Network Meta-Analysis for Evaluating Interventions in Implant Dentistry: The Case of Peri-Implantitis Treatment

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ABSTRACT

Background/Aim: Evidence from head-to-head comparison trials on peri-implantitis treatment is limited, and it is therefore impossible to conduct a direct meta-analysis. We propose an alternative statistical method, network meta-analysis, for evidence synthesis, which enables to compare the results of multiple treatments.

Methods: We searched, in triplicate, for randomized controlled trials (RCTs) and controlled trials in the PubMed, Cochrane Central Register of Controlled Trials, Clinicaltrials.gov, and Latin American and Caribbean Health Sciences Literature databases up to and including August 2010. We also conducted a manual search of the reference lists regarding published systematic reviews and searched for gray literature in OpenSIGLE. We assessed changes in clinical attachment level (CAL) and pocket probing depth (PPD) after nonsurgical and surgical treatments of peri-implantitis. The risk of bias of selected studies was determined by the use of specific criteria, and it was performed in triplicate and independently. We used multilevel mixed modeling to perform the network meta-analysis and Markov Chain Monte Carlo simulation to obtain confidence intervals for the fixed and random effects.

Results: Eleven studies were included in the review. All RCTs are at unclear or high risk of bias. Surgical therapy in conjunction with bone grafts and non-resorbable membranes achieved 3.52 mm greater PPD reduction than nonsurgical therapy alone, 95% high-probability density (HPD) intervals: −0.19, 6.81. Surgical treatment in conjunction with bone grafts and resorbable membranes achieved 2.80 mm greater CAL gain than nonsurgical therapy alone, 95% HPD intervals: −0.18, 5.59.

Conclusion: Surgical procedures in peri-implantitis treatment achieve more PPD reduction and CAL gain than nonsurgical approaches. Nevertheless, these results should be interpreted with caution because of the limited number of studies included and their low methodological quality. Network meta-analysis is a useful statistical methodology for evidence synthesis and to summarize the strength and limitation in the current evidence.

KEY WORDS: network meta-analysis, nonsurgical treatment, peri-implantitis, surgical treatment

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DOI 10.1111/j.1708-8208.2011.00384.x

INTRODUCTION

Peri-implantitis is an inflammatory reaction in the tissues surrounding a dental implant and is characterized by loss of supporting bone.[1] Depending on its severity, implant failure can occur as a consequence of loss of bone around the implants. In recent decades, a variety of therapies has been proposed for treatment and control of the disease. Conservative approaches, for example, dental implant surface scaling with/without application of adjunctive materials, such as irrigation substance[2,3] or antibiotics,[2] have resulted in improved outcomes, such as clinical attachment level (CAL) gain and pocket probing depth (PPD) reduction. Furthermore, there is some evidence that surgical procedures with or without

bone regeneration might promote greater PPD and CAL changes than nonsurgical approaches of peri-implantitis treatment.[4,5] Nevertheless, a systematic comparison of different peri-implant treatment alternatives has not yet been undertaken, most likely because of great heterogeneity among studies.

Several systematic reviews on peri-implantitis treatment have been published in the last few years.[6–12] These studies identified great heterogeneity in the methods of treatment and in the study designs among studies and therefore, preferred not to conduct meta-analyses for comparing the effects of different treatment approaches. Despite nearly a dozen different nonsurgical and surgical methods for treatment being included in the published studies, traditional meta-analysis is, moreover, only applicable for pairwise comparisons.[13,14] Nevertheless, estimation of the effect of different therapeutic alternatives is pivotal for clinical decision-making. For example, surgical regenerative procedures can substantially increase treatment costs but justification of their use requires evidence of additional treatment benefits in comparison with other (less costly) options.

In recent years, a new method has been developed for evidence synthesis. Network meta-analysis combines results from multiple treatments and enables statistical comparison.[15–24] The technique enables estimation of both the heterogeneity in the effect of any given treatment and the inconsistency in the evidence from different pairs of treatments.[15] In this way, studies with different research protocols can be compared indirectly.

The objective of this study was, therefore, to demonstrate the application of network meta-analysis in implant dentistry using peri-implantitis treatment as an example.

MATERIALS AND METHODS

Literature Search Process

We conducted a literature search in triplicate (CF, LC, and SL) for relevant articles in the PubMed, Cochrane Central Register of Controlled Trials (CENTRAL), and Latin American and Caribbean Health Sciences Literature (LILACS) databases up to and including August 2010. The key word terms related to the researched topic were dental and implant* and infect*, dental and implant* and inflammation, dental and implant* and bone inflammation, dental and implant* and bone defect*, and perimplantitis and peri-implantitis. We combined all six key word terms with the Boolean logic strategy "OR." We also conducted a manual search of reference lists of five recently published systematic reviews on treatment of peri-implantitis.[9–12,14] Moreover, we searched for unpublished and published randomized clinical trials (RCTs) in ClinicalTrials.gov and used the Internet search engine "Google" in English, French, German, Italian, Portuguese, and Spanish. We used the key word "peri-implantitis" for articles published in the language of the original search engine (e.g., articles in Italian in Google Italy, articles in German in Google Germany, etc.). We also searched for gray literature in the OpenSIGLE – System for Information on Grey Literature in Europe (http://opensigle.inist.fr/) and Clinicaltrials.gov (http://www.clinicaltrials.gov).

