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REVIEW ARTICLE

Boric acid as an adjunct to periodontal therapy: A systematic review and meta-analysis

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ABSTRACT

Objective: To evaluate the efficacy of boric acid as an adjunct to non-surgical periodontal therapy, in comparison with a placebo adjunct, in terms of changes in probing pocket depth (PPD) and clinical attachment level (CAL), in patients with periodontitis.

Methods: Four electronic databases were searched from inception to May 2020 (PubMed, Cochrane CENTRAL, EMBASE via OVID and Web of Science). Clinical outcomes were extracted, pooled and meta-analyses conducted using mean difference with standard deviations.

Results: For PPD, a mean additional reduction of 0.58 mm (95% CI: -0.03–1.19 mm, $p = 0.06$) was observed at 3 months and a mean additional reduction of 1.18 mm (95% CI: 0.97–1.40 mm, $p < 0.05$) at 6 months, compared with placebo.

For CAL, a mean additional gain of 0.62 mm (95% CI: -0.07–1.32 mm, $p = 0.08$) was observed at 3 months and a mean additional gain of 1.24 mm (95% CI: 0.89–1.58 mm, $p < 0.05$) at 6 months, compared with placebo. No adverse events were reported in any studies.

Conclusions: The adjunctive use of boric acid in non-surgical periodontal therapy results in improved treatment outcomes at 3 and 6 months, with no adverse events reported.

KEYWORDS

boric acid, meta-analysis, outcomes, periodontitis, scaling and root planing, systematic review

1 | INTRODUCTION

Periodontitis is a chronic inflammatory disease characterized by the loss of periodontal attachment and mediated by the host-bacteria interaction.¹ The management of the disease fundamentally involves the elimination of pathogenic microbiota in order to arrest the inflammatory response and induce healing.² The foundation of effective periodontal therapy is mechanical debridement of the root surface, with a view to disrupt the established biofilm; all other treatments and agents are considered adjunctive to this.³ Non-surgical periodontal therapy is efficacious, eliciting improvements in

clinical outcomes in the majority of cases.⁴ Adjunctive treatments have been shown to improve treatment outcomes and may be of particular use when non-surgical therapy is not effective, and the disease process continues to persist.⁵

Numerous drugs, therapies and other alternative remedies, each with their own drawbacks, have been studied for use as adjunctive treatments.^{6–9} Antibiotics, administered systemically or locally, have been proven to be efficacious across numerous studies and are one of the most common adjunctive treatments.^{10,11} However, the critical issue of antimicrobial resistance greatly restricts their use.¹² Photodynamic therapy has been investigated, and numerous

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different methods of photosensitization have been explored; however, systematic reviews reveal very limited clinical benefit.^{13,14}

Boric acid is one agent which has been postulated to convey benefits in the management of periodontitis, with animal models demonstrating a reduction in periodontal inflammation and attachment loss.¹⁵ This is thought to be due a combination of the antimicrobial, anti-inflammatory and immune regulatory effects of boron-containing compounds.¹⁵⁻¹⁷ The boron-containing compound AN0128, a derivative of boric acid, is thought to contribute to the anti-inflammatory and immune regulatory effects by inhibiting the release of tumour necrosis factor- α (TNF- α).^{15,17} In addition, boric acid is osteogenesis-promoting through its actions on stromal cells within bone marrow, where it promotes the differentiation of osteogenetic cells.^{15,17,18} A clinical application of these properties has been demonstrated in a randomized controlled trial in which boric acid was found to induce significantly more bony infill in furcation defects, as compared with placebo.¹⁷ Despite these potentially beneficial properties, to the authors' knowledge, there are no existing systematic reviews evaluating the adjunctive use of boric acid in the management of periodontitis.

The aim of this systematic review was to assess the efficacy of boric acid as an adjunct to non-surgical periodontal therapy, as compared to placebo, in patients with periodontitis.

2 | MATERIALS AND METHODS

2.1 | Protocol and registration

Prior to starting the study, the authors outlined a review protocol. The protocol was approved and registered in the International Prospective Register of Systematic Reviews, PROSPERO (CRD42020187484). This review is reported according to PRISMA guidelines, and all methods used in conducting the review were taken from the *Cochrane Handbook for Systematic Reviews of Interventions*.¹⁹

2.2 | Study eligibility: inclusion and exclusion criteria

Studies were included according to the PICOS criteria:

2.2.1 | (P)opulation

Patients with periodontitis, defined as either PPD ≥ 5 mm and / or ≥ 4 mm loss of CAL.²⁰

2.2.2 | (I)ntervention

Supra- and subgingival debridement (ie scaling and root planing or root surface debridement) plus adjunctive boric acid administered to the sites being treated.

2.2.3 | (C)omparison

Supra- and subgingival debridement plus adjunctive placebo administered to the sites being treated.

2.2.4 | (O)utcome

There were two primary outcome measures: change in PPD and change in CAL. Secondary outcome measures evaluated were adverse events due to adjunctive boric acid therapy.

2.2.5 | (S)udy design

Randomized controlled trials with at least 3 months of follow-up.

No restrictions were placed on the studies according to the date of publication, phase of the trials or method of boric acid administration. Studies were excluded if they did not meet the PICOS parameters outlined above, if they were not in English language or if they evaluated outcomes in patients below 18 years of age.

2.3 | Information sources and search

Four electronic databases were searched from inception to May 2020: PubMed, Cochrane Central Register of Controlled Trials, EMBASE via OVID and Web of Science. Additionally, reference list follow-ups of all included studies were conducted.

The following search term was used: "((((((((boric acid) OR orthoboric acid) OR boracic acid) OR sassolite) OR optibor) OR borofax) OR trihydroxyborane) OR boron trihydroxide)) AND ((periodont*) OR gum disease)". The full search strategy for PubMed, with MeSH terms, is outlined in Appendix 1.

