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REVIEW ARTICLE

Clarithromycin as an adjunct to periodontal therapy: a systematic review and meta-analysis

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Abstract

Objective: To collate the literature evaluating the efficacy of clarithromycin as an adjunct to non-surgical periodontal therapy and conduct meta-analyses for changes in probing pocket depth (PPD) and clinical attachment level (CAL).

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

Results: *Systemic delivery*: 0.65 mm (95% CI: 0.02 to 1.27 mm) mean additional PPD reduction was observed at 3 months and 0.28 mm (95% CI: −0.32 to 0.87 mm) at 6 months. 0.41 mm (95% CI: −0.12 to 0.95 mm) mean additional CAL gain was observed at 3 months, and 0.16 mm (95% CI: −0.41 to 0.74 mm) at 6 months. Increased risk of adverse events was observed; RR: 5.13 (95% CI: 0.63 to 41.98). *Local delivery*: 1.01 mm (95% CI: 0.84 to 1.17 mm) mean additional PPD reduction was observed at 3 months, and 1.20 mm (95% CI: 0.76 to 1.64 mm) at 6 months. 0.56 mm (95% CI: 0.46 to 0.66 mm) mean additional CAL gain was observed at 3 months, and 0.83 mm (95% CI: 0.65 to 1.02 mm) at 6 months. No adverse events were observed.

Conclusions: The use of locally delivered clarithromycin significantly improves treatment outcomes.

KEYWORDS
anti-bacterial agents, clarithromycin, periodontitis, root surface debridement, treatment outcome

1 | INTRODUCTION

Periodontitis is a chronic inflammatory disease modulated by host-bacteria interactions and characterized by loss of attachment.[1] Management of the disease centres around eliminating the pathogenic microbiota, with a view to dampen the inflammatory response and promote healing.[2] Non-surgical periodontal therapy forms the cornerstone of treatment; mechanical debridement of the root surface has been shown to be efficacious, inducing improvements in clinical outcomes.[3] If managed inappropriately, the disease ultimately leads to loss of the affected dentition, and untreated periodontal disease stands as the most common cause of tooth loss.[4] In addition, the detrimental effects of the disease extend beyond the oral cavity, and periodontitis has been associated with a number of other chronic, non-communicable, inflammatory conditions, such as diabetes mellitus, cardiovascular disease, chronic kidney disease and chronic obstructive pulmonary disease.[5-8]

For periodontitis, given that the causative agent is bacterial, the efficacy of antimicrobial agents has been investigated extensively. Antibiotics have been shown to produce additional improvements in treatment outcomes and tend to be of particular use in areas of deep pockets, or in instances when non-surgical therapy alone does not prove to be efficacious.[9,10] However, it should be stressed that antibiotics are not an alternative treatment method to non-surgical therapy, rather, they may be used as an adjunctive treatment, in some, selected cases. The use of antimicrobials is judicious due to concerns around antimicrobial resistance.[11]

Among antimicrobials in use for periodontitis, the greatest volume of evidence exists for amoxicillin and metronidazole as systemic agents and chlorhexidine as a local agent. Aside from azithromycin, the macrolide family of antibiotics have not been investigated as thoroughly, despite the fact that this family of antibiotics have properties which may confer clinical benefits in the management of periodontitis. Macrolides are known to display anti-inflammatory actions through their immunomodulatory effects on pro-inflammatory cytokines, which is enhanced by their ability to inhibit neutrophil chemotaxis and suppress the production of reactive oxygen species—all of which are key components in the pathophysiology of periodontal disease.[12,13] Furthermore, macrolides are effective against a broad spectrum of bacteria, which is important, given that periodontitis is a complex disease in which a disparate group of bacteria are implicated.[14,15] Clarithromycin is an antibiotic in the macrolide family which possesses these potentially beneficial properties and, therefore, may convey benefits as an adjunctive agent in periodontal treatment. The drug is a second-generation derivative of erythromycin A used to treat conditions such a gastric ulcers caused by *Helicobacter pylori* and AIDS-associated respiratory disease caused by *Mycobacterium avium*.[14] Clarithromycin has a number of beneficial properties for management of bacterial conditions, such as a high oral bioavailability combined with an extended plasma half-life allowing for lower dosages to be used, lipophilic properties resulting in enhanced tissue penetration, structural modifications to its lactone ring which make it immune to acid-induced inactivation, and potency against a wide spectrum of bacterial species.[14] This combination of properties makes clarithromycin a promising drug for the management of periodontal disease. Some potentially hazardous effects of clarithromycin use include anaphylaxis and adverse gastrointestinal reactions, as well as the risks of macrolide resistance which are associated with abuse of any antibiotic medication.[14,15] Despite possessing potentially beneficial properties, to the authors' knowledge there are no systematic reviews evaluating the efficacy of clarithromycin in periodontal therapy. The aim of this systematic review is to assess the efficacy of clarithromycin, either systemically or locally delivered, as an adjunct to non-surgical periodontal therapy, as compared to placebo, in patients with periodontitis. The primary outcomes being assessed were change in probing pocket depth (PPD) and clinical attachment level (CAL).

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 (CRD42020187766). 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. [16]

2.2 | Study eligibility

Studies were included according to PICOS criteria.

