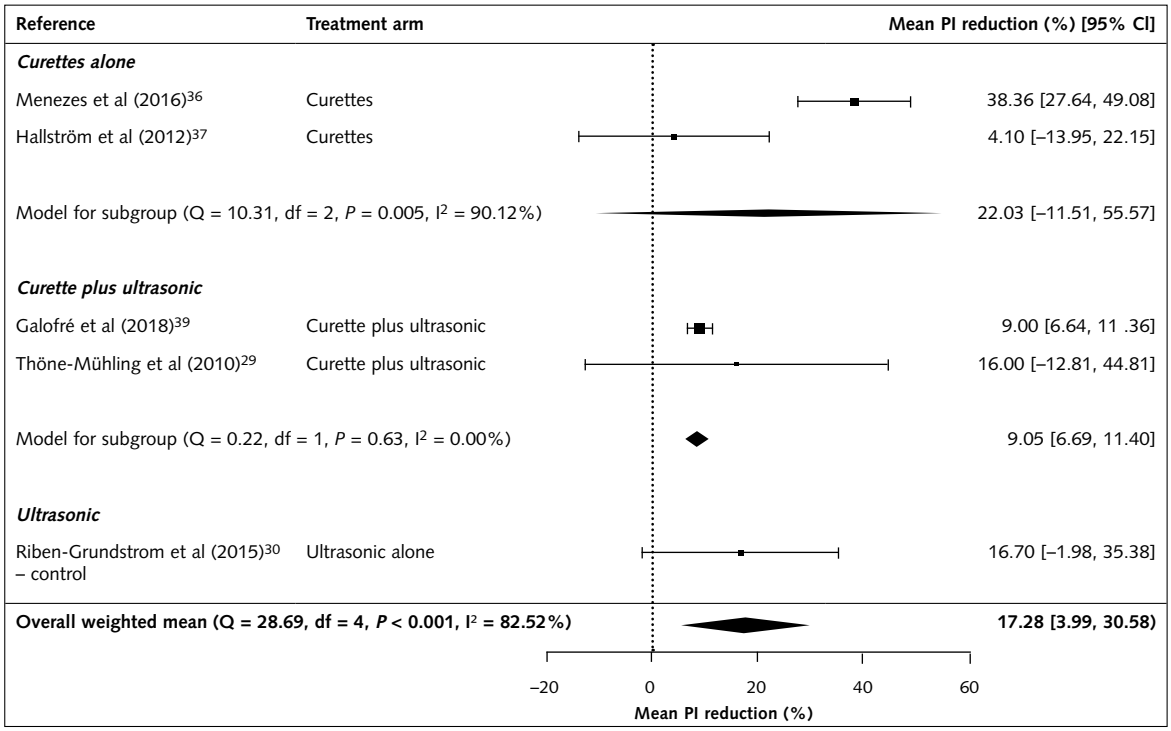

Fig 4 Forest plots showing the WM value for plaque index (PI) reduction for eight treatment groups, and subgroup analysis for the use of 'curettes alone', and 'curettes + ultrasonic' devices.

mucositis[14,29,31,34-36]. Menezes et al[36] reported that the nonsurgical therapy alone was sufficient to improve the clinical parameters, since the combined use with chlorhexidine lacked additional benefits. Similar conclusions were reported by two other trials using both chlorhexidine gel and mouthrinse[14,29]. Hallström et al (2017)[34] studied different forms of chlorhexidine (gel or mouthrinse) in addition to mechanical debridement, to evaluate which was most effective in improving clinical parameters. Again, no differences were found between test and control[34].