2.4 | Study selection

The studies were independently screened by the two review authors, initially according to relevance of the title and relevance of the abstract, in accordance with the eligibility criteria outlined. Following this, the remaining articles then underwent full-text analysis and excluded articles were documented, with reasons for exclusion. Discrepancies between the reviewers regarding any specific paper were settled through discussion until a consensus was reached. Inter-reviewer agreement for screening and inclusion of articles was assessed via kappa scores.

2.5 | Data extraction

Data were extracted into a custom-designed spreadsheet made in Microsoft Excel (2019). A standardized data sheet was pre-piloted and then implemented for data extraction by a single reviewer (NZB). The

second reviewer (MK) verified the accuracy of data obtained from the studies. The unpopulated spreadsheet into which data were input is presented in Appendix 2.

2.6 | Risk of bias

The risk of bias of the included studies was evaluated using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions*.¹⁹ The following parameters were assessed: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other bias.

2.7 | Data synthesis

Meta-analyses were conducted for treatment outcomes at 3 months and 6 months. Data from the included studies were pooled, using mean difference (mm) with standard deviations. Where standard deviations were not provided, authors were contacted for individual patient data to allow for calculation. If these data could not be obtained, standard deviations were imputed using the correlation coefficient method recommended in the *Cochrane Handbook for Systematic Reviews of Interventions*.¹⁹

The secondary outcome measure, adverse events, was assessed through calculation of risk ratios.

Data were pooled using both a fixed effects model and a random effects model, and if significant heterogeneity was identified, the findings from the random effects model were presented. Fixed effects models were only used if there was no significant methodological heterogeneity and no significant statistical heterogeneity. Forest plots were generated to illustrate the findings of the meta-analyses. Review Manager 5.3 (Review Manager Web (RevMan Web)). The Cochrane Collaboration (2019) was used to perform all analyses.

Heterogeneity was assessed on the basis of two parameters: (i) assessing the characteristics of the included studies and (ii) statistical assessment of heterogeneity through calculation of appropriate statistical parameters. Methodological heterogeneity was assessed by evaluating differences in the treatment protocols used, study designs, sampled populations, methods of boric acid delivery used across the studies, methods of placebo administration across the studies and disease definition used across the studies. Statistical heterogeneity was assessed through Cochran's Q chi-squared testing and calculation of the I^2 index. In accordance with the *Cochrane Handbook for Systematic Reviews of Interventions*, I^2 values between 0 and 40% were deemed as not representing significant heterogeneity, and values above 40% were considered to represent significant heterogeneity.¹⁹

2.8 | Additional tests

The following additional tests were conducted as per the guidelines in the *Cochrane Handbook for Systematic Reviews of Interventions*¹⁹:

Meta-regressions would be conducted if there were an adequate number of studies (10 or more).

Risk of bias across studies (publication bias) would be evaluated through generation of funnel plots and Egger's tests, if there were an adequate number of studies (10 or more).

Sensitivity analyses were conducted to assess the contribution of each individual study on the totality of the evidence.

2.9 | Certainty assessment

Assessment of certainty in the overall body of evidence for each outcome was performed using Grading of Recommendations, Assessment, Development and Evaluations (GRADE) criteria. The following parameters were assessed: risk of bias, imprecision, inconsistency, indirectness and publication bias.

3 | RESULTS

3.1 | Selected studies

The initial search returned 64 articles, of which 25 articles were identified as duplicates. The remaining 39 articles were screened according to the title and abstract, and 35 were excluded ($\kappa = 1.00$, 95% CI: 1.00–1.00). The remaining 4 studies underwent full-text analysis, of which all 4 met the inclusion criteria. All 4 studies were suitable for meta-analyses ($\kappa = 1.00$, 95% CI: 1.00–1.00). The study selection process is outlined as a PRISMA flowchart in Figure 1.

3.2 | Study characteristics

3.2.1 | Study design and demographics

The author, year, country, study setting, age range of participants, sample size, treatment protocols and time at which outcomes were evaluated are outlined in Table 1.

Across the four included trials, three were of parallel-arm design, and one was of split-mouth design (Singhal et al., 2017). All trials were conducted in a university hospital setting, with three being in India and one being in Turkey (Saglam et al., 2013). Across the trials, the ages of the included participants ranged from 18 to 63 years. Three trials evaluated delivery of boric acid as a 0.75% concentration gel, which was deposited subgingivally using a syringe with a blunt cannula, following non-surgical therapy. Of these, 2 trials explicitly stated the use of 0.1 mL of the gel, and one did not specify the volume of boric acid gel used (Mamajiwal et al., 2019). The remaining trial evaluated delivery of boric acid as a 0.75% concentration irrigant, where 10 mL of the irrigant was applied subgingivally to each site for 1 min, following non-surgical therapy. All studies investigating boric acid gel reported the site-specific change in PPD and CAL for the areas receiving therapy, whilst the study investigating boric acid irrigation reported whole-mouth parameters.