(P)opulation: Patients with periodontitis, where periodontitis is defined as PPD ≥5 mm and / or ≥4 mm loss of CAL.[17]

(I)ntervention: Subgingival debridement (i.e. scaling and root planing or root surface debridement) plus adjunctive clarithromycin, delivered either systemically or locally.

(C)omparison: Subgingival debridement plus adjunctive placebo, delivered either systemically or locally.

(O)utcome: There were two primary outcome measures: change in PPD and change in CAL compared with baseline. Secondary outcome measures evaluated were adverse events due to adjunctive clarithromycin therapy.

(S)tudy design: Randomized controlled trials with at least 3 months of follow-up.

Studies were included if they were of randomized controlled design with a minimum of 3-month follow-up period and gave quantitative changes in PPD and CAL, and if they were in the English language. Studies were excluded if they evaluated outcomes in participants below the age of 18 years, evaluated outcomes in implants, if they were animal trials, or if they evaluated outcomes with surgical periodontal therapy. No restrictions were placed on the studies according to date of publication, phase of the trials or method of clarithromycin administration.

2.3 | Information sources and search

Five electronic databases were searched from inception to May 2020: PubMed, Cochrane Central Register of Controlled Trials, EMBASE via OVID, Web of Science and OpenGrey. Additionally, reference list follow-ups of all included studies were conducted. Search terms were developed by expanding upon the subject headings of 'clarithromycin' and 'periodontitis', using synonyms, indexed terms and author knowledge. A search strategy was developed by combining these terms using Boolean operators. The full search strategy for PubMed, with MeSH terms, is presented in Supplementary Table S1.

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 extraction sheet was pre-piloted and then implemented for data extraction by a single reviewer (NZB). The second reviewer (PS) verified the accuracy of data obtained from the studies.

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.[16] 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

Data from the included studies were pooled, using mean difference (mm) and standard deviations (SDs) in PPD and CAL at 3- and 6-month time periods, compared with baseline. Where SDs were not provided, authors were contacted for individual patient data to allow for calculation. If these data could not be obtained, SDs were imputed using the correlation coefficient method recommended for missing SDs in the Cochrane Handbook for Systematic Reviews of Interventions.[16] The secondary outcome measure, adverse events, was assessed through calculation of risk ratios. Forest plots were generated to present the findings of the meta-analyses.

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. Forest plots were generated to illustrate the findings of the meta-analyses. All analyses were programmed in Stata version 16.0 (StataCorp).

Statistical heterogeneity was assessed through calculation of the inconsistency (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.

The following additional tests were conducted as per the guidelines in the Cochrane Handbook for Systematic Reviews of Interventions:[16]

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.

2.8 | Certainty assessment

Assessment of certainty in the overall body of evidence 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. GRADE assessments were made separately for outcomes with systemically and locally delivered clarithromycin.

3 | RESULTS

3.1 | Selected studies

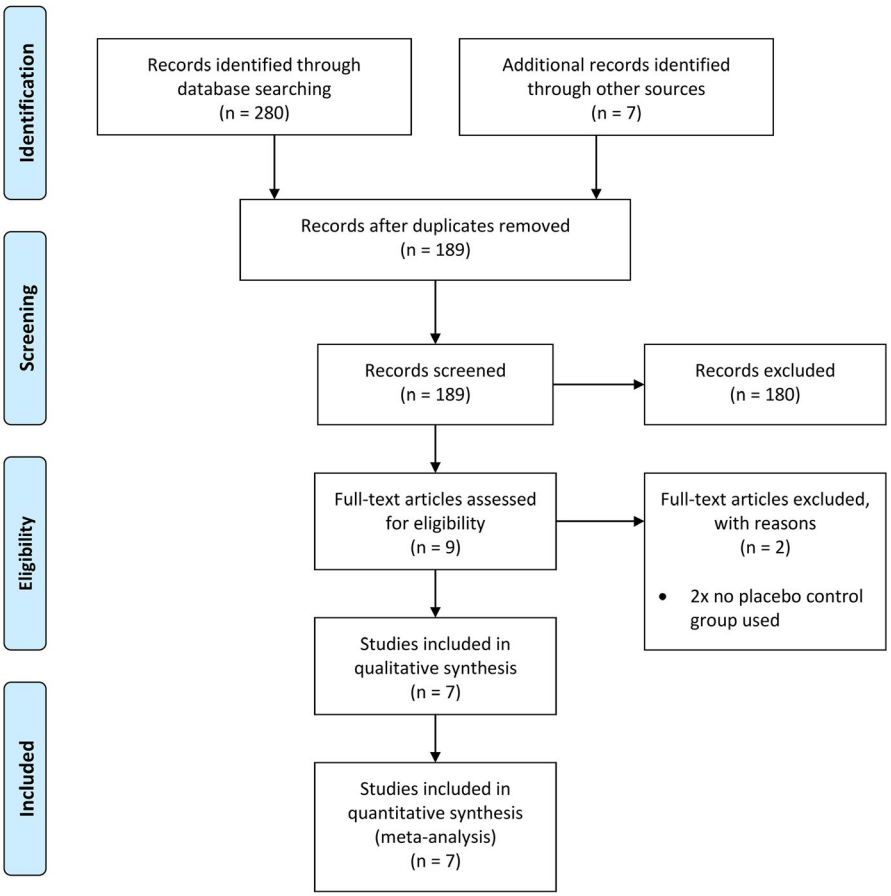
The initial search returned 287 articles. Ninety-eight articles were identified as duplicates. The remaining 189 articles were screened according to title and abstract, and 180 were excluded (kappa = 1.00, 95% CI: 1.00–1.00). The remaining 9 studies underwent full-text analysis, of which 7 were suitable for meta-analysis (kappa = 1.00, 95% CI: 1.00–1.00). Two articles were excluded at full-text analysis due to lack of a placebo-control group.[18,19] The study selection process is outlined as a PRISMA flow chart in Figure 1.