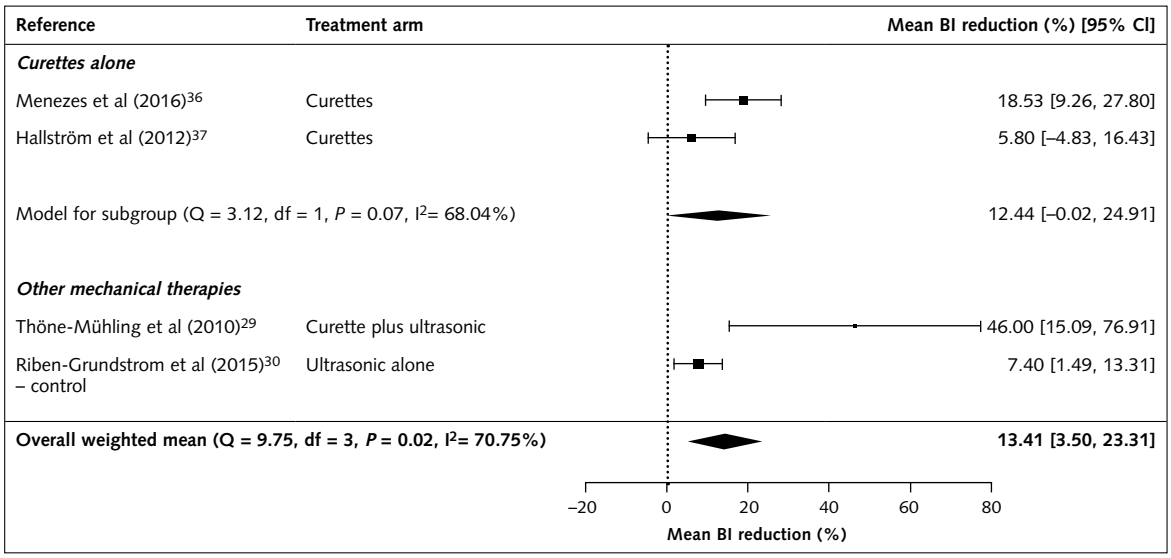

Fig 5 Forest plots showing the WM value for bleeding index (BI) reduction for five treatment groups, and subgroup analysis for the use of 'curettes alone'.

Heitz-Mayfield et al[35] compared a nonsurgical mechanical therapy for implants diagnosed with peri-implant mucositis with a 4-week chlorhexidine gel treatment (test) and without (control), and concluded that both groups showed significant reduction in clinical signs of inflammation around the implants, while lacking statistically significant differences between test and control groups. Finally, De Siena et al (2013)[31] evaluated the effect of daily brushing with a full brush 0.2% chlorhexidine gel versus placebo gel after mechanical debridement, and reported that the active treatment reduced the local bleeding on probing when compared with placebo.

Meta-analysis of nonsurgical mechanical therapy alone versus nonsurgical mechanical therapy + chlorhexidine

Three trials evaluating the adjunct application of chlorhexidine for the treatment of peri-implant mucositis were compared via a meta-analysis for the clinical parameters: PPD reduction and attachment level changes[14,29,36]. Data from the baseline (before treatment) and at 3-[14,36] and 4-month[29] follow-up visits were extracted for a more homogenous and uniform comparison among the trials. The results of the meta-analyses were captured by forest plots (Fig 6).

1) PPD reduction:
Based on the three studies included, the WMD in PPD reduction between the test group (patients who received adjunct chlorhexidine) and control (patients who received mechanical therapy alone) was –0.07 mm (95% CI [–0.33 to 0.20]), which lacked statistical significance ($P = 0.62$) and heterogeneity ($I^2 = 0.0\%$, $P = 0.43$).

2) Relative gain in attachment level:
The comparison between changes in attachment level was only possible for two studies[14,29], where a WMD of –0.13 mm (95% CI [–0.60 to 0.35]) failed to demonstrate any significant difference between the test and control groups ($P = 0.6$) and a low heterogeneity was noted ($I^2 = 0.0\%$, $P = 0.04$).

Glycine powder air-polishing (GPAP)

A 3-month RCT[16] evaluated the efficacy of adjunct GPAP to the use of curettes and ultrasonic devices. The results demonstrated that the nonsurgical therapy alone could effectively improve clinical outcomes such as PPD, PI and BI, not justifying the additional use of GPAP[16]. Riben-Grundstrom et al[30] compared the effectiveness of ultrasonic devices versus GPAP alone in the reduction of peri-implant inflammation and concluded that both treatment modalities were equally effective in maintaining health around implants. The authors