Inclusion and Exclusion Criteria

We included RCTs and clinical trials (CTs) with two or more treatment groups related to peri-implantitis treatment in humans. The following study designs were excluded from the present systematic review: case series or reports, cross-sectional studies, animal studies, narrative and systematic reviews, consensus reports, expert opinion articles, letters, and editorials. Potential studies published in other languages than those described in the "literature search process" were excluded. Studies that did not present PPD and CAL as measure of outcomes were excluded from this review. We did not set a minimum follow-up time for the studies included.

Data Extraction

Two independent reviewers (CF and LC) screened the titles, abstracts, and full texts of the articles identified by searching using specially designed data extraction forms. Disagreement between the reviewers was resolved by discussion. If there was no agreement, a third reviewer (YKT) gave his opinion.

Rationale of Comparisons and Outcome Measures

Because there are no true endpoints for the assessment of the efficacy of peri-implantitis treatments in RCTs and CTs, we decided to assess clinical surrogate end points. PPD and CAL changes in nonsurgical and surgical treatments for peri-implantitis were therefore assessed. For traditional pairwise meta-analysis, we broadly classified the treatment into two groups, that is, nonsurgical and surgical therapies.

Nonsurgical therapy means all types of treatment approaches without open-flap procedures, for example, implant scaling with curettes or other instruments and implant scaling plus adjunctive antimicrobial treatment with local disinfectants or antibiotics. Surgical therapy included open-flap procedures with implant scaling or implant scaling plus implant surface treatment or modification with or without any form of regenerative procedure (autogenous/substitute bone with or without membranes). For the network meta-analysis, surgical treatment groups with and without regenerative procedures were treated as different groups. Any combination of different procedures or materials was treated as a distinct treatment group, resulting in 11 groups in the final analysis (see Figure 2).

Assessment of Risk of Bias

We assessed the risk of bias of RCTs by using components from the Cochrane tool and one item related to imprecision (item not related to internal validity), and potential biases in the study designs were evaluated as described in the *Cochrane Handbook for Systematic Reviews of Interventions 4.2.6* (section 6.3): (A) adequate, (B) unclear, (C) inadequate or (A) yes, (B) no, (C) unclear, (D) not possible. After this assessment, we grouped the studies selected into three categories: low risk of bias if all the criteria described in the *Cochrane Handbook for Systematic Reviews of Interventions 4.2.6* (section 6.7) were met; high risk of bias if one or more criteria were not met; and unclear risk of bias if insufficient detail is reported of what happened in the study. We conducted this methodological assessment in triplicate and independently (CF, LC, and SL). Any disagreements were resolved by consensus.

Network Meta-Analysis

We used weighted multilevel mixed modeling to undertake the network meta-analysis as described by Glenny and colleagues,[19] Tu and colleagues,[24] and Whitehead.[25] This approach took into account heterogeneity across treatment groups and studies by incorporating fixed and/or random effects for the heterogeneity in the study designs. Outstanding covariates, such as follow-up length, were adjusted for in the same way as fixed effects. Interactions between studied characteristics were modeled as random effects. Furthermore, we used Markov Chain Monte Carlo simulation[26] to obtain high-probability density (HPD) intervals for the fixed and random effects. In network meta-analysis, HPDs are the equivalent of confidence intervals (CIs). Because the number of studies included was small, the assumption of normal distribution for the fixed and, especially, random effects is unlikely to be appropriate.

We performed the network meta-analysis in two stages. First, we assumed that there was no difference between additional treatment effects for nonsurgical and surgical treatments in conjunction with different adjunctive materials (laser, antibiotics, bone grafts, and membranes). Second, we estimated the treatment effects of different nonsurgical and surgical combination therapies.

The results from network meta-analysis were compared with those from traditional pairwise random effect meta-analysis. Forest plots were used to present the results from the traditional meta-analysis, and heterogeneity was assessed using I-squared statistics. The mixed model function lmer in the library lme4 for the software package R [R: R Development Core Team (2009). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. ISBN 3-900051-07-0, URL: http://www.R-project.org/] was used to conduct the network meta-analysis, and STATA, version 10.1 (StataCorp, College Station, TX, USA), was used for traditional meta-analysis.

RESULTS

Selected Studies

We initially screened 1,926 titles. After detailed assessment, 11 manuscripts were included in the network meta-analysis. Figure 1 depicts the literature-search process and the reasons for exclusion of articles. Tables 1 and 2 summarized the studies selected for the network meta-analysis.

Risk of Bias

Although seven[2–4,29,30,32] of the 11 studies were RCTs, we assessed the methodology of six only because one[28] was a follow-up report of a previous study.[29] The methodological quality results of the RCT and their level of risk of bias are depicted in Table 3.

Network Meta-Analysis

Eleven treatment groups within 11 studies were included in the network meta-analysis, and results