3.2 | Study characteristics

3.2.1 | *Study design and demographics*

All studies were double-blinded, randomized, placebo-controlled, clinical trials. The author and year, study design, disease type, country, setting, mean age of participants, sample size, treatment protocols and time at which outcomes were evaluated are outlined in Table 1. Four studies evaluating systemically delivered clarithromycin were included,[20-23] and three studies evaluating locally delivered clarithromycin were included.[24-26] All studies excluded at full-text analysis are presented in Table 2, with reasons for exclusion.

FIGURE 1 PRISMA flow chart



3.2.2 | *Disease studied*

All studies used diagnostic terminology outlined in the 1999 Periodontal Disease Classification System.[27] Two of the studies evaluated the efficacy of adjunctive clarithromycin in patients with 'generalised aggressive periodontititis'. The remaining five studies evaluated the efficacy of adjunctive clarithromycin in patients with 'chronic periodontitis'.

3.2.3 | *Outcome assessment*

All studies reported on changes in PPD and CAL from baseline to 3-month and / or 6-month post-intervention. Bechara Andere et al., 2018 only reported site-specific changes for outcomes at 3 months and was, therefore, excluded from the meta-analyses for 3-month outcomes, as all other studies on systemic administration reported full-mouth outcomes. Kathariya et al., 2014 reported changes at 4 weeks, 8 weeks and 12 weeks post-therapy; the results at 12 weeks were incorporated into the meta-analyses for outcomes at 3 months, and the study was excluded from the meta-analyses for outcomes at 6 months. All studies evaluating systemic administration evaluated changes in PPD and CAL at full-mouth level, while all studies evaluating local administration evaluated changes at the site-specific level.

The data for changes in PPD and CAL for all included studies are presented in Table 3.

3.2.4 | *Risk of bias*

A risk of bias summary for all included studies is provided in Figure 2.

A narrative description, with authors' judgements and evidence for these judgements, regarding each risk of bias parameter was documented. This is presented in Supplementary Table S2.

3.3 | Synthesis of results

3.3.1 | *Systemic administration*

The adjunctive use of systemically administered clarithromycin resulted in a mean additional reduction in PPD of 0.65 mm (95% CI: 0.04 to 1.26 mm; $p = 0.04$) at 3 months, a mean additional reduction in PPD of 0.28 mm (95% CI: −0.25 to 0.80 mm; $p = 0.30$) at 6 months, a mean additional gain in CAL of 0.41 mm (95% CI: −0.11 to 0.92 mm; $p = 0.12$) at 3 months and a mean additional gain in CAL of 0.16 mm (95% CI: −0.37 to 0.70 mm; $p = 0.55$) at 6 months (Figure 3). Studies evaluating PPD at 3 months, PPD at 6 months, CAL at 3 months, and CAL at 6 months all displayed significant heterogeneity ($I^2 > 40\%$). Therefore, random effects models were used for all meta-analyses.

In trials investigating systemically administered clarithromycin, adverse events were observed in two of the studies, and the events comprised gastrointestinal discomfort and unpalatable

TABLE 1 Characteristics of included studies

Reference	Study design	Disease type	Setting	Age range (years)	Test group (*n*)	Test group protocol	Placebo group (*n*)	Placebo group protocol	Outcomes evaluated At	Outcome assessment method
Studies evaluating systemically delivered clarithromycin										
Andere NMRB et al., 2017[20]	Double-blind randomized controlled trial	Generalized aggressive periodontitis	Hospital	Age range not given (all patients >35 years of age)	(20)	500 mg clarithromycin tablets BD for 7 days	(20)	Placebo tablets prescribed	Baseline 3 months 6 months	Full-mouth
Bechara Andere NMR et al., 2018[21]	Double-blind randomized controlled trial	Generalized aggressive periodontitis	Hospital	Age range not given (all patients >35 years of age)	(18)	500 mg clarithromycin tablets BD for 3 days	(18)	Placebo tablets prescribed	Baseline 3 months 6 months	Full-mouth
Pradeep AR et al., 2011[22]	Double-blind randomized controlled trial	Chronic periodontitis	Hospital	26–48	(18)	500 mg clarithromycin tablets BD for 3 days	(19)	Placebo tablets prescribed	Baseline 1 month 3 months 6 months 9 months	Full-mouth
Suryaprasanna J et al., 2018[23]	Double-blind randomized controlled trial	Chronic periodontitis	Hospital	30–50	(15)	500 mg clarithromycin tablets TDS for 7 days	(15)	Placebo tablets prescribed	Baseline 3 months 6 months	Full-mouth
Studies evaluating locally delivered clarithromycin										
Agarwal E et al., 2012[24]	Double-blind randomized controlled trial	Chronic periodontitis	Hospital	30–50	(28)	0.5% clarithromycin gel placed *in situ*	(27)	Placebo gel placed *in situ*	Baseline 1 month 3 months 6 months	Site-specific
Bajaj P et al., 2012[25]	Double-blind randomized controlled trial	Chronic periodontitis	Hospital	30–50	(29)	0.5% clarithromycin gel placed *in situ*	(27)	Placebo gel placed *in situ*	Baseline 1 month 3 months 6 months	Site-specific
Kathariya et al., 2014[26]	Double-blind randomized controlled trial	Chronic periodontitis	Hospital	25–50	(50)	0.5% clarithromycin gel placed *in situ*	(48)	Placebo gel placed *in situ*	Baseline 4 weeks 8 weeks 12 weeks	Site-specific