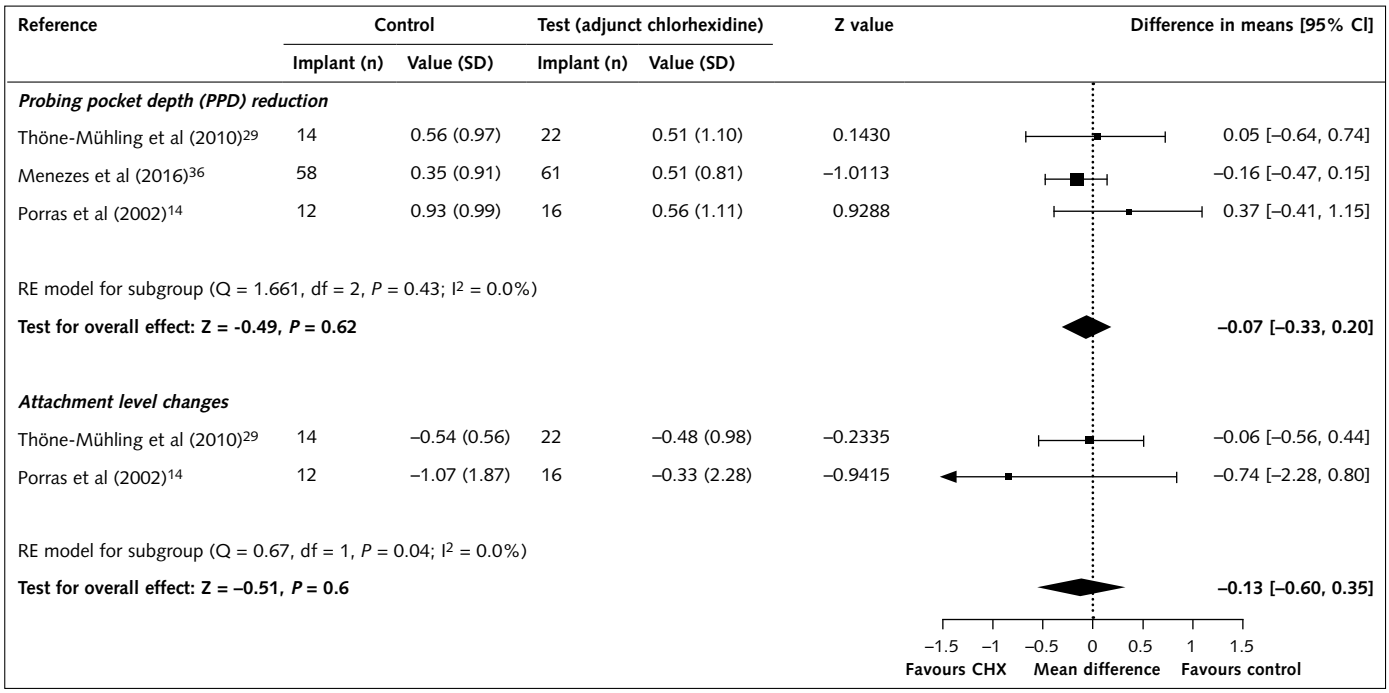

Fig 6 Forest plots of meta-analysis evaluating the additional effect of chlorhexidine. Weighted mean values for the parameters: probing pocket depth (PPD) reduction and attachment level changes. CHX, chlorhexidine.

further highlighted the difficulties they encountered in achieving complete resolution of the pre-existing inflammation in all tissues.

Triclosan

The possible benefits of toothpastes containing triclosan was examined in a parallel-arm study[33]. The results showed that the use of this agent could lead to improved overall clinical signs of peri-implant inflammation when compared with fluoride, during a period of 4 months.

Antimicrobials

The supplemental use of antibiotics in the treatment of peri-implant mucositis was tested in two RCTs. Schenk et al[32] studied the additional benefits of locally delivered tetracycline when inserted and maintaining the peri-implant tissues for 10 days. The slightly better results found in the antibiotic group lacked statistical significance[32]. Hallström et al[37], in a 6-month study, evaluated the short-term use of a systemic antibiotic (azithromycin) in addition to nonsurgical mechanical debridement. Statistical analyses failed to identify microbial advantages for the adjunct treatment with azithromycin when compared with the control group (without azithromycin), and there were no significant clinical benefits due to the medication[37].