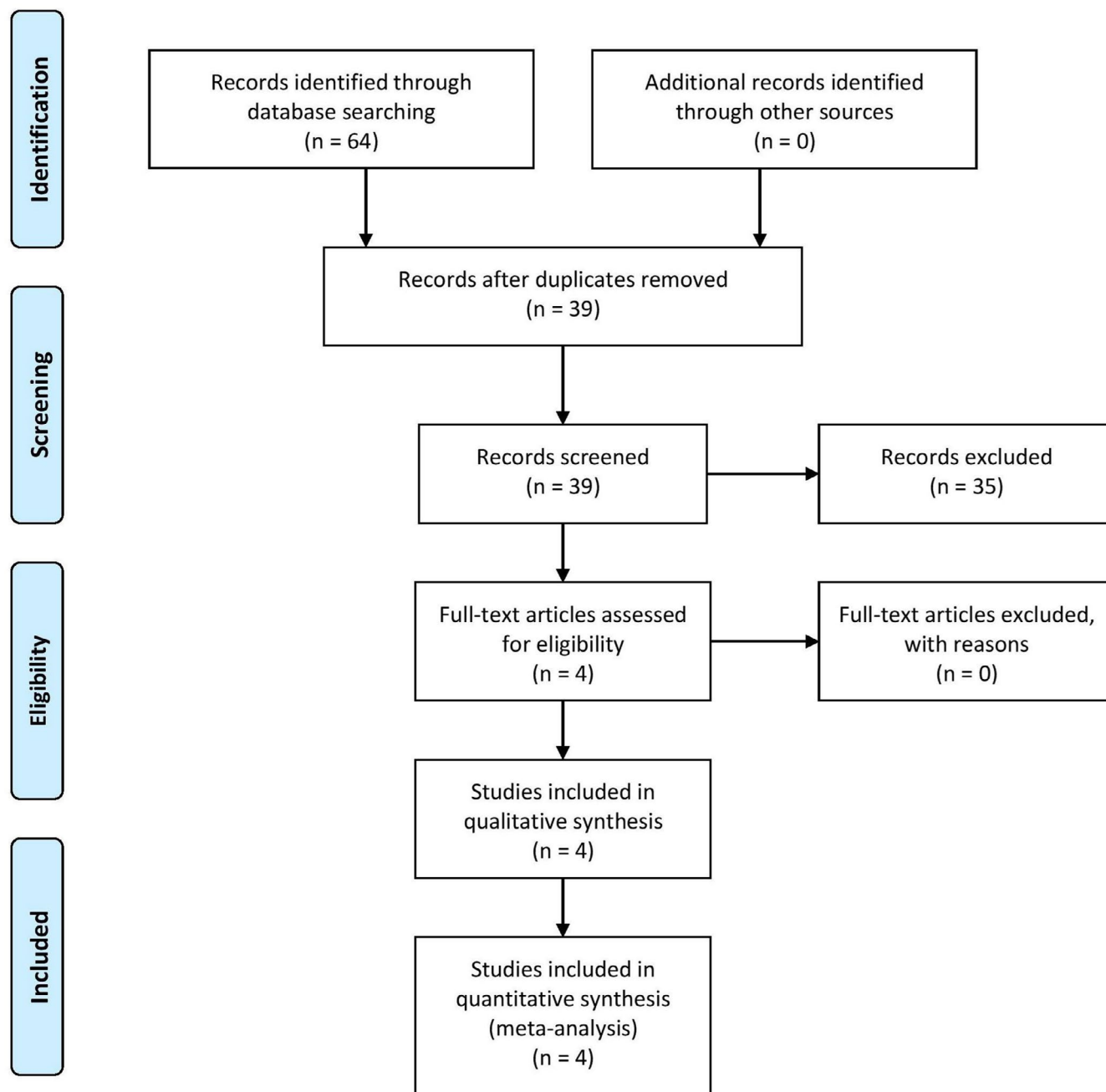


FIGURE 1 PRISMA flowchart outlining the study selection process

3.2.2 | Disease definition

All studies defined the condition being evaluated as 'chronic periodontitis'. Three studies defined chronic periodontitis as PPD ≥ 5 mm.^{17,21,22} One study defined it as PPD ≥ 5 mm or ≥ 4 mm loss of CAL.²³

3.2.3 | Outcome assessment

All studies reported on changes in PPD and CAL, and these were extracted to allow for meta-analyses. Not all studies reported outcomes at both 3 months and 6 months (see Table 1). One study did not provide standard deviations for changes in PPD and CAL from baseline.²¹

The corresponding author was contacted for individual patient data, but no reply was received. Therefore, standard deviations were imputed using the correlation coefficient method recommended by the Cochrane Collaboration. The correlation coefficient calculations and subsequent generation of standard deviations for Mamajiwala et al. (2019) are outlined in Appendix 3. The data for changes in PPD and CAL for all included studies are presented in Table 2.

3.2.4 | Risk of bias

A risk of bias summary for all included studies is provided in Figure 2. As per Cochrane guidelines, a narrative description, with authors'

TABLE 1 Characteristics of included studies

Study	Country	Setting	Age range	Test group (sample size)	Boric acid administration protocol	Placebo group (sample size)	Placebo administration protocol	Outcomes evaluated at
Kanoriya et al., 2018	India	University	25–55 years	(20)	0.75% boric acid gel deposited <i>in situ</i>	(19)	Placebo gel deposited <i>in situ</i>	Baseline 3 months 6 months
Mamajiwala et al., 2019	India	University	18–55 years	(15)	0.75% boric acid gel deposited <i>in situ</i>	(15)	Placebo gel deposited <i>in situ</i>	Baseline 6 months
Saglam et al., 2013	Turkey	University	32–63 years	(15)	Subgingival irrigation with 0.75% boric acid solution	(15)	Subgingival irrigation with saline solution	Baseline 3 months
Singhal et al., 2017	India	University	30–50 years	(25)	0.75% boric acid gel deposited <i>in situ</i>	(23)	Placebo gel deposited <i>in situ</i>	Baseline 3 months 6 months

judgements and evidence for these judgements, regarding each risk of bias parameter was documented. This is presented in Appendix 4.

3.3 | Synthesis of results

3.3.1 | Probing pocket depth

Sub-group meta-analyses were conducted for outcomes at 3 months and 6 months post-therapy. The adjunctive use of boric acid resulted in a mean additional reduction in PPD of 0.58 mm (95% CI: −0.03–1.19 mm) at 3 months and of 1.18 mm (95% CI: 0.97–1.40 mm) at 6 months.

Studies evaluating outcomes at 3 months demonstrated significant heterogeneity ($I^2 > 40\%$), so the findings from the random effects model are presented. Studies evaluating outcomes at 6 months demonstrated low heterogeneity ($I^2 = 0\%$), so the findings from the fixed effects model are presented (Figure 3). No adverse events were reported in any of the participants; risk ratios could not be calculated.

3.3.2 | Clinical attachment level

Sub-group meta-analyses were conducted for outcomes at 3 months and 6 months post-therapy. The adjunctive use of boric acid resulted in a mean additional gain in CAL of 0.62 mm (95% CI: −0.07–1.32 mm) at 3 months and of 1.24 mm (95% CI: 0.89–1.58 mm) at 6 months.