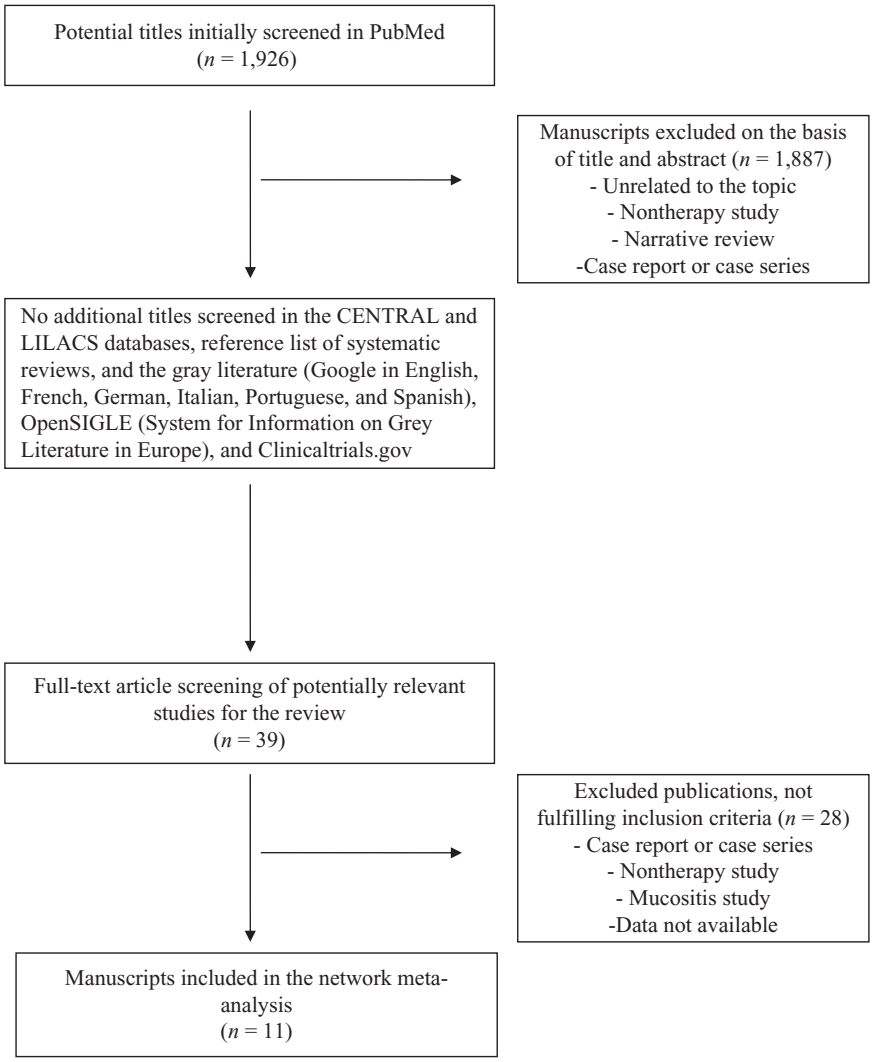

Figure 1 Flow chart of manuscripts screened throughout the review process.

reported at (up to) 4, 6, and 12 months were all included. At stage one, mean PPD reduction for nonsurgical therapy at 4 months was 0.77 mm, which was 2.06 mm (95% HPD intervals: 0.39, 3.37) smaller than that for surgical approaches. The estimated differences in PPD reduction for nonsurgical therapy with different lengths of follow-up up to 12 months were not statistically significant (Table 4).

For CAL gain, network meta-analysis showed that nonsurgical therapy achieved 0.79 mm at 4 months, which was 1.08 mm (95% HPD intervals: –2.32, 4.33) smaller than that for surgical approaches. The estimated CAL gain for nonsurgical therapy at 12 months was 0.17 mm more than at 4 months; but the CIs were large (95% HPD intervals: –3.10, 3.50) (Table 4).

At stage two, surgical procedures combined with bone grafts and non-resorbable membranes seemed to achieve the greatest treatment effect (3.52 mm greater than nonsurgical therapy, 95% HPD intervals: –0.19, 6.81). Use of antibiotics only and nonsurgical therapy combined with antibiotics did not show significant additional treatment effects. The estimated PPD reduction for nonsurgical therapy alone at 12 months was 0.24 mm more than at 4 months (95 % HPD intervals: –1.46, 2.67).

Surgical procedures combined with bone grafts and laser treatment achieved the greatest CAL gain (4.21 mm greater than nonsurgical therapy alone, 95% HPD intervals: 0.21, 8.34); but the CIs were large. Surgical therapy only and nonsurgical therapy combined with laser treatment achieved slightly better results for

TABLE 1 Summary of Randomized Controlled Trials and Controlled Trials Included in the Network Meta-Analysis for PPD Reduction