Probiotics therapy

The clinical and microbiological effects of oral probiotic bacteria apllied as adjuvants to nonsurgical therapy were evaluated by Galofré et al[39], who used a conventional mechanical prophylaxis with a probiotic (*Lactobacillus reuteri*); the administration was compared with nonsurgical therapy plus placebo tablets throughout a period of 30 days. Over the follow-up period, the probiotic group showed a significant overall improvement in the clinical outcomes (full-mouth and implant PI, BOP and PPD reduction). However, only limited effects on the sub-gingival microbiota were noted. Mongardini et al[38] assessed the adjunct clinical use of probiotics (*L. plantarum* and *L. brevis*) combined

with professionally administered plaque removal and PDT. At 6 weeks, both test and control (placebo) groups showed a significant reduction in the number of bleeding on probing positive sites, however additional results with the probiotic regimen were not found[38].

Discussion

In the current literature, different inclusion criteria have been used to define peri-implant mucositis. Several studies have implemented common parameters such as the presence of bleeding of probing and absence of marginal bone loss, with other factors such as supra and sub-gingival plaque[14,31], pocket depth[14,34] and gingival index ≥ 1[29]. However, regardless of the different definitions available for this disease, the main goal of the treatment of peri-implant mucositis is the elimination of calculus and biofilm around dental implants, to promote health and prevent breakdown of the peri-implant tissues[35].

The aim of the present systematic review and meta-analysis was to assess the reduction of clinical parameters after nonsurgical therapy, and whenever possible, to compare the effectiveness of different treatment protocols introduced to manage inflammation around implants in both edentulous and partially edentulous patients. It should be noted that articles investigating the efficacy of patient-administered plaque control regimens, employing different kinds of toothpastes/toothbrushes or other devices, have been excluded[41,42] from the analysis. Indeed, the main objective of the present study was to study a sample of 'diseased' patients rather than assessing the efficacy of different protocols aimed at preventing the development of peri-implant mucositis caused by experimental undisturbed peri-implant plaque accumulation. Furthermore, to increase the quality of the review and guarantee a fair comparison between patient-administered mechanical and/or chemical plaque control protocols, only RCTs were selected.

The literature search and an in-depth review of the articles revealed that the test and control groups of only a few studies were statistically comparable due to the wide heterogeneity observed among groups and the lack of standardisation in reporting outcomes. An example was the comparison between mechanical scaling alone (debridement of the implant surface, abutment and neck) and the adjunctive effect of chlorhexidine. Indeed, only three[14,29,36] out of the six RCTs[14,29,31,34-36] utilising chlorhexidine, allowed us to perform a meta-analysis, and this was limited at PPD reduction and RAL changes. However, it should be noted that to the best of our knowledge, the present meta-analysis is the first study on the effectiveness of different protocols used to treat peri-implant mucositis.

The lack of a statistically significant benefit from the additional use of chlorhexidine is in agreement with Heitz-Mayfield et al[35] who conducted a randomised placebo-controlled double-blind study, where implants diagnosed with peri-implant mucositis were treated and followed for a 3-month period. Further histological evidence confirmed the lack of additional benefits of the mechanical therapy when the experimental peri-implant mucositis lesions were induced in cynomolgus monkeys. Indeed, histometric analyses showed that the mechanical treatment alone was effective in the resolution of peri-implant lesions[43]. From the results of the above-mentioned studies, it can be concluded that mechanical debridement alone, without the need for the additional use of chlorhexidine, is effective in reducing the number of bacteria below the critical mass[44], and in re-establishing peri-implant health.

The effectiveness of air-polishing in removing dental plaque around teeth has been shown in several clinical studies[45-47], prompting the introduction of this device in the treatment of peri-implant mucositis. However, as previously observed with chlorhexidine, air-polishing failed to provide additional benefits as an adjunct to nonsurgical therapies[16], demonstrating equal effectiveness to ultrasonic debridement in a 12-month study[30]. This confirms that regardless the treatment selected, an effective plaque control is the primary factor to re-establish peri-implant health.

Based on the successful results of adjunct antibiotics in the treatment of periodontitis[48,49], further attempts of improving clinical parameters have

been made by implementing nonsurgical therapies with systemic[37] or controlled local antibiotics[32]. Once again, the absence of clinical benefits was reported for both local and systemic antibiotics.

Although the beneficial results of nonsurgical therapy with or without adjuvants in the treatment of peri-implant mucositis are evident, it should be noted that none of the studied protocols reported a complete resolution of all the inflamed peri-implant sites. In our analysis, an important factor to consider was that the reduction in the analysed clinical parameters might have depended on the initial baseline values, which were not equal among the selected trials. Consequently, the computed results should be interpreted with caution as they only indicate the approximative improvement of a certain outcome after nonsurgical therapy. Indeed, the considerable heterogenicity and the limited comparable articles in the meta-analysis restricted the power of the analysis, and hence the reliability of our results. Therefore, more RCTs with a larger sample size are necessary to confirm our findings.