Studies evaluating outcomes at 3 months and 6 months demonstrated significant heterogeneity ($I^2 > 40\%$), so the findings from the random effects models are presented (Figure 4). No adverse events were reported in any of the participants; risk ratios could not be calculated.

3.4 | Additional Tests

3.4.1 | Meta-regression

The number of studies included in the systematic review was below the threshold required to conduct meta-regressions.

3.4.2 | Risk of bias across studies

The number of studies included in the systematic review was below the threshold required to generate funnel plots and conduct Egger's tests.

3.4.3 | Sensitivity analyses

The results of the sensitivity analyses are presented in Table 3. Outlined in Table 3 is the outcome measure which the analysis was

TABLE 2 Changes in PPD and CAL
observed in included studies

Study	Outcomes measured at	Mean reduction in PPD \pm SD (mm)	Mean gain in CAL \pm SD (mm)
Kanoriya et al., 2018	3 months	Boric acid = 1.85 ± 0.48 Placebo = 0.89 ± 0.31	Boric acid = 1.45 ± 0.51 Placebo = 0.68 ± 0.47
	6 months	Boric acid = 3.15 ± 0.74 Placebo = 1.89 ± 0.45	Boric acid = 2.65 ± 0.58 Placebo = 1.31 ± 0.82
Mamajiwala et al., 2019	3 months	Data not available	Data not available
	6 months	Boric acid = 2.43 ± 1.29 Placebo = 1.44 ± 0.50	Boric acid = 0.94 ± 0.89 Placebo = 0.23 ± 0.87
Saglam et al., 2013	3 months	Boric acid = 0.90 ± 0.17 Placebo = 0.88 ± 0.33	Boric acid = 0.90 ± 0.17 Placebo = 0.88 ± 0.34
	6 months	Data not available	Data not available
Singhal et al., 2017	3 months	Boric acid = 2.20 ± 0.41 Placebo = 1.43 ± 0.51	Boric acid = 2.04 ± 0.54 Placebo = 0.95 ± 0.36
	6 months	Boric acid = 3.51 ± 0.51 Placebo = 2.34 ± 0.49	Boric acid = 2.92 ± 0.49 Placebo = 1.52 ± 0.51

performed for, the study being excluded and the new observed change in outcome measure. In bold are the studies for which, when excluded, a change in statistical significance in the results was observed.

Regardless of the study excluded, adjunctive boric acid produced an improvement in both treatment outcomes for both time periods assessed. Changes in significance were observed when Saglam et al. (2013) were excluded from the analyses, and this made the improvement in both PPD and CAL at 3 months post-therapy statistically significant ($p < 0.05$).

3.5 | GRADE assessment

GRADE certainty in the body of evidence for PPD reduction and CAL gain at 3 months post-therapy was very low ($\oplus\oplus\oplus\oplus$).

GRADE certainty in the body of evidence for PPD reduction and CAL gain at 6 months post-therapy was moderate ($\oplus\oplus\oplus\oplus$).

4 | DISCUSSION

4.1 | Summary of evidence

This systematic review identified 4 randomized controlled trials evaluating the efficacy of boric acid as an adjunct to non-surgical periodontal therapy. The trials evaluated boric acid delivered subgingivally to the base of the probing pocket, either as a gel or an irrigant, immediately following non-surgical periodontal therapy. The results of the meta-analyses suggest that boric acid used as an adjunct to non-surgical periodontal therapy produces an improvement in treatment outcomes, as compared to placebo. For PPD, a 0.58 mm mean additional reduction is seen at 3 months and a 1.18 mm mean additional reduction at 6 months. For CAL, a 0.62 mm mean additional gain is seen at 3 months and a 1.24 mm mean additional gain is seen at 6 months. These improvements

are not statistically significant (PPD: $p = 0.06$, CAL: $p = 0.08$) at 3 months post-therapy, but they are statistically significant at 6 months post-therapy ($p < 0.05$). There is a very low certainty in the body of evidence for outcomes at 3 months and a moderate certainty in the body of evidence for outcomes at 6 months. No adverse effects were observed in patients where boric acid was administered as an adjunct.

4.2 | Level of evidence

Whilst all studies were of randomized controlled design, not all studies were of equal quality with regard to the risk of bias assessment. The trial presenting with the most concerning findings for risk of bias was Saglam et al. (2013), where the study was described by the authors as being 'single-masked', that is the personnel administering treatment and analysing outcome data were unblinded. This is highlighted within the article as an issue which should be addressed in future trials, and this poses a risk of introducing biased results into the meta-analyses. This is addressed and highlighted in the sensitivity analyses (Table 3), where exclusion of the study leads to an observed increase in the efficacy of boric acid, as well as a reduction in the heterogeneity between studies.

It should be noted that whilst Mamajiwala et al. (2019) provided data to a high standard, the authors did not report standard deviations for changes from baseline. These values had to be imputed using the correlation coefficient method recommended by the Cochrane Collaboration, leading to an 'unclear' risk of reporting bias. In addition, Mamajiwala et al. (2019) do not make it entirely clear as to whether the personnel providing treatment were blinded. As the statements made in the article could have been interpreted in multiple ways, the study was assigned an 'unclear' risk of bias for this parameter.

The quality of evidence in future systematic reviews on the subject may be particularly improved if future trials report on, and implement, blinding for participants, personnel and outcome assessors, where this is feasible.