Study	Treatment Method	PPD Reduction (mm)	SD (Change)	SD (Baseline)	SD (Final)	Follow-Up (Months)	Baseline PPD
Máximo et al. 2009(1)*[27]	Abrasive sodium carbonate air powder and resin curettes	1.3	1.2	1.3	0.7	3	5.2
Máximo et al. 2009(2)*[27]	Open surgical debridement using abrasive sodium carbonate air powder and resin curettes	3.1	1.7	2.2	1.1	3	7.5
Schwarz et al. 2008(1)†[28]	AFS + NHA	1.5	0.6	0.6	0.7	12	6.9
Schwarz et al. 2008(2)†[28]	AFS + NBM + CM	2.4	0.8	0.8	0.7	12	7.1
Schwarz et al. 2006(1)†[29]	AFS + NHA	2.1	0.5	0.6	0.6	6	7.0
Schwarz et al. 2006(2)†[29]	AFS + NBM + CM	2.6	0.4	0.8	0.7	6	7.1
Roos-Jansåker et al. 2007(1)*[5]	Open flap + Algipore	2.2	NA	1.84	1.58	12	5.64
Roos-Jansåker et al. 2007(2)*[5]	Open flap + Algipore + membrane	2.58	NA	1.78	2.0	12	5.44
Deppe et al. 2007(1)*[31]	Open flap + air flow + in residual bone	0.8	NA	1.3	1.2	60	5.1
		1.9	NA	1.3	0.9	4	5.1
Deppe et al. 2007(2)*[31]	Open flap + air flow + in augmented bone	2.3	NA	1.4	1.1	60	4.8
		2.4	NA	1.4	0.7	4	4.8
Deppe et al. 2007(3)*[31]	Open flap + air flow + placed in residual bone + laser	2.7	NA	1.6	1.5	60	6.1
		4.0	NA	1.6	1.3	4	6.1
Deppe et al. 2007(4)*[31]	Open flap + air flow + placed in augmented bone + laser	2.5	NA	1.3	1.4	60	5.0
		4.0	NA	1.3	0.7	4	5.0
Romeo et al. 2005(1)[4]	Resective surgery + surface modification	2.41	NA	1.69	0.89	6	5.79
		2.36	NA	1.69	0.94	12	5.79
		2.21	NA	1.69	1.06	24	5.79
		2.58	NA	1.69	0.56	36	5.79
Romeo et al. 2005(2)[4]	Resective surgery	1.11	NA	1.62	2.09	6	6.52
		0.61	NA	1.62	2.53	12	6.52
		1.02	NA	1.62	1.47	24	6.52
Schwarz et al. 2005(1)[3]	Er:YAG laser instrumentation	0.8	NA	1.2	1.1	6	5.4
Schwarz et al. 2005(2)[3]	Curette + chlorhexidine	0.7	NA	1.5	1.4	6	5.5
Karring et al. 2005(1)[30]	Vector system	0	NA	1.1	1.2	6	5.8
Karring et al. 2005(2)[30]	Curette	−0.1	NA	1.6	2.2	6	6.2
Büchter et al. 2004(1)[2]	Curette + doxycycline	1.15	0.23	0.32	0.29	4	5.64
Büchter et al. 2004(2)[2]	Curette	0.56	0.30	0.28	0.34	4	5.68
Tang et al. 2002(1)[32]	Ultrasonic	0.9	NA	1.1	1.2	3	4.0
Tang et al. 2002(2)[32]	Metronidazole gel	0.7	NA	0.9	0.4	3	3.9
Khoury and Buchmann 2001(1)*[33]	Open flap + autogenous bone	5.1	2.7	0.5	0.6	36	8.0
		5.4	NA	0.5	0.5	12	8.0
		1.5	NA	0.5	0.8	6	8.0
Khoury and Buchmann 2001(2)*[33]	Open flap + autogenous bone + NRM	5.4	3.0	1.0	1.3	36	8.2
		4.8	NA	1.0	1.2	12	8.2
		1.5	NA	1.0	1.1	6	8.2
Khoury and Buchmann 2001(3)*[33]	Open flap + autogenous bone + RM	2.6	1.6	0.5	1.2	36	7.7
		3.3	NA	0.5	0.8	12	7.7
		1.3	NA	0.5	0.9	6	7.7

*Nonrandomized study.
†Same study with different follow-ups.
( ): The different treatment groups within the same study.
AFS + NHA = access flap surgery + nanocrystalline hydroxyapatite; NA = data not available; NBM + CM = natural bone mineral + combination with a collagen membrane; NRM = non-bioabsorbable barrier; PPD = pocket probing depth; RM = bioabsorbable barrier; SD = standard deviation; YAG = yttrium aluminum garnet.

TABLE 2 Summary of Randomized Controlled Trials and Controlled Trials Included in the Network Meta-Analysis for CAL Gain

Study	Treatment Method	CAL Gain (mm)	SD (Change)	SD (Baseline)	SD (Final)	Follow-Up (Months)	Baseline CAL
Máximo et al. 2009(1)*[27]	Abrasive sodium carbonate air powder and resin curettes	1.4	1.2	0.3	NA	3	2.3
Máximo et al. 2009(2)*[27]	Open surgical debridement using abrasive sodium carbonate air powder and resin curettes	2.3	1.6	1.1	NA	3	1.1
Schwarz et al. 2008(1)†[28]	AFS + NHA	1.0	0.4	0.8	0.9	12	7.3
Schwarz et al. 2008(2)†[28]	AFS + NBM + CM	2.0	0.8	1.0	1.0	12	7.5
Schwarz et al. 2006(1)†[29]	AFS + NHA	1.8	0.6	0.8	1.0	6	7.5
Schwarz et al. 2006(2)†[29]	AFS + NBM + CM	2.3	0.6	1.0	0.8	6	7.5
Roos-Jansåker et al. 2011(1)[5]	Open flap + Algipore	5.29	NA	2.1	1.37	12	7.09
Roos-Jansåker et al. 2011(2)[5]	Open flap + Algipore + membrane	5.23	NA	1.98	2.0	12	6.82
Deppe et al. 2007(1)[31]	Open flap + air flow + in residual bone	0.0	NA	0.9	0.9	60	7.0
		0.7	NA	0.9	1.1	4	7.0
Deppe et al. 2007(2)[31]	Open flap + air flow + in augmented bone	2.1	NA	1.1	0.5	60	5.9
		2.7	NA	1.1	1.2	4	5.9
Deppe et al. 2007(3)[31]	Open flap + air flow + placed in residual bone + laser	0.3	NA	0.8	0.7	60	6.9
		1.4	NA	0.8	0.9	4	6.9
Deppe et al. 2007(4)[31]	Open flap + air flow + placed in augmented bone + laser	2.7	NA	1.3	1.4	60	6.3
		4.7	NA	1.3	1.5	4	6.3
Romeo et al. 2005(1)[4]	Resective surgery + surface modification	−0.13	NA	1.49	1.65	6	5.5
		−0.59	NA	1.49	1.74	12	5.5
		−0.39	NA	1.49	2.02	24	5.5
		0.32	NA	1.49	1.49	36	5.5
Romeo et al. 2005(2)[4]	Resective surgery	−0.41	NA	1.56	2.12	6	5.95
		−1.35	NA	1.56	2.33	12	5.95
		−1.09	NA	1.56	1.67	24	5.95
Schwarz et al. 2005(1)[3]	Laser instrumentation	0.7	NA	0.9	0.9	6	5.8
Schwarz et al. 2005(2)[3]	Curette + chlorhexidine	0.6	NA	1.5	1.4	6	6.2
Karring et al. 2005(1)[30]	Vector system	NA	NA	NA	NA	NA	NA
Karring et al. 2005(2)[30]	Curette	NA	NA	NA	NA	NA	NA
Büchter et al. 2004(1)[2]	Curette + doxycycline	1.17	0.27	0.33	0.30	4	5.32
Büchter et al. 2004(2)[2]	Curette	0.56	0.30	0.27	0.33	4	5.51
Khoury and Buchmann 2001(1)[33]	Open flap + autogenous bone	NA	NA	NA	NA	NA	NA
Khoury and Buchmann 2001(2)[33]	Open flap + autogenous bone + NRM	NA	NA	NA	NA	NA	NA
Khoury and Buchmann 2001(3)[33]	Open flap + autogenous bone + RM	NA	NA	NA	NA	NA	NA