Conclusions

Within the limitation of the present study, it can be concluded that adjunctive chlorhexidine (gel, irrigation or rinse), glycine powder air-polishing and local or systemic antibiotics, do not significantly improve the clinical outcomes when compared with nonsurgical mechanical debridement alone. Additionally, while the effect of nonsurgical therapy on the treatment of peri-implant mucositis has shown significant improvements in clinical trials, the complete resolution of peri-implant inflammation was not achieved.

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Supplementary

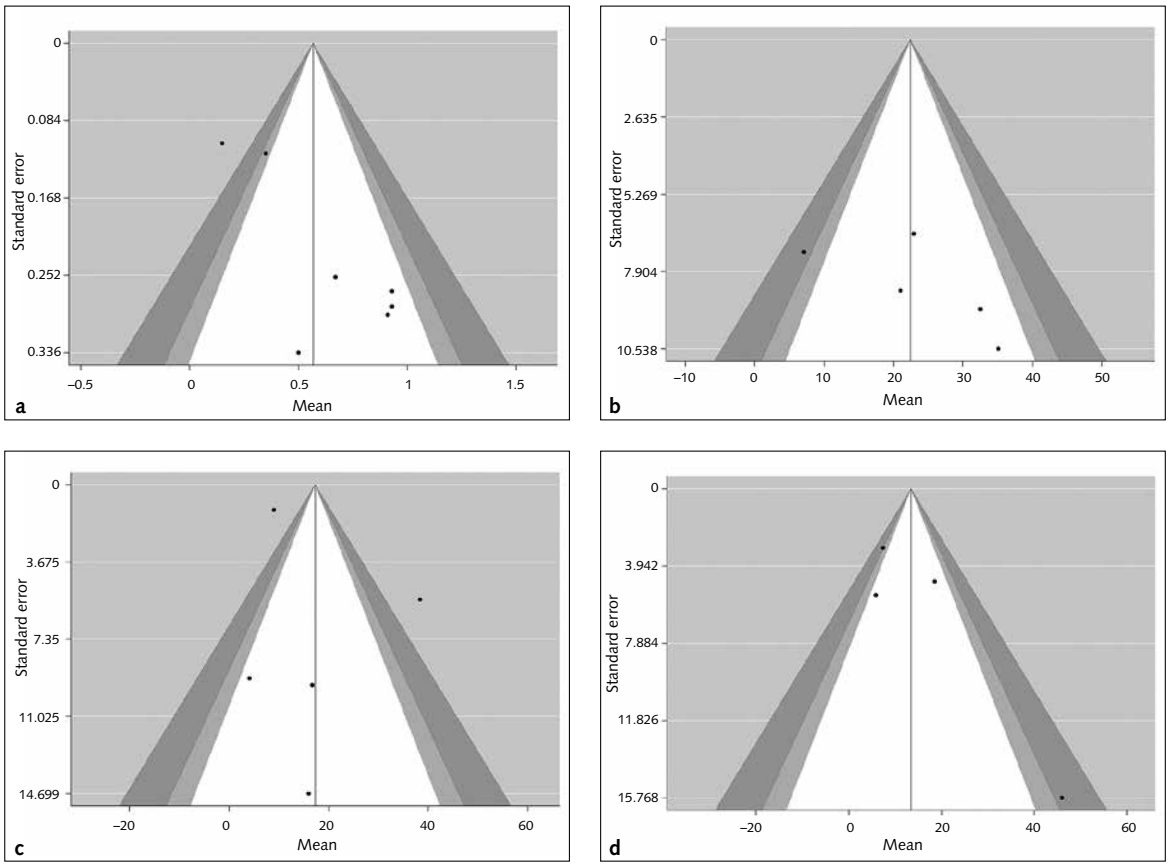
Supplementary Table 1 Clinical studies that were excluded and reasons for exclusion performed at the second stage of the selection of articles