TABLE 2 Studies excluded at full-text analysis

Study excluded	Reason for exclusion
Araujo CF et al., 2019[18]	No placebo-control group used
Li CX et al., 2017[19]	No placebo-control group used

taste. Log risk ratios for adverse events with systemically administered clarithromycin were −0.11 (95% CI: −0.24 to 0.02; p = 0.09) (Figure 4).

3.3.2 | *Local administration*

Locally administered clarithromycin resulted in a mean additional reduction in PPD of 1.01 mm (95% CI: 0.87 to 1.15 mm; p = 0.00) at 3 months, a mean additional reduction in PPD of 1.20 mm (95% CI: 0.76 to 1.64 mm; p = 0.00) at 6 months, a mean additional gain in CAL of 0.56 mm (95% CI: 0.44 to 0.68 mm; p = 0.00) at 3 months and a mean additional gain in CAL of 0.83 mm (95% CI: 0.64 to 1.03 mm; p = 0.00) at 6 months (Figure 5). Studies evaluating PPD at 3 months, CAL at 3 months and CAL at 6 months all displayed low heterogeneity (I^2 = 0%). Therefore, fixed effects models were used for these meta-analyses. Studies evaluating PPD at 6 months displayed significant heterogeneity (I^2 > 40%). Therefore, a random effects model was used for this meta-analysis.

In the trials investigating locally administered clarithromycin, no adverse events were observed, so risk ratios could not be calculated.

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

The results of the sensitivity analyses are presented in Supplementary Table S3. Outlined in is the outcome measure which the analysis was performed for, the study being excluded, and the new observed change in outcome measure.

TABLE 3 Changes in outcome in included studies

Study	Outcome		Test Group (mm ± SD)	Placebo Group (mm ± SD)
Studies evaluating systemically administered clarithromycin				
Andere NMRB et al., 2017	PPD reduction	3 months	0.80 ± 0.38	0.76 ± 0.38
		6 months	0.81 ± 0.40	0.76 ± 0.40
	CAL gain	3 months	0.76 ± 0.34	0.70 ± 0.37
		6 months	0.77 ± 0.40	0.69 ± 0.40
Bechara Andere NMR et al., 2018	PPD reduction	3 months	Data not available	Data not available
		6 months	0.66 ± 0.36	0.88 ± 0.28
	CAL gain	3 months	Data not available	Data not available
		6 months	0.63 ± 0.31	0.80 ± 0.21
Pradeep et al., 2011	PPD reduction	3 months	2.04 ± 0.37	1.16 ± 0.33
		6 months	2.00 ± 0.36	1.00 ± 0.31
	CAL gain	3 months	1.85 ± 0.35	0.93 ± 0.22
		6 months	1.81 ± 0.36	0.86 ± 0.23
Suryaprasanna J et al., 2018	PPD reduction	3 months	3.88 ± 0.45	2.84 ± 0.54
		6 months	3.00 ± 0.48	2.73 ± 0.56
	CAL gain	3 months	3.17 ± 0.35	2.93 ± 0.22
		6 months	2.42 ± 0.50	2.64 ± 0.25
Studies evaluating locally administered clarithromycin				
Agarwal et al., 2012	PPD reduction	3 months	2.28 ± 0.41	1.25 ± 0.55
		6 months	2.53 ± 0.46	1.10 ± 0.58
	CAL gain	3 months	1.71 ± 0.35	1.11 ± 0.24
		6 months	1.52 ± 0.70	0.68 ± 0.28
Bajaj et al., 2012	PPD reduction	3 months	2.36 ± 0.38	1.35 ± 0.53
		6 months	2.15 ± 0.40	1.17 ± 0.58
	CAL gain	3 months	1.64 ± 0.31	1.12 ± 0.19
		6 months	1.37 ± 0.66	0.54 ± 0.24
Kathariya et al., 2014	PPD reduction	3 months	3.23 ± 1.37	2.33 ± 1.12
		6 months	Data not available	Data not available
	CAL gain	3 months	2.87 ± 1.34	2.15 ± 1.00
		6 months	Data not available	Data not available