*Nonrandomized study.

†Same study with different follow-ups.

( ): The different treatment groups within the same study.

AFS + NHA = access flap surgery + nanocrystalline hydroxyapatite; CAL = clinical attachment level; NA = data not available; NBM + CM = natural bone mineral + combination with a collagen membrane; NRM = non-bioabsorbable barrier; RM = bioabsorbable barrier; SD = standard deviation.

TABLE 3 Methodological Assessment of Randomized Controlled Trials Included in the Systematic Review

Study	Described as Randomized	Sequence Generation	Allocation Concealment	Patient Blinding	Caregiver Blinding	Examiner Blinding	All Patients Accounted for at End of Study	Sample Size/Statistical Power Calculation	Risk of Bias
Schwarz et al. 2006[29]	Yes/abstract	Yes/adequate	Unclear	Not applicable	Not applicable	Yes	Yes	Not reported	Unclear
Schwarz et al. 2005[3]	Yes/abstract	Yes/adequate	Unclear	Not applicable	Not applicable	Yes	No	Not reported	High
Romeo et al. 2005[4]	Yes/abstract	Yes/adequate	Unclear	Not applicable	Not applicable	Unclear	No	Not reported	High
Karring et al. 2005[30]	Yes/abstract	Yes/adequate	Unclear	Not applicable	Not applicable	Yes	Yes	Not reported	Unclear
Büchter et al. 2004[2]	Yes/title	Yes/adequate	Unclear	Not applicable	Not applicable	Unclear	Yes	Not reported	Unclear
Tang et al. 2002[32]	Yes/abstract	Yes/adequate	Unclear	Not applicable	Not applicable	Unclear	No	Not reported	High

CAL gain than nonsurgical therapy did. The estimated CAL gain for surgical therapy at 12 months was 0.77 mm less than at 4 months; but the CIs were large (95% HPD intervals: −3.23, 2.03) (Table 4).

Standard Meta-Analysis

Nonsurgical therapy resulted in mean PPD reduction of 0.66 mm (95% CI: 0.32, 0.99) at 4 months in comparison with 3.10 mm (95% CI: 2.26, 3.93) of mean PPD reduction in the surgical therapy group. Surgical approaches reduced mean PPD by 2.84 mm (95% CI: 1.71, 3.97) at 12 months. At 6 months, nonsurgical and surgical therapies resulted in mean CAL gains of 0.67 mm (95% CI: 0.19, 1.16) and 1.10 mm (95% CI: 0.17, 2.04), respectively (Figures 2 and 3).

Standard pairwise meta-analysis revealed slightly better results than network meta-analysis for PPD reduction with nonsurgical therapy alone at 6 months. For CAL gain, standard pairwise meta-analysis and network meta-analysis revealed slightly worse results at 6 months than those at 4 months, although differences were small.

DISCUSSION

The aim of this study was to demonstrate how direct and indirect evidence can be synthesized into one meta-analysis. This methodology is useful for implant dentistry because evidence about treatments of peri-implantitis is quite sparse. Some consider indirect comparisons less biased than direct comparisons.[34] Traditional pairwise meta-analysis is well-established, albeit restricted to the availability of "head-to-head" trials. However, interpreting traditional meta-analyses is difficult when there are no direct comparisons between several different treatment approaches. By using a network approach, we add substantial new information, which can provide a holistic overview of current evidence. Both approaches (traditional and network meta-analyses) generated consistent results (same direction), and this may strengthen the currently available evidence for the purpose of clinical decision-making.