4.3 | Comparison with other studies and reviews

Whilst there are no existing reviews evaluating the efficacy of adjunctive boric acid use in the management of periodontitis, this systematic review does conform with the existing evidence that suggests boron, and its derived compounds, possess anti-inflammatory properties.²⁴⁻²⁷ It has been postulated that boron-containing compounds may be efficacious in the management of chronic inflammatory conditions, and the results of this meta-analysis are in line with these findings.^{28,29} The reasons for its efficacy may be largely attributable to the immune-dampening properties of boron derivatives, particularly with regard to pro-inflammatory cytokines such as TNF- α and C-reactive protein.^{23,30} These inflammatory mediators

are known to be critical in the pathophysiology of periodontitis, and downregulation by boric acid may be part of the reason for the observed improvement in treatment outcomes.³¹

The improvements in treatment outcomes observed in this review are similar to, or greater than, the improvements in treatment outcomes which have been observed in meta-analyses evaluating the efficacy of locally administered antibiotics.³² This is of particular importance as it indicates that similar clinical benefits to those derived from the use of antibiotics may be attained through the use of boric acid, without the same drawbacks, namely antibiotic resistance. Direct comparisons between boric acid and antibiotics in future trials would be beneficial in order to validate these findings.

An important consideration when evaluating the clinical application of boric acid is its low pH and the potential for deleterious effects on the tooth structures. Boric acid is a weak acid which dissociates to give solutions of around pH 5.1; in comparison with the pH of conventional phosphoric acid etchant protocols (pH 0.1–0.4), this is far higher, and therefore, the potential for damage of the tooth surfaces is minimal.³³ Another concern associated with an acidic pH is the potential for inducing dentine hypersensitivity, as this can be caused by acidic agents.³⁴ Whilst dentine hypersensitivity was not observed as an adverse event across the included trials, this is not to say that it does not occur; rather, the sample sizes within the meta-analyses may be inadequately powered to pick up these events. Furthermore, a challenge for clinicians would be to identify when hypersensitivity is occurring due to boric acid therapy and when it is simply due to natural recession of the gingivae following periodontal therapy. Whilst statistical computation

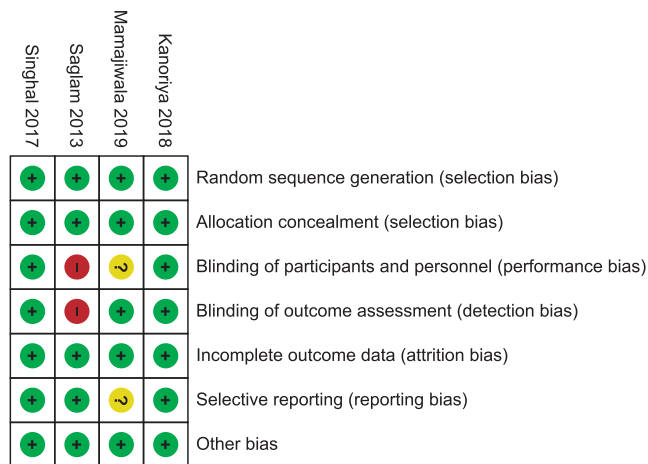
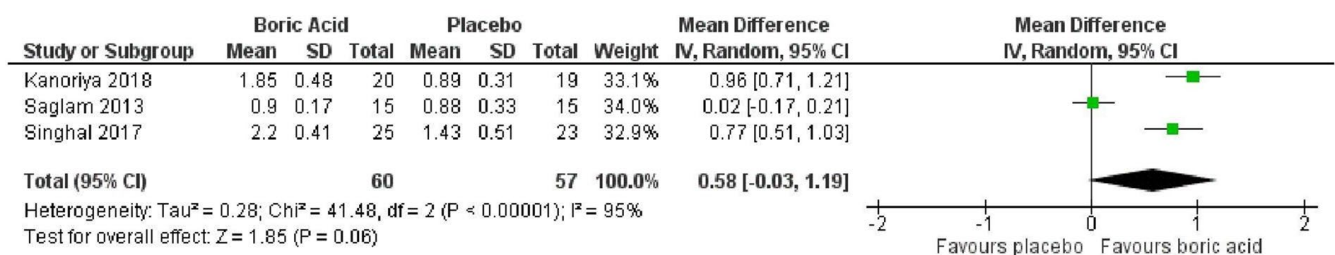


FIGURE 2 Risk of bias summary for all included studies

(A) Effect of boric acid on PPD reduction at 3 months post-therapy



(B) Effect of boric acid on PPD reduction at 6 months post-therapy

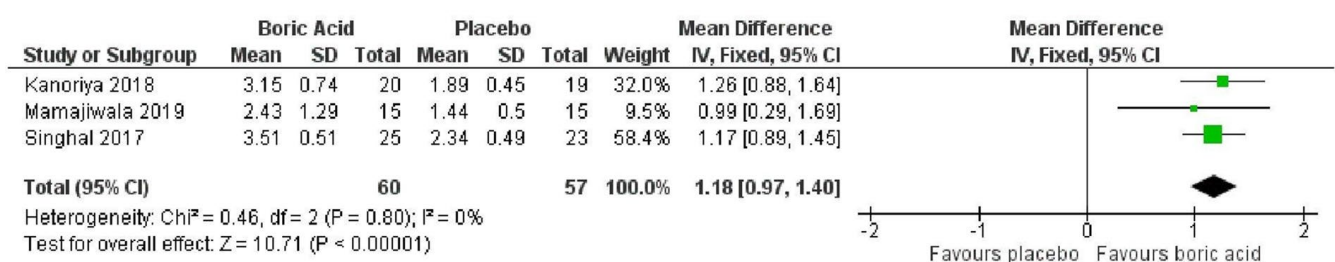
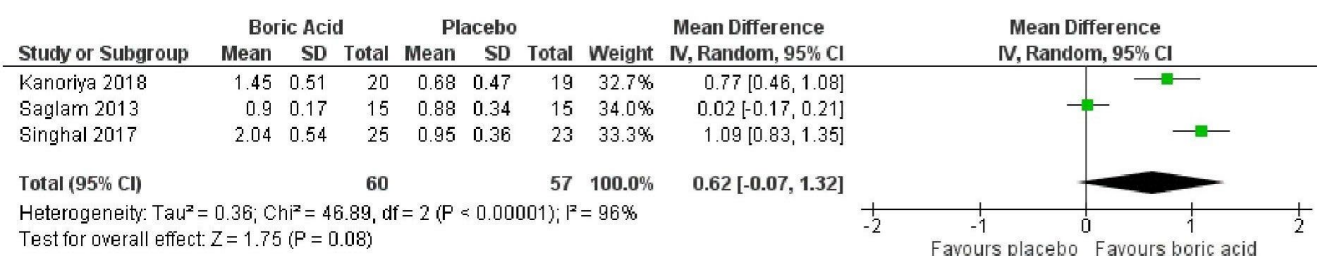


