

The impact of systemic and topical antimicrobial therapy combined with non-surgical periodontal therapy: A meta-analysis

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A – research concept and design; B – collection and/or assembly of data; C – data analysis and interpretation; D – writing the article; E – critical revision of the article; F – final approval of the article

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Abstract

Background. Combining antibiotics with non-surgical periodontal therapy has a beneficial impact in case of infection while its role for dental-related outcomes is still unclear.

Objectives. The current study's main objective was to evaluate the impact of adding adjuvant systemic and topical antimicrobial therapy to non-surgical periodontal therapy.

Materials and methods. A systematic literature search was accomplished and 1,093 study participants with periodontal diseases were recruited to the current study; 541 of them were treated with adjuvant systemic or topical antimicrobial agents and 552 with non-surgical interventions. The inclusion criteria of the current study took into account only randomized clinical trials.

Results. Adding systemic antibiotics to non-surgical intervention resulted in a significant enhancement regarding probing pocket depth reduction (PPD). Metronidazole/amoxicillin showed a significant impact on PPD and the clinical attachment level (CAL), while doxycycline showed no significant impact regarding CAL. Using topical antimicrobial agents showed a significant beneficial role in reducing PPD regarding doxycycline, while non-significant effects were seen with metronidazole.

Conclusions. Adding adjuvant systemic and topical antimicrobial agents to non-surgical periodontal therapy showed a beneficial impact regarding PPD and CAL (metronidazole/amoxicillin and doxycycline). In addition, using doxycycline as a topical agent showed a beneficial impact on the reduction of PPD.

Key words: periodontal therapy, antimicrobials, CAL, PPD

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Background

Periodontitis is a condition marked by an imbalance in the microbial community, leading to the breakdown of the tissues supporting the teeth, including the alveolar bone, cementum, periodontal ligament, and gingiva. It is widely recognized as the primary reason for tooth loss.¹ Periodontitis affects almost 50% of the world's population, with 11% experiencing a severe version of the disease.² Periodontitis is linked to a transition from a mutually beneficial periodontal microbiome to an imbalanced one. The presence of dysbiosis is linked to a greater occurrence of anaerobic bacteria, specifically *Porphyromonas gingivalis*, which is recognized as a major pathogen.^{3,4} This pathogen has the ability to penetrate tissues and trigger inflammatory signaling pathways, leading to inflammation. Periodontitis is characterized by the loss of attachment between the teeth and gums, an increase in the depth of the pockets around the teeth, bleeding when probed, and can be accompanied by purulence, pain and swelling of the gums. These symptoms can negatively impact the long-term health of the affected teeth.^{5,6} The current objective of periodontal treatment is to restore the balance between organisms living in the periodontium and reduce inflammation, while also enhancing the clinical attachment level (CAL). In addition to providing guidance on oral hygiene and making adjustments to potential local and systemic risk factors, the primary focus of the current treatment strategy is non-surgical periodontal treatment, specifically scaling and root planing (SRP).⁷ Nevertheless, in instances of severe infections, the effectiveness of treatment may be hindered by challenges in gaining instrumental access to the affected area, bacterial infiltration of the surrounding soft tissues and a persistent inflammatory response.⁸ This underscores the necessity of employing additional treatments, such as surgical interventions. Adjuvants have been suggested in the early stages of periodontal therapy to enhance the response to treatment, given specific circumstances.⁹

To minimize the indications for surgical operations that are invasive and need advanced technical skills, various additional methods of SRP have been suggested, including the administration of antibiotics or anti-inflammatory medications. These additional therapies enhanced treatment outcomes by reducing probing pocket depth (PPD) and increasing CAL acquisition.¹⁰ Nevertheless, the administration of these pharmaceuticals through enteral routes necessitates the utilization of large amounts of active substances to achieve optimal concentration at the targeted location. Additionally, patient adherence to the prescribed administration schedule is crucial, and there is a possibility of encountering adverse effects. As a result, many localized, topical therapies, such as gels, fibers or chips containing diverse, active compounds and medications, have been created and assessed in clinical

environments. The primary benefits of these treatments include targeted administration of potent medications directly to the affected areas, minimized potential for adverse reactions, and the potential for 3-dimensional stability of the blood clot.¹¹ Periodontitis (which comes in a variety of forms) is one of the leading causes of tooth loss in adults. The most damaging kind of periodontitis among them is called aggressive periodontitis (AgP). Periodontitis is often characterized by 3 factors: A decrease in CAL, radiographic bone loss, and 1 or more sites with inflammation (bleeding on probing). In patients with AgP, SRP treatment by itself does not produce satisfactory outcomes. Thus, it is advised to treat this condition with additional systemic antibiotics. Hence, analysis of previous studies could provide clinical guidance that would aid in the practical management of periodontitis and enhance clinical outcomes. In addition, the findings of the current study would be valuable for determining the impact of different antimicrobial therapies on the clinical outcomes of periodontitis and enhance the ability to select specific antimicrobial therapies.

Objectives

The primary purpose of this investigation was to assess the effects of including adjuvant systemic and topical antimicrobial medications in non-surgical periodontal care on clinical parameters such as CAL and PPD reduction.

Method

Study design

For this meta-analysis, researchers looked at studies that followed a specific protocol to determine the epidemiological impact.¹² Several scientific databases, including Ovid, PubMed, Google Scholar, Cochrane Library, and Embase,¹³ were used to collect and analyze data from the included studies, following the inclusion criteria provided. The entire study sequence is shown in Fig. 1.