When all surgical approaches or nonsurgical ones were pooled together, surgical approaches showed greater changes in PPD and CAL than nonsurgical ones. Nevertheless, when different surgical and nonsurgical approaches were treated separately, the differences became no longer statistically significant probably because of the small number of studies included and the

TABLE 4 Results of Network Meta-Analysis for PPD and CAL Changes

	Estimates	95% HPD Intervals
PPD		
Stage 1		
(Intercept)	0.77	−0.13 to 1.75
Surgical	2.06	0.39 to 3.37
6 months f/u	−0.70	−2.06 to 0.52
12 months f/u	0.06	−1.27 to 2.29
Stage 2		
Nonsurgical (Ref)	0.54	−1.26 to 2.59
Nonsurgical + antibiotics	0.09	−2.13 to 1.98
Nonsurgical + laser	0.66	−1.69 to 2.76
Surgical (resective)	0.42	−2.57 to 3.29
Surgical + antibiotics	1.45	−1.52 to 4.27
Surgical + bone grafts	2.24	−2.01 to 5.22
Surgical + bone grafts + laser	1.97	−0.95 to 4.40
Surgical + bone grafts + non-resorbable membranes	3.52	−0.19 to 6.81
Surgical + bone grafts + resorbable membranes	2.40	−1.10 to 5.27
Surgical + laser	2.05	−0.89 to 4.55
Vector system	3.52	−0.66 to 7.28
Antibiotics only	0.19	−3.43 to 2.60
6 months follow-up	−0.54	−2.14 to 1.30
12 months follow-up	0.24	−1.46 to 2.67
CAL		
Stage 1		
(Intercept)	0.79	−1.61 to 3.35
Surgical	1.08	−2.32 to 4.33
6 months f/u	−0.04	−2.82 to 2.35
12 months f/u	0.17	−3.10 to 3.50
Stage 2		
Nonsurgical (Ref)	0.91	−1.07 to 2.40
Nonsurgical + antibiotics	0.59	−1.32 to 2.35
Nonsurgical + laser	0.17	−2.17 to 2.89
Surgical (resective)	0.17	−2.36 to 3.14
Surgical + antibiotics	0.55	−4.07 to 3.58
Surgical + bone grafts	2.28	−0.78 to 4.62
Surgical + bone grafts + laser	4.21	0.21 to 8.34
Surgical + bone grafts + resorbable membranes	2.80	−0.18 to 5.59
Surgical + laser	0.91	−2.22 to 3.86
6 months follow-up	−1.09	−2.83 to 1.60
12 months follow-up	−0.77	−3.23 to 2.03

Baseline PPD is the covariate in the adjusted network meta-analysis. Note that HPD intervals are not necessarily symmetrical around the estimates of fixed effects.
CAL = clinical attachment level; F/u = length of follow-up in months; HPD = high probability density; PPD = pocket probing depth.

lack of statistical power. In order to reduce bias in the network meta-analysis, some recommendations for performing indirect comparisons have been described[35] (Table 5). We followed these suggestions in this study wherever possible.

While network meta-analysis is a very useful tool for evidence synthesis for multiple intervention comparisons, the interpretation of its results still needs to take into account the limitations in the study design and the methodology. First, we only identified a limited number