FIGURE 3 Forest plots summarizing effect of adjunctive boric acid on probing pocket depth

(A) Effect of boric acid on CAL gain at 3 months post-therapy



(B) Effect of boric acid on CAL gain at 6 months post-therapy

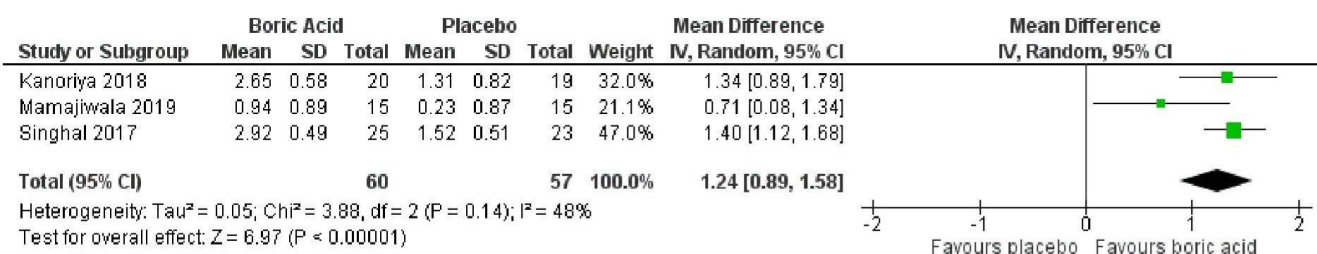


FIGURE 4 Forest plots summarizing effect of adjunctive boric acid on clinical attachment level

of risk ratios or odds ratios would allow for quantifiable risks of hypersensitivity with boric acid therapy, this is infeasible in the present meta-analyses, due to no observed events amongst the included participants.

The findings of this review indicate that the adjunctive use of boric acid may provide improvements in periodontal treatment outcomes, particularly when administered as a gel *in situ*. It has been demonstrated to be safe for human gingival fibroblasts and human periodontal ligament fibroblasts at a concentration of 0.75%.²² However, high-quality literature surrounding the field is scarce, and further investigations into the efficacy, safety and any adverse effects of boric acid should be investigated further before recommendations for its use can be made.

4.4 | Limitations

Whilst the authors endeavoured to locate all relevant studies, it is acknowledged that there may have been studies which were not published, registered or presented. At the time of writing, there was one randomized controlled trial indexed in the Cochrane Library and registered in the WHO International Clinical Trials Registry Platform (Main ID: CTRI/2019/04/018697) with no published results. The protocol outlined for this trial indicates that it would not meet the inclusion criteria for this systematic review, as the control group received adjunctive treatment with curcumin.

All included studies evaluated the pre-defined outcome measures outlined in the review protocol. One of the primary limitations of this systematic review is the quantity of evidence, both in terms of

the number of trials and number of participants within trials. Across the meta-analyses, the total sample size for comparison of boric acid versus placebo was 117 (individual study sample sizes ranging from 30 to 48), which may not be adequately powered to allow for precise estimation of effect size. In addition, not all trials evaluated outcomes at both 3 months and 6 months post-therapy, further reducing the overall sample size incorporated into the meta-analyses. Of the four trials, three were conducted in India and one was conducted in Turkey. Therefore, the external validity of the findings from the meta-analyses in application to cohorts of patients from other countries is unknown.

There was significant heterogeneity for all studies evaluating outcomes at 3 months. This may be largely attributed to the difference in treatment protocols used; 3 of the studies^{17,21,23} evaluated the use of boric acid as a subgingival gel, whilst 1 of the studies²² evaluated its use as a subgingival irrigant. The contribution of Saglam et al. (2013) to the findings of this review is highlighted in the sensitivity analyses (Table 3). The exclusion of this study, where boric acid was administered as an irrigant, results in the observed changes in treatment outcomes at 3 months becoming statistically significant ($p < 0.05$). This indicates that inclusion of this study introduced heterogeneity into the meta-analyses, which led to underestimation of the improvements in PPD and CAL at 3 months, provided that boric acid is administered as a gel *in situ* rather than as an irrigant.

Other sources of heterogeneity include the fact that there was no standardized protocol for non-surgical periodontal therapy across the studies, and the level of disease evaluated across the studies may not have been identical. Whilst all studies defined the patients as having 'chronic periodontitis', no stage and grade of disease was

TABLE 3 Results of sensitivity analyses

Outcome measure	Study excluded	New observed effect
PPD reduction (3 months post-therapy)	Kanoriya et al., 2018	0.39 mm (95% CI: -0.35–1.12 mm)
	Saglam et al., 2013	0.87 mm (95% CI: 0.68–1.05 mm)
	Singhal et al., 2017	0.49 mm (95% CI: -0.44–1.41 mm)
PPD reduction (6 months post-therapy)	Kanoriya et al., 2018	1.13 mm (95% CI: 0.88–1.39 mm)
	Mamajiwala et al., 2019	1.20 mm (95% CI: 0.97–1.43 mm)
	Singhal et al., 2017	1.18 mm (95% CI: 0.86–1.49 mm)
CAL gain (3 months post-therapy)	Kanoriya et al., 2018	0.53 mm (95% CI: -0.50–1.60 mm)
	Saglam et al., 2013	0.94 mm (95% CI: 0.63–1.25 mm)
	Singhal et al., 2017	0.39 mm (95% CI: -0.35–1.12 mm)
CAL gain (6 months post-therapy)	Kanoriya et al., 2018	1.11 mm (95% CI: 0.45–1.78 mm)
	Mamajiwala et al., 2019	1.38 mm (95% CI: 1.14–1.62 mm)
	Singhal et al., 2017	1.07 mm (95% CI: 0.45–1.68 mm)

given as defined in the 2017 World Workshop on the Classification of Periodontal and Peri-Implant Diseases and Conditions. This may make comparison across studies less accurate if the level of disease is not the same between the participants. In addition, the exact sites evaluated differed; Singhal et al. (2017) evaluated outcomes in areas of furcation defects, whilst all other studies evaluated full mouth outcomes.