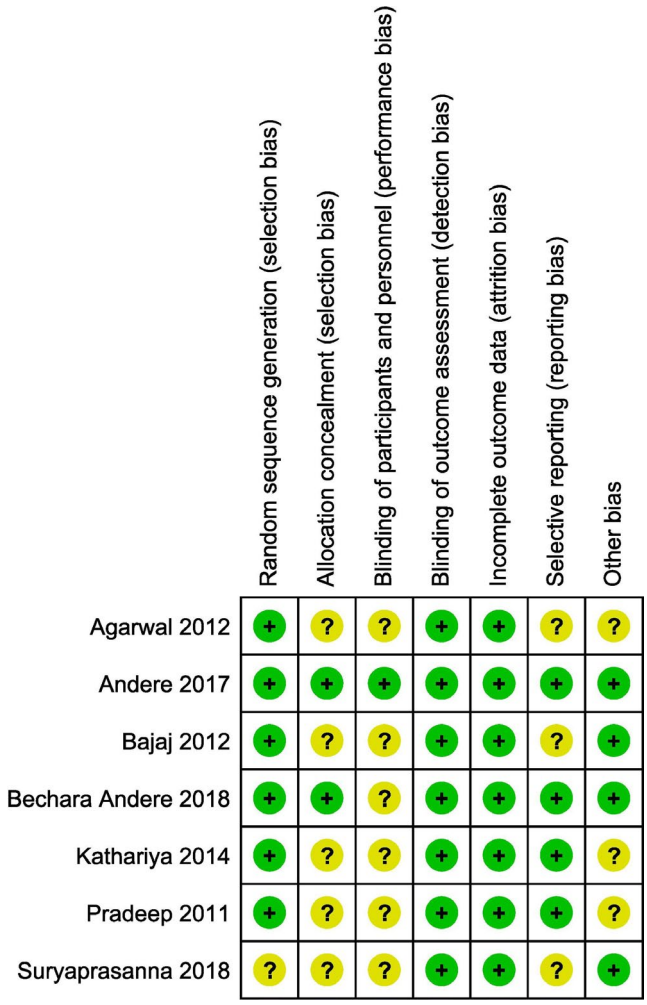


FIGURE 2 Risk of bias summary

GRADE assessment for all outcomes with systemically delivered clarithromycin was assessed as low (⊕⊕○○). GRADE assessment for all outcomes with locally delivered clarithromycin was assessed as moderate (⊕⊕⊕○).

4 | DISCUSSION

4.1 | Summary of evidence

This systematic review identified seven randomized controlled trials evaluating the efficacy of clarithromycin as an adjunct to non-surgical periodontal therapy. Of these, four trials evaluated systemic drug administration, and three trials evaluated local drug administration. The results of the meta-analyses suggest that clarithromycin used as an adjunct to non-surgical periodontal therapy produces an improvement in treatment outcomes, as compared to placebo.

For systemically administered clarithromycin, an additional 0.65 mm of PPD reduction is observed at 3 months, an additional 0.28 mm of PPD reduction is observed at 6 months, an additional 0.41 mm of CAL gain is observed at 3 months, and an additional 0.16 mm of CAL gain is observed at 6 months. Of these results, only the additional PPD reduction at 3 months is statistically significant ($p < 0.05$).

For locally administered clarithromycin, an additional 1.01 mm of PPD reduction is observed at 3 months, an additional 1.20 mm of PPD reduction is observed at 6 months, an additional 0.56 mm of CAL gain is observed at 3 months, and an additional 0.83 mm of CAL gain is observed at 6 months. All of these results are statistically significant ($p < 0.05$).

An increased risk of adverse events is observed with systemic administration of clarithromycin, and this increased risk is not statistically significant ($p > 0.05$). No adverse events are observed with local administration.

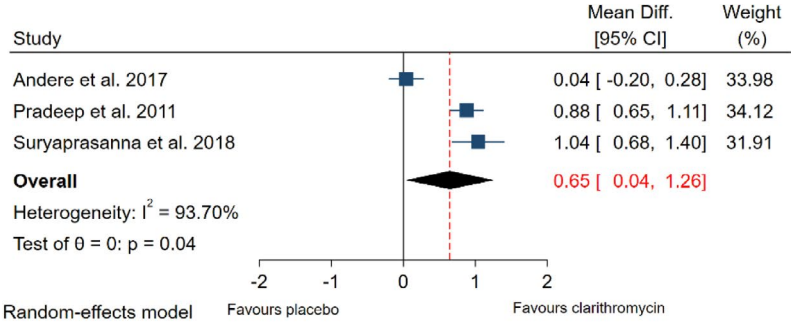
4.2 | Level of evidence

While all studies were of double-blind, randomized, controlled design, not all studies were of equal quality with regard to the risk of bias assessment. The most common finding in the risk of bias assessment was an 'unclear' risk of bias with regard to blinding of the participants and personnel. The reasons for this were largely down to lack of clarity within the trials as to exactly who was blinded and how this was achieved. As all studies were declared as 'double-blind', it would be implied that blinding was implemented, but a lack of clarity from the authors in describing exactly which personnel were blinded lead to an 'unclear' risk assessment for the majority of studies. The next most common finding was an 'unclear' risk of bias assessment for allocation concealment. Again, no unsatisfactory methods of allocation concealment were implemented in any of the trials, but, rather, reporting on the method of allocation concealment was not clear in many of the studies, leading to an 'unclear' risk of bias assessment for this parameter.