Reason for exclusion	Reference
Exclusive treatment of peri-implantitis	Yu et al (2016)[54], Renvert et al (2009)[55], John et al (2015)[56], Machtei et al (2012)[57], Persson et al (2011)[58], Deppe et al (2013)[59], Schwarz et al (2015)[60], Arısan et al (2015)[61], Bassetti et al (2014)[62], Esposito et al (2013)[63]
Lack of a control group to treat peri-mucositis	Schwarz et al (2018)[64], Schwarz et al (2018)[65], Flichy-Fernández et al (2015)[66]
Non-randomised clinical trials	De Siena et al (2015)[67]
Experimental design (preventive measures for maintaining peri-implant health; not treating peri-mucositis)	Ribeiro et al (2019)[68], Swierkot et al (2013)[69], Ghazal et al (2017)[70], Tawse-Smith et al (2002)[71], Sreenivasan et al (2011)[72]
Combined treatment of per-mucositis and peri-implantitis	Kashefimehr et al (2017)[73]
Case definition not reported	Lavigne et al (1994)[74]
Treatment of peri-mucositis exclusively among smokers	Javed et al (2017)[75], Al Rifaiy et al (2018)[76]

Supplementary Table 2 Risk of bias for the included RCTs according to the Cochrane recommendations

Reference	Adequate sequence generation	Allocation concealment	Blinding of patients, personnel and examiners	Incomplete outcome data addressed	Outcomes free of selective reporting	Study free of other sources of bias	Total
Schenk et al (1997)[32]	Unclear	No	No	No	No	Unclear	High
Porras et al (2002)[14]	Unclear	No	No	Yes	No	No	High
Ramberg et al (2009)[33]	Unclear	Yes	Yes	Unclear	Unclear	Unclear	High
Thöne-Mühling et al (2010)[29]	No	N/R	No	No	Yes	No	High
Heitz-Mayfield et al (2011)[35]	Yes	Yes	N/R	Yes	Yes	Yes	Moderate
Ji et al (2014)[16]	Yes	N/R	No	Yes	Yes	Unclear	High
De Siena et al (2013)[31]	Yes	Yes	N/R	Unclear	Yes	Unclear	High
Ji et al (2014)[16]	Yes	Unclear	No	Yes	Yes	Yes	Low
Hallström et al (2012)[37]	Yes	Yes	No	Yes	Yes	Yes	Moderate
Riben-Grundstrom et al (2015)[30]	Yes	Yes	N/R	Yes	Yes	Unclear	High
Hallström et al (2017)[34]	Yes	Yes	N/R	No	Yes	Yes	High
Menezes et al (2016)[36]	Yes	Unclear	Yes	Yes	Yes	Yes	Moderate
Mongardini et al (2017)[38]	Yes	Yes	Yes	Yes	Yes	Yes	Low
Galofré et al (2018)[39]	Yes	Yes	Yes	Yes	Yes	Yes	Low

N/R, not reported.



Supplementary Fig 1a-d Funnel plots showing the heterogeneity and/or possible publication bias in the investigated outcomes of: **(a)** probing pocket depth (PPD) reduction; **(b)** bleeding on probing (BOP) reduction; **(c)** plaque index (PI) reduction; **(d)** bleeding index (BI) reduction.

Supplementary Table 3 Nonsurgical mechanical treatment of peri-implant mucositis, intervention, and the main outcomes of the selected RCTs