Inclusion of a trial with high risk of bias²² may affect the validity of the meta-analyses. As aforementioned, this was addressed through means of sensitivity analyses, which brought up two pertinent points: (i) whether inclusion of this study resulted in underestimation of the efficacy of adjunctive boric acid as a whole and (ii) whether administration of boric acid as an irrigant is less effective than administration as an *in situ* gel. These observed differences in the efficacy of delivery as a gel versus delivery as an irrigant may be accounted for by two main reasons: (i) it is postulated that a gel may remain *in situ* for a greater period of time than an irrigant and hence exert its beneficial antimicrobial and immunomodulatory properties for a greater length of time, and (ii) differences in the measurement protocols used: the study investigating boric acid delivered as an irrigant (Saglam et al., 2013) provided both whole-mouth and site-specific changes and found significant differences between boric acid and placebo at the site-specific level, but not the whole-mouth level. However, the site-specific measures could not be incorporated for meta-analysis due to the authors only reporting on site-specific measures for the three deepest, non-contiguous sites, and it is likely that if the site-specific measures for all sites were provided (allowing for inclusion in meta-analyses), then significant

improvements with boric acid would also be seen, in line with the trials investigating gel delivery.

Furthermore, outcomes were only reported up to 6 months post-therapy. Longer follow-up periods are needed before judgements on the long-term effectiveness of boric acid can be made.

In order to allow for more accurate pooling of data, it would be advised that future researchers:

1. Enrol a greater number of participants into randomized controlled trials
2. Implement methods to minimize risk of bias, such as a triple-blind study design
3. Develop and use a standardized protocol for the administration of boric acid
4. Develop and use a standardized protocol for the administration of non-surgical periodontal therapy
5. Report on stage and grade of the periodontitis being evaluated
6. Evaluate outcomes over a longer time period

5 | CONCLUSIONS

Within the limitations of this review, it can be concluded that:

1. Boric acid as an adjunct to non-surgical periodontal therapy may improve treatment outcomes
2. Adjunctive boric acid at 0.75% concentration does not increase the risk of adverse events, as compared with placebo
3. There is a paucity of literature surrounding the subject, necessitating more high-quality, adequately powered, randomized controlled trials

6 | CLINICAL RELEVANCE

6.1 | Scientific rationale for the study

Despite trials having been conducted on the subject, there have been no systematic reviews evaluating the efficacy of boric acid as an adjunct to non-surgical periodontal therapy.

6.2 | Principal findings

Adjunctive boric acid use is associated with improvements in clinical outcomes compared to non-surgical periodontal therapy alone. Improvements are seen in both probing pocket depth and clinical attachment level, with no adverse events reported thus far.

6.3 | Practical implications

There is evidence that boric acid used as an adjunctive agent may improve the outcomes of non-surgical periodontal therapy.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

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Nil.

AUTHOR CONTRIBUTIONS

NZB conceived the idea. NZB and MK designed the study. NZB and MK collected the data. NZB analysed the data. NZB and MK drafted and revised the report.

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APPENDIX 1

Full electronic search strategy for PubMed

PubMed input query	Items returned
(((((("boric acid"[Supplementary Concept] OR "boric acid"[All Fields]) OR ((("boric acid"[Supplementary Concept] OR "boric acid"[All Fields]) OR "orthoboric acid"[All Fields])) OR ("boracic"[All Fields] AND ((("acids"[MeSH Terms] OR "acids"[All Fields]) OR "acid"[All Fields]))) OR "sassolite"[All Fields]) OR (((((((("boron"[MeSH Terms] OR "boron"[All Fields]) OR "borons"[All Fields]) OR "boronate"[All Fields]) OR "boronated"[All Fields]) OR "boronates"[All Fields]) OR "boronation"[All Fields]) OR "boronic"[All Fields]) OR "borons"[All Fields] AND "trihydroxide"[All Fields])) AND ("periodont**"[All Fields] OR (((("gingival diseases"[MeSH Terms] OR ("gingival"[All Fields] AND "diseases"[All Fields])) OR "gingival diseases"[All Fields]) OR ("gum"[All Fields] AND "disease"[All Fields])) OR "gum disease"[All Fields]))	13

APPENDIX 2

Data extraction spreadsheet

Author	Year	Country	Setting	Age	Test group (n)	Boric acid administration	Placebo group (n)	Placebo administration	Outcomes evaluated at

APPENDIX 3

Correlation coefficient calculations

All imputations were conducted using the correlation coefficient formulae outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins et al., 2019):

$$Corr_E = \frac{SD_{E(baseline)}^2 + SD_{E(final)}^2 - SD_{E(change)}^2}{2 \times SD_{E(baseline)} \times SD_{E(final)}}$$

$$SD_{E(change)} = \sqrt{SD_{E(baseline)}^2 + SD_{E(final)}^2 - (2 \times Corr \times SD_{E(baseline)} \times SD_{E(final)})}$$

Kanoriya et al. (2018) was identified as a study reporting all necessary detail to allow for correlation coefficient calculations. These correlation coefficients were then used alongside the data available from Mamajiwala et al. (2019) in order to impute standard deviations.