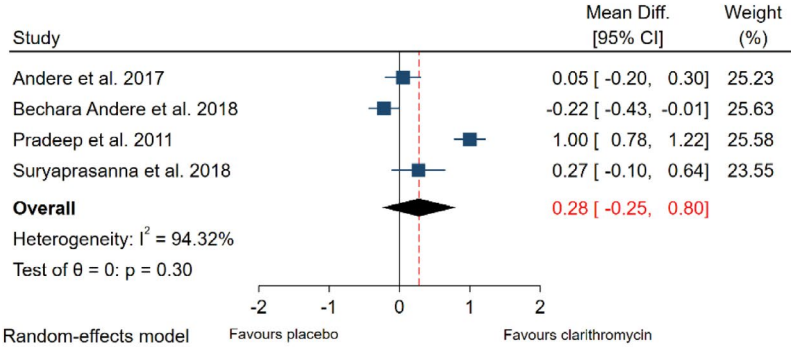
Reporting bias was also deemed as 'unclear' for the three trials where standard deviations for changes from baseline were missing. Reasons for this data not being provided was not made clear and standard deviations had to be imputed using correlation coefficients, as recommended by the Cochrane Collaboration. Three trials were deemed as being at 'unclear' in the risk assessment for other bias, as the clarithromycin used was provided by an external healthcare company. However, the external provider did not appear to have any impact on the methods used in the trials, the reporting or publishing of results and no competing interests were still declared in all three of these trials. Hence, the impact of the external provider on the risk of bias was deemed as 'unclear'. One study did not describe the method of randomization used, leading to an 'unclear' risk of bias assessment 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 and personnel, where this is feasible. In addition, clear reporting of other factors such as allocation concealment, the impact of any external bodies involved, and

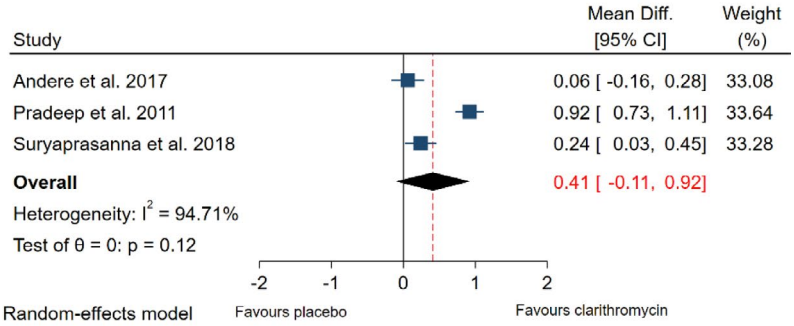
(A) Effect of systemically delivered clarithromycin on PPD reduction at 3-months post-therapy



(B) Effect of systemically delivered clarithromycin on PPD reduction at 6-months post-therapy



(C) Effect of systemically delivered clarithromycin on CAL gain at 3-months post-therapy



(D) Effect of systemically delivered clarithromycin on CAL gain at 6-months post-therapy

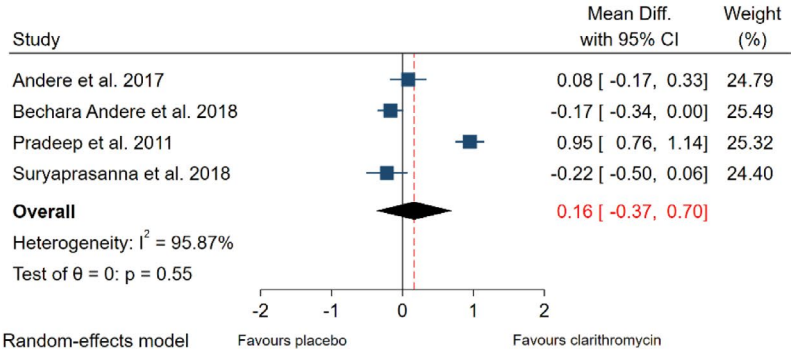


FIGURE 3 Effect of systemically delivered clarithromycin on treatment outcomes

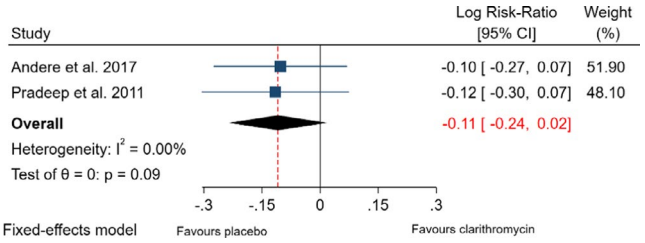


FIGURE 4 Risk of adverse events with systemically delivered clarithromycin

reasons for any unreported data, would reduce the risk of bias of studies incorporated into quantitative synthesis.

4.3 | Comparison with other studies and reviews

While there are no existing reviews evaluating the efficacy of adjunctive clarithromycin use in the management of periodontitis, this systematic review does conform with the existing evidence that suggests antibiotics provide clinical benefits above and beyond non-surgical periodontal therapy alone.[28,29] When administered systemically, clarithromycin produces improvements in PPD and CAL greater than the improvements which have been observed when comparing amoxicillin or metronidazole (alone or in combination) with placebo.[30,31] When administered locally, clarithromycin produces improvements in clinical outcomes greater than those observed with locally administered chlorhexidine, metronidazole, doxycycline, minocycline or photodynamic therapy.[32-35] Future trials directly comparing clarithromycin with other adjunctive agents would be useful in validating these findings.