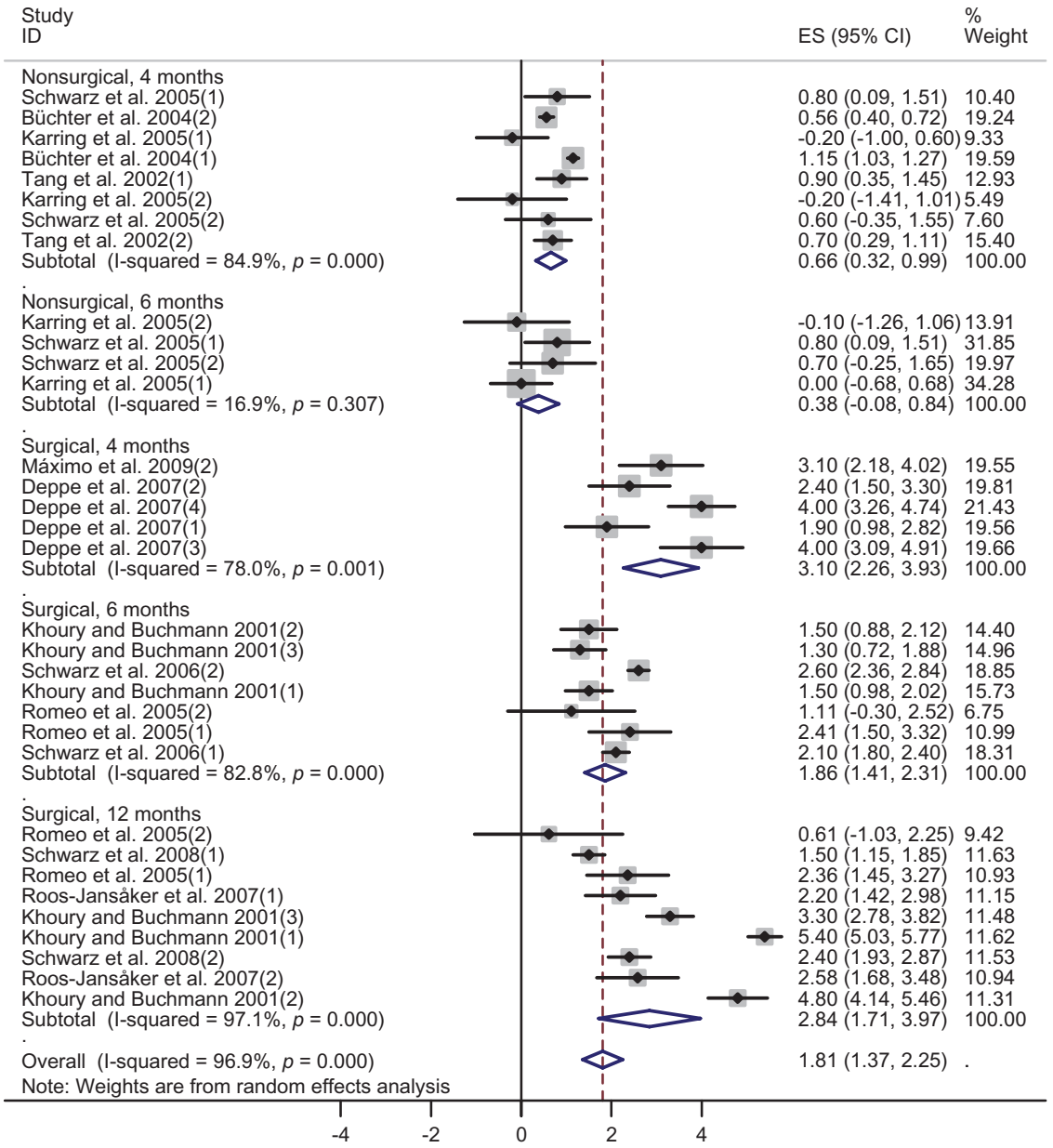

Figure 2 Forest plot of the standard pairwise meta-analysis for pocket probing depth changes when different types of nonsurgical and surgical treatments were treated as separate groups. (CI = confidence interval; ES = estimate.)

of studies that could be included in the meta-analysis, and the lack of statistical power resulted in wide CIs.[36] Similar results with regard to large CIs were obtained in a previous network meta-analysis in dentistry.[24] Tu and colleagues suggested that large CIs were also because of the heterogeneity of the observed differences. Treatment effects might, moreover, be overestimated when indirect comparisons are based on low-quality trials with high risk of bias.[22] This was true for the studies included in our review. We found significant heterogeneity for the majority of the outcomes in the pairwise meta-analysis; while the statistical models for the network meta-analysis in our study took into account the heterogeneity, it nevertheless gave rise to greater uncertainty in the results reflected by the wide CIs.

Second, the assumption that treatment effects based on surrogate end points (e.g., changes in PPD and CAL) will capture the clinical outcome may be misleading.[37] It has been reported, for example, that end points such as CAL may be a weak surrogate marker for tooth loss.[38] Surrogate end points such as PPD and CAL might be regarded as relevant when they

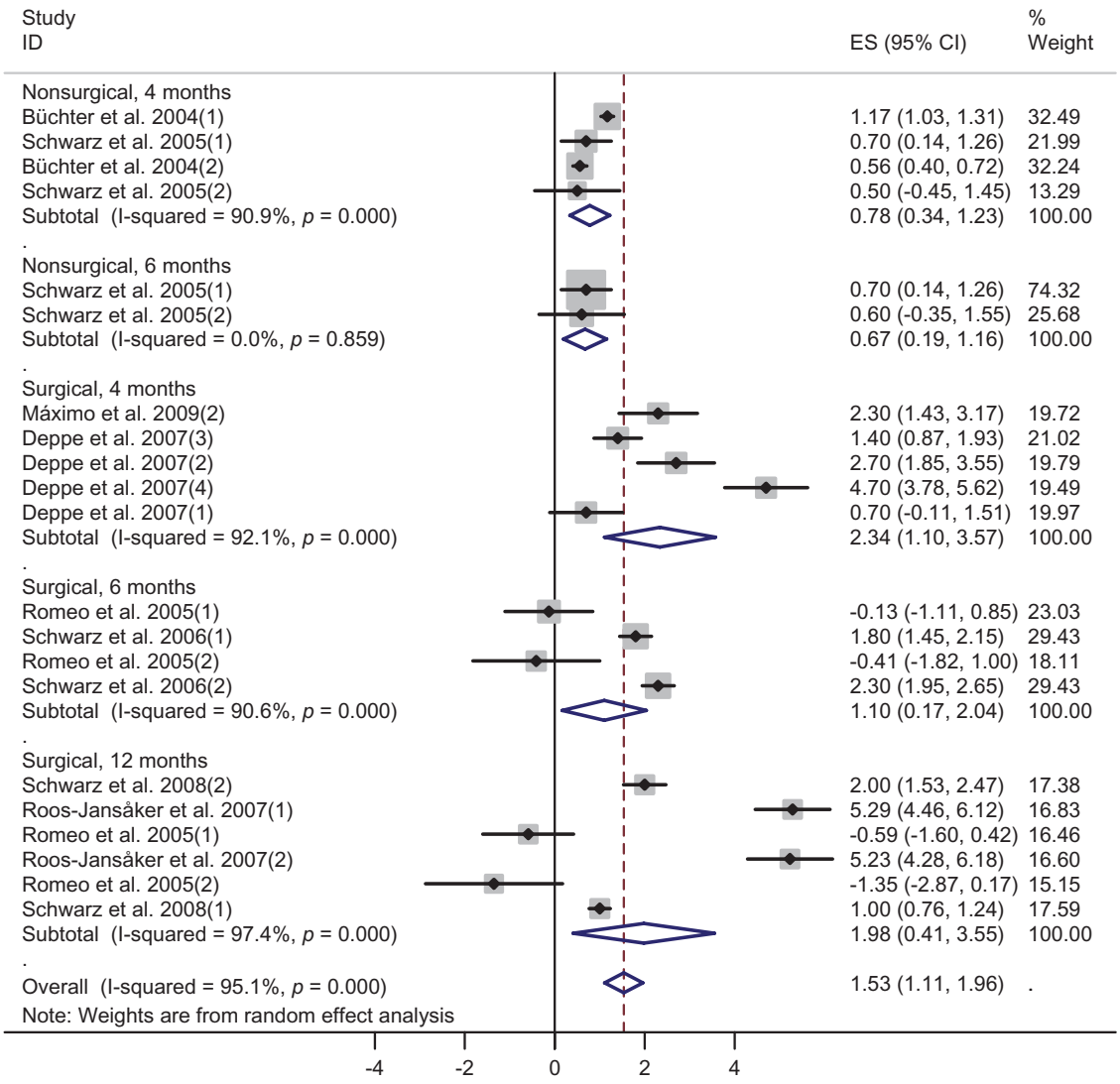

Figure 3 Forest plot of the standard pairwise meta-analysis for clinical attachment level changes when different types of nonsurgical and surgical treatments were treated as separate groups. (CI = confidence interval; ES = estimate.)