PROBING POCKET DEPTH

$$Corr_{boric\ acid} = \frac{0.85^2 + 0.50^2 - 0.74^2}{2 \times 0.85 \times 0.50} = \frac{4249}{8500}$$

$$SD_{boric\ acid\ (change)} = \sqrt{1.48^2 + 0.62^2 - \left(2 \times \frac{4249}{8500} \times 1.48 \times 0.62\right)} = 1.29$$

$$Corr_{placebo} = \frac{0.91^2 + 0.70^2 - 0.45^2}{2 \times 0.91 \times 0.70} = \frac{2789}{3185}$$

$$SD_{placebo (change)} = \sqrt{0.97^2 + 1.01^2 - \left(2 \times \frac{2789}{3185} \times 0.97 \times 1.01\right)} = 0.50$$

CLINICAL ATTACHMENT LEVEL

$$Corr_{boric acid} = \frac{0.65^2 + 0.60^2 - 0.58^2}{2 \times 0.65 \times 0.60} = \frac{1487}{2600}$$

$$SD_{boric acid (change)} = \sqrt{1.01^2 + 0.89^2 - \left(2 \times \frac{1487}{2600} \times 1.01 \times 0.89\right)} = 0.89$$

$$Corr_{placebo} = \frac{1.08^2 + 0.61^2 - 0.82^2}{2 \times 1.08 \times 0.61} = \frac{2887}{4392}$$

$$SD_{placebo (change)} = \sqrt{0.98^2 + 1.11^2 - \left(2 \times \frac{2887}{4392} \times 0.98 \times 1.11\right)} = 0.87$$

APPENDIX 4

Narrative description for risk of bias assessment

Bias	Authors' judgement	Support for judgement
Kanoriya et al., 2018		
Random sequence generation (selection bias)	Low risk	Explicitly states use of a computer-generated method: 'Randomly (computer generated) assigned into two treatment groups.'
Allocation concealment (selection bias)	Low risk	Explicitly states concealment: 'Patients, as well as investigators, were masked for allocation into the BA group or placebo group.'
Blinding of participants and personnel (performance bias)	Low risk	Explicitly states blinding: 'A single clinician (DK) provided treatment to both groups, and all clinical parameters pre- and post-treatment were recorded by another examiner (ARP) who was also blinded to the type of treatment received by the patients.'
Blinding of outcome assessment (detection bias)	Low risk	Explicitly states blinding: 'A single clinician (DK) provided treatment to both groups, and all clinical parameters pre- and post-treatment were recorded by another examiner (ARP) who was also blinded to the type of treatment received by the patients.'
Incomplete outcome data (attrition bias)	Low risk	All outcomes were reported on. There was a 93% recall rate and a per protocol analysis was carried out. Intention-to-treat analysis would be difficult given that the data evaluated was continuous.
Selective reporting (reporting bias)	Low risk	Outcomes were evaluated against the methods section of the paper and no discrepancies were found.
Other bias	Low risk	No other sources of bias were identified.
Mamajiwala et al., 2019		
Random sequence generation (selection bias)	Low risk	Explicitly states use of a computer-generated method: 'Randomly divided into three groups using computer-generated random sequence table.'
Allocation concealment (selection bias)	Low risk	Explicitly states concealment: 'The examiner who performed the enrolment process was blinded to the randomization procedure.'

APPENDIX 4 (Continued)

Bias	Authors' judgement	Support for judgement
Blinding of participants and personnel (performance bias)	Unclear risk	The statement made regarding concealment is not clear in whether all personnel were blinded or not: 'The examiner who performed measurements were blinded to the type of treatment given to the participants and other examiner performed all treatment procedures.'
Blinding of outcome assessment (detection bias)	Low risk	Explicitly states blinding: 'The examiner who performed measurements were blinded to the type of treatment given to the participants.'
Incomplete outcome data (attrition bias)	Low risk	All outcomes were reported on. This meant they had to be imputed using a correlation coefficient method. There was a 93% recall rate and a per protocol analysis was carried out. Intention-to-treat analysis would be difficult given that the data evaluated was continuous.
Selective reporting (reporting bias)	Unclear risk	Outcomes were evaluated against the methods section of the paper and no discrepancies were found. Standard deviations for change from baseline were not provided and had to be imputed; reasons for this were not provided.
Other bias	Low risk	No other sources of bias were identified.
Saglam et al., 2013		
Random sequence generation (selection bias)	Low risk	Explicitly states use of a digital method: 'The same examiner had only digital cards of patients (a plastic card contains patient information and can only be read with a computer program).'
Allocation concealment (selection bias)	Low risk	Explicitly states blinding: 'SSH drew cards blindly'.
Blinding of participants and personnel (performance bias)	High risk	Explicitly states the study is 'single-masked', meaning personnel were not blinded.
Blinding of outcome assessment (detection bias)	Low risk	Explicitly states the study is 'single-masked', meaning outcome assessment was not blinded.
Incomplete outcome data (attrition bias)	Low risk	All outcomes were reported on. There was a 100% recall rate and a per protocol analysis was carried out. Intention-to-treat analysis would be difficult given that the data evaluated was continuous.
Selective reporting (reporting bias)	Low risk	Outcomes were evaluated against the methods section of the paper and no discrepancies were found.
Other bias	Low risk	No other sources of bias were identified.
Singhal et al., 2017		
Random sequence generation (selection bias)	Low risk	Explicitly states use of a computer-generated method: 'sites were then randomly assigned (by a computer-generated system)'.
Allocation concealment (selection bias)	Low risk	Explicitly states masking of participants in the trial protocol.
Blinding of participants and personnel (performance bias)	Low risk	Explicitly states blinding: 'SRP local delivery of .75% BA gel or placebo gel in the BA group and placebo groups was done by the same operator (S.S) who was blinded to the treatment groups.'
Blinding of outcome assessment (detection bias)	Low risk	Explicitly states blinding: 'The examiner (A.R.P), who was masked to the type of treatment received at the site, recorded all pre- and post-treatment clinical parameters.'
Incomplete outcome data (attrition bias)	Low risk	All outcomes given as means and standard deviations. There was an 83% recall rate and a per protocol analysis was carried out. Intention-to-treat analysis would be difficult given that the data evaluated was continuous.
Selective reporting (reporting bias)	Low risk	Outcomes were evaluated against the methods section of the paper and no discrepancies were found.
Other bias	Low risk	No other sources of bias were identified.