Furthermore, the improved efficacy of clarithromycin when administered locally rather than systemically is an observation which is also seen in other antibiotics; for example, metronidazole appears to be more effective when delivered subgingivally rather than systemically.[31,34] This difference may be explained by the fact that local administration ensures that antibiotics can be delivered in a high concentration to the affected areas, whereas systemic antibiotics provide no guarantee that the maximum dose of the drug will be able to reach the bacteria harboured in the gingival crevice.

The adverse events seen across these trials were only observed with systemic administration and mainly comprised gastrointestinal discomfort, which conforms with existing systematic reviews which have found gastrointestinal effects to be the most commonly experienced adverse events in patients receiving macrolide therapy.[36]

It should be noted that a high efficacy, in and of itself, does not justify routine use of clarithromycin. There are significant drawbacks to using antibiotics which need to be weighed against the meagre clinical benefits provided by these medications. It would be advised that clarithromycin, as well as all other antibiotics, are only implemented in patients who have established good oral hygiene and have had at least one course of periodontal therapy, with appropriate maintenance. In these cases, it would be advised to use locally administered clarithromycin in areas which do not respond to conventional treatment. The routine use of systemically administered clarithromycin cannot be recommended as it confers no clinical benefit which significantly outweighs the drawbacks, yet it is broader spectrum than other drugs, such as amoxicillin and metronidazole, which can give rise to even greater issues regarding antibiotic resistance.

4.4 | Limitations

While the authors endeavoured to locate all relevant studies, it is acknowledged that there may have been studies which were not published, registered or presented.

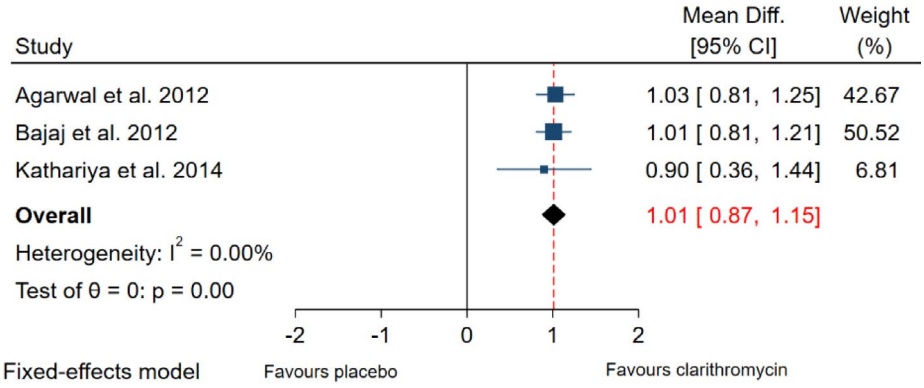
All included studies evaluated the pre-defined outcome measures outlined in the review protocol. One of the primary limitations of this systematic review is the quantity of evidence, both in terms of the number of trials and number of participants within trials. Across the seven trials, the maximum number of participants enrolled comparing clarithromycin and placebo was 98. In addition, not all trials evaluated outcomes at both 3-month and 6-month post-intervention, further reducing the overall sample size incorporated into the meta-analyses.

There was significant heterogeneity for studies evaluating outcomes with systemically administered clarithromycin. This may be explained my two key factors: differences in the populations sampled between the trials, and differences in the treatment protocols implemented between the trials. For studies assessing systemically administered clarithromycin, two of the studies evaluated patients with generalized aggressive periodontitis and two of the studies evaluated patients with chronic periodontitis. It is unknown whether the efficacy of clarithromycin differs greatly between these patient cohorts, contributing to the heterogeneity. Furthermore, the protocols of clarithromycin administration differed between the studies; two studies administered 500 mg clarithromycin BD for 3 days, one study administered 500 mg clarithromycin BD for 7 days, and one study administered clarithromycin TDS for 7 days.

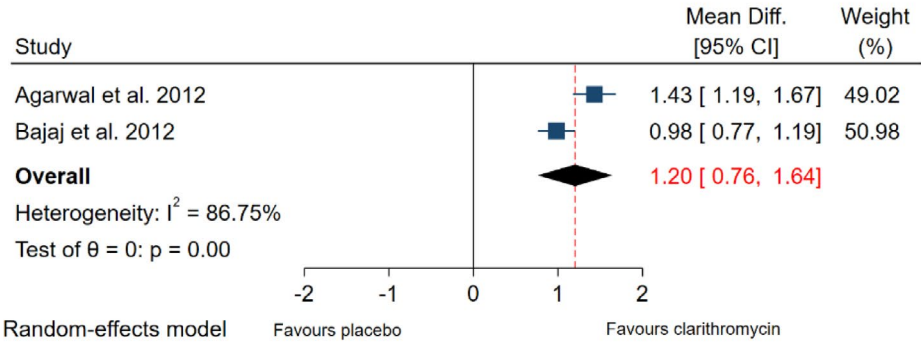
Heterogeneity was less significant in studies evaluating locally administered clarithromycin, possibly due to the same disease process being evaluated in all studies (chronic periodontitis), and the same method of drug administration being implemented (0.5% clarithromycin gel placed *in situ*). However, some heterogeneity was still observed, and this may be explained by the specific patient demographics in these trials; one study evaluated healthy patients with chronic periodontitis, one study evaluated current smokers with chronic periodontitis, and one study evaluated patients with well-controlled type II diabetes and chronic periodontitis.