capture the characteristics of the true endpoint (implant failure) to a large extent (e.g., >50 or >75%).[37,39] More specifically, lower and upper bounds of CIs should exceed these values with regard to the risk of implant failure.[37] There is, however, no easy means of assessing implant failure in RCTs of peri-implantitis treatment. Some argue that it may be unethical to maintain a noneffective therapy until the phase of implant explantation. One alternative would be to assess existing data on implant failure (even data from lower study designs) after peri-implantitis treatment[40] to validate surrogate end points, such as PPD and CAL. Therefore, we used surrogate endpoints as outcome measures in our network meta-analysis because there was no study on peri-implantitis treatment that used implant failure as true endpoint. In fact, only two RCTs, one noncontrolled study and three case series, have reported implant failure as a consequence of therapy instead of main outcome measure.[40]

Our results also demonstrated that there is room for improvement of clinical trials on peri-implantitis treatment. After the assessment of the quality of study methodology, we concluded that all RCTs were at unclear or high risk of bias (Table 3). These results are in accordance with the results of another systematic review on peri-implantitis therapy[10] that included five of the seven RCTs assessed in our review.[2,3,29,30,32] The other nonrandomized studies included[5,27,31,33] were not methodologically assessed because of the lack of randomization that is very likely to lead to selection bias.[41]

TABLE 5 Recommendations for Conducting Indirect Comparisons in Dentistry

Recommendations
■ More explicit and elaborate description and discussion of underlying assumptions in methodological studies and in systematic reviews in which different interventions are indirectly compared
■ Literature search needs to be systematic in order to identify all relevant studies
■ The evidence from head-to-head comparison trials should not be excluded in reviews that use indirect comparison
■ The availability of all active treatment controlled studies that are suitable for adjusted indirect comparison should be explicitly discussed, and justifications are provided if only placebo controlled trials are used for adjusted indirect comparison
■ Naive indirect comparison of different arms from different trials should be avoided
■ Data from trials with multiple arms should be appropriately analyzed to avoid both downgrading direct evidence and using the same control group more than once in adjusted indirect comparison
■ Methods for investigating heterogeneity in standard meta-analysis can be adopted to assess trial similarity in adjusted indirect comparison, including subgroup analysis, meta-regression, and experts' subjective judgment. However, further research is needed
■ Direct and indirect evidence should be separately presented and explicitly compared whether or not the two sets of data are subsequently combined
■ Possible reasons for any observed discrepancies between direct and indirect evidence should be investigated
■ The consistency assumption should be explicitly assessed before direct evidence is combined with indirect evidence

Adapted from Song et al. (2009).[35]

Furthermore, the available studies reported a great variety of implant types and systems. One study[28] reported five different implant surfaces receiving peri-implantitis therapies. Implant surface characteristics may be of decisive importance for the outcome of various treatment protocols, and therefore, treatments in different surfaces might play a role as potential confounder in the size of treatment effects of peri-implantitis treatment.

This study differs from other recently published systematic reviews in its meta-analytical component. Decision-makers and clinicians are interested in quantifying the effects of treatment, especially to consider the cost-effectiveness of different treatment options. In fact, indirect comparisons had been used in economic evaluation because researchers may have to use the available data to estimate the incremental cost-effectiveness of competing interventions.[35] Clinicians and health-care decision-makers must often compromise between attainable level of treatment effectiveness and available monetary resources.[42] This particularly applies to peri-implantitis treatment, in which surgical techniques may be more effective but also are at a higher cost than non-surgical techniques. Moreover, given that the clinical evidence for various peri-implantitis treatment techniques may be regarded as limited only, consideration of economic aspects may also give guidance for setting priorities in funding future research.[43] In the lack of a large and definitive RCT, meta-analysis of studies can provide a reasonable estimate of the treatment effect for use in a cost-effectiveness analysis.[44]

In summary, our study demonstrated state-of-the-art evidence synthesis methodologies for comparisons of several different interventions in the same meta-analysis by including direct and indirect evidence. Our results showed that surgical therapy is, in the short term, more effective than nonsurgical approaches in the treatment of peri-implantitis. These results should, however, be interpreted with caution because of several limitations in the included trials. It is necessary to conduct well-designed RCTs or observational studies with longer follow-ups to assess the accurate effectiveness of therapies.

CONFLICT OF INTEREST AND SOURCE OF FUNDING STATEMENT

The authors declare that they have no conflict of interests. The first and third authors are both affiliated with the University of Heidelberg. The first author was partially funded by a postdoctoral fellowship from the Medical Faculty of the University of Heidelberg. The third author is also affiliated with MEA and was fully funded through a postdoctoral fellowship by the Medical Faculty of the University of Heidelberg. The last

author was funded by the United Kingdom government's Higher Education Funding Council for England and currently holds a UK Research Council Fellowship.

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