Study characteristics			Patients/ implants (n)	Probing pocket depth (SD)			
Reference	Follow-up	Treatment		Baseline	Final	Reduction, *P* value	
Porras et al (2002)[14]	3 months	Mechanical cleansing + OHI	N.A./12	3.48 (0.61)	2.55 (0.72)	0.93 (0.99)*, ($P < 0.01$)	
Thöne-Mühling et al (2010)[29]	8 months	One-session SRP with curettes and ultrasonic	5/14	3.48 (0.69)	2.82 (0.59)	0.67 (0.95)*, ($P < 0.01$)	
Heitz-Mayfield et al (2011)[35]	3 months	One-time debridement with curettes and polishing pastes + OHI twice a day with placebo gel around implant (for 4 weeks)	14/14	Significant reduction in mean PPD from baseline to 1 month (> 0.5 mm, $P < 0.01$), with little change from 1 to 3 months†			
Menezes et al (2016)[36]	6 months	Full mouth SRP + OHI + placebo mouthwash + prescription of twice daily mouthrinse for 14 days	15/58	2.72 (0.68)	2.49 (0.67)	0.35 (0.91)*, ($P < 0.001$)	
Hallström et al (2017)[34]	3 months	OHI + mechanical debridement (titanium curettes and rubber cup) + once a day brushing with a full brush of placebo gel for 12 weeks	19/19	Number of sites with ≥ 4 mm PPD: 6%	Number of sites with ≥ 4 mm PPD: 4%	Overall 15% reduction in sites with ≥ 4 mm PPD	
Ji et al (2014)[16]	3 months	OHI + nonsurgical debridement (ultrasonic)	12/16	4.5 (0.55)	3.6 (1)	0.91 (1.18)*, ($P < 0.001$)	
Riben-Grundstrom et al (2015)[30]	12 months	OHI + three times treatment with ultrasonic device throughout the entire follow-up (at baseline, 3 and 6 months)	18/18	Number of sites with ≥ 4 mm PPD: 34%	Number of sites with ≥ 4 mm PPD: 20%	14% reduction in sites with ≥ 4 mm PPD*, ($P < 0.001$)	
Hallström et al (2012)[37]	6 months	OHI + mechanical debridement (curettes and rubber cups)	21 patients	4.6 (0.9)	4.1 (1.2)	0.5 (1.54)*, ($P < 0.01$)	
Galofré et al (2018)[39]	3 months	Supra-gingival prophylaxis + 30 (placebo) tablets to be dissolved in the oral cavity once daily (30 days)	11/11	3.82 (0.64)	3.66 (0.62)	0.15 (0.36), ($P = 0.187$)	

Positive changes indicate a decrease from start (baseline) to the end of the study, while negative changes are indicative of an increase in the values.

*Calculated by the authors based on reported values in the article.

BOP, bleeding on probing; n, number; N.A., not available; NSSD, no statistically significant differences; OHI, oral hygiene instructions; PPD, probing pocket depth; SD, standard deviation; SRP, scaling and root planing.

	Bleeding on probing (SD)			Bleeding index (SD)			Plaque index/modified plaque index (SD)		
	Baseline	Final	Reduction, *P* value	Baseline	Final	Reduction, *P* value	Baseline	Final	Reduction, *P* value
	No significant difference at any site of the examination period			NSSD at any evaluation period ($P > 0.05$)			Significant reduction from baseline to 1 month (maintained until 3 months) ($P < 0.05$)		
	38% (29%)	17% (11%)	21% (32%)*	89% (56%)	43% (37%)	46% (59%)*	36% (47%)	2% (24%)	16% (55%)*
	Mean number of BOP-positive sites: 2.3 (1)†	Mean number of BOP-positive sites: 0.7 (0.9)	Change in mean number of BOP-positive sites: 1.6, ($P < 0.05$)	N.A.			N.A.		
	67.54% (34.38%)	41.08% (41.0%)	22.95% (50.38%)*, ($P < 0.001$)	28.01% (32.47%)	10.77% (18.8%)	18.53% (36.01%)*, ($P < 0.001$)	52.15% (32.2%)	12.06 (21.58%)	38.36% (41.65%)*, ($P < 0.001$)
	18%	14%	4% ($P < 0.05$)	N/A			23%	23%	0% decrease ($P > 0.05$)
	N.A.			1.7 (1.0)	0.9 (1.1)	0.8 (1.53)*, ($P < 0.001$)	0.6 (0.68)	0.4 (0.53)	0.2 (0.89)*, ($P = 0.01$)
	53.7% (31.81%)	18.6% (27.15%)	35.1% (44.71%)*, ($P < 0.001$)	9.6% (11.87%)	2.2% (3.39%)	7.4% (12.8%)*, ($P < 0.05$)	24.1% (28%)	7.4% (27.15%)	16.7% (40.44%)*, ($P < 0.05$)
	80% (25%)	47.5% (32.3%)	32.5% (42.11%)*, ($P < 0.02$)	24.2% (16.7%)	18.4% (17.4%)	5.8% (24.86)*, ($P < 0.01$)	22% (29.2%)	17.9% (28.7%)	4.1% (42.21%)*, ($P < 0.01$)
	42% (18%)	35% (22%)	7.1% (24%), ($P = 0.377$)	N.A.			39% (10%)	29% (10)	9% (4%), ($P < 0.001$)