As well as heterogeneity between the included studies, the quality of the included trials may also pose a limitation. Only one of the included trials was considered to be of low risk of bias, and

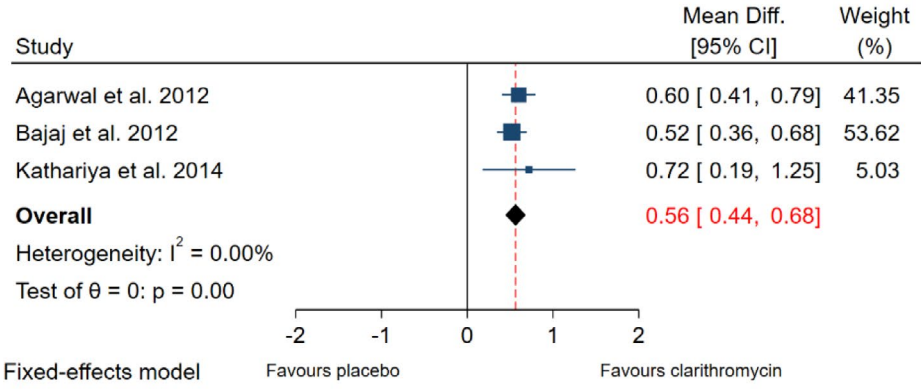
(A) Effect of locally delivered clarithromycin on PPD reduction at 3-months post-therapy



(B) Effect of locally delivered clarithromycin on PPD reduction at 6-months post-therapy



(C) Effect of locally delivered clarithromycin on CAL gain at 3-months post-therapy



(D) Effect of locally delivered clarithromycin on CAL gain at 6-months post-therapy

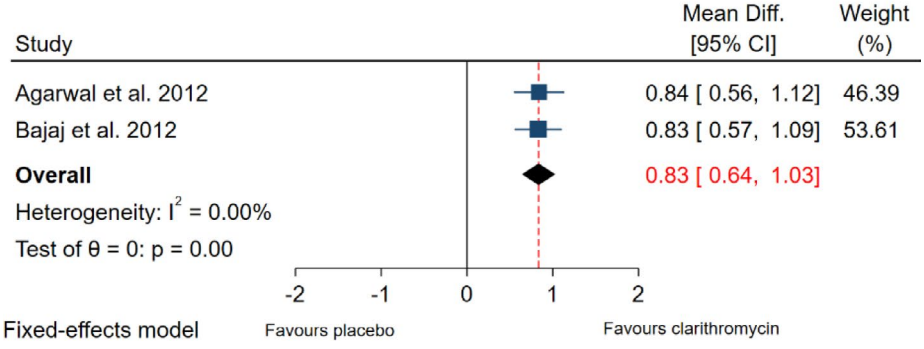


FIGURE 5 Effect of locally delivered clarithromycin on treatment outcomes

the remainder were at unclear risk. Unclear reporting on parameters such as allocation concealment and blinding of participants of personnel means the extent of bias incorporated into the meta-analyses cannot be accurately determined. Furthermore, some trials reported receiving equipment from private pharmaceutical companies, and the potential biases associated with this are also unknown. In addition, all studies evaluate the efficacy of clarithromycin when administered as first-line therapy, alongside non-surgical periodontal therapy. However, in practice, patients would typically receive at least one round of non-surgical periodontal therapy without any adjunctive agents, before the use of clarithromycin is considered and, therefore, this limits the clinical applicability of the results. Finally, the methods used for enrolling patients into the trials are unknown, that is whether complete and consecutive patient enrolment was employed or whether patients were selected by the investigators.

Furthermore, outcomes were only reported up to 6-month post-therapy. Longer follow-up periods are needed before judgements on the long-term effectiveness of clarithromycin can be made. Another limitation is that making direct comparison between systemic versus local administration is not possible, given that studies evaluating systemic administration looked at full-mouth outcomes, while studies evaluating local administration looked at site-specific outcomes.

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

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

5 | CONCLUSIONS

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

- Clarithromycin as an adjunct to non-surgical periodontal therapy may improve treatment outcomes.
- Adjunctive clarithromycin increases the risk of adverse events when administered systemically, but not when administered locally
- There is a paucity of literature surrounding the subject, necessitating more high-quality, adequately powered, randomized controlled trials
- Clinicians must weigh up the detrimental risks of antibiotic usage with the limited clinical benefits they provide when deciding to implement them as adjuncts to periodontal therapy

6 | CLINICAL RELEVANCE

6.1 | Scientific rationale for the study

Recently developed S3 guidelines from the European Federation of Periodontology indicate a number of adjunctive agents which may be considered for use in periodontal therapy, but clarithromycin has not yet been evaluated.

6.2 | Principal findings

Locally delivered clarithromycin significantly improves treatment outcomes, more so than other currently recommended agents, in terms of probing pocket depth and clinical attachment level, without any observed increase in the risk of adverse events.

6.3 | Practical implications

There is evidence to suggest that locally delivered clarithromycin may improve the outcomes of non-surgical periodontal therapy; future research should aim to validate these findings.

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Nil

CONFLICTS OF INTEREST

The authors explicitly declare no competing interests.

AUTHOR CONTRIBUTIONS

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

DATA AVAILABILITY STATEMENT

No new data were created in preparation of this manuscript.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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