Eligibility and inclusion

The inclusion criteria were examination of the effects of adjuvant systemic and topical antimicrobial treatment as an adjunct to non-surgical periodontal therapy. Only articles that specifically looked at how various therapies (such as systemic or topical adjuvant antibacterial medication or non-surgical periodontal therapy) reduced the PPD and CAL were included in the sensitivity research. To do subclass and sensitivity analysis, the medical intervention groups were compared to various types of antimicrobials and routes of delivery.

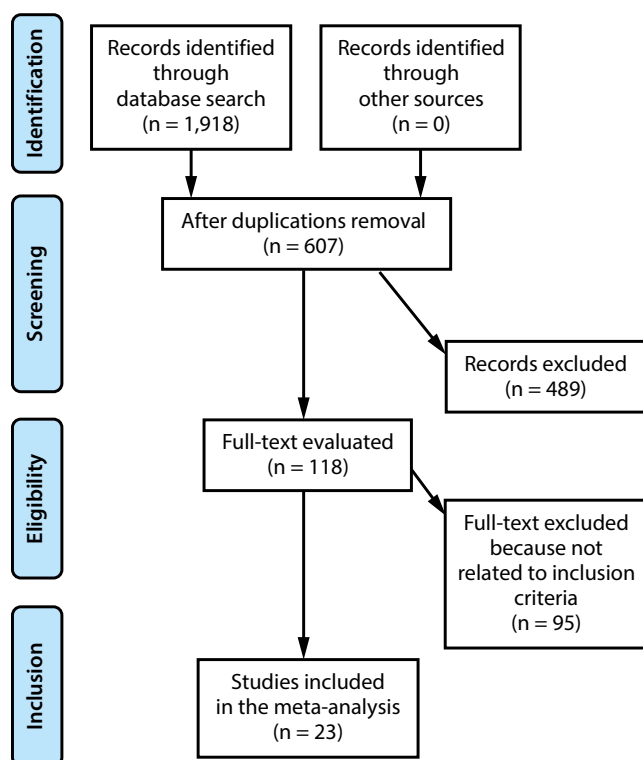


Fig. 1. Study inclusion flowchart

Inclusion criteria

The current study only incorporated randomized clinical trials that were published up until December 2023. In addition, studies including patients who had periodontal conditions treated with SRP were subject to the study. Study designs that compared the effects of 2 interventions (adjuvant antimicrobial agent + non-surgical interventions compared to non-surgical intervention alone) were required for inclusion.

Exclusion criteria

Articles that were unable to convey the results of a comparison between different interventions in a suitable manner, such as interquartile range or median, were excluded. Failure to use mean ($\pm$ standard deviation ($\pm$ SD)) to express all results of diverse outcomes was excluded. Finally, we excluded cases where the research was published as a book chapter, letter or review article.

Identification

First, we conducted our research up until December 2023 utilizing a set of terms related to periodontal disorders, antibiotics, CAL, reduction of probing pockets, doxycycline, metronidazole, and amoxicillin. A protocol for the search strategies was defined in accordance with the PICOS principle as follows: P (population) – periodontal conditions; I (intervention/exposure) – non-surgical periodontal

therapy and adjuvant antimicrobial agents (topical or systemic); C (comparison) – non-surgical periodontal therapy plus adjuvant antimicrobial agents (topical or systemic) compared with control; O (outcome) – PPD reduction and CAL; S (study design) – randomized clinical trial.

The author did a thorough search of the PubMed, Cochrane Library, Embase, Ovid, and Google Scholar databases until December 2023 using the keywords and related terms. Any article that did not discuss and evaluate the role of early supported discharge compared to traditional care was disregarded after an evaluation of the titles and abstracts of the articles that had been collected into Endnote v. 20 (Clarivate Analytics, London, UK).

Screening

To narrow down the data, certain criteria were used. These criteria included the following: the author's surname, year of publication, country, type of study, length of the study, demographic information, clinical and treatment characteristics, total number of study participants, methods used, information sources, and outcomes. The writer examined the selected papers' methodological quality and checked each study for possible bias.

Through the use of Review Manager v. 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark), we were able to determine whether the included pieces of research had a low, medium or high potential for bias.

Statistical analyses

The mean difference (MD) was calculated with a 95% confidence interval (95% CI) using a random-effect model with continuous analysis.¹⁴ The data were fitted with a random-effects model due to a lack of high-level similarity between the included studies. Results of the analysis were expressed in the form of forest plots, which indicated the 95% CI of each group and displayed a visual direction (positive or negative) of the different studies in the same analysis. Group and subgroup analysis were performed for different models; the group analysis reflected the overall results of all included studies, while the subgroup analysis showed the effect of additional factors shared between a small number of studies with the same outcome under investigation.

Tau², the degree of heterogeneity, was determined using the constrained maximum-likelihood estimator. A numerical value between 0 and 100, known as the I² index, was calculated. Jamovi software (<https://www.jamovi.org/>) was used to obtain this index. Percentages representing low, moderate and high levels of heterogeneity were also used to display the heterogeneity level, which can range from 0% to 100%. Quantitative research on publication bias was carried out using Begg's and Egger's tests and visual evaluation of funnel plots.

Table 1. Characteristics of clinical trials recruited in the analysis

Study	Country	Year	Intervention type	Intervention	Control	Total
Vyas et al. ¹⁵	India	2019	doxycycline	26	26	52
Al-Nowaiser et al. ¹⁶	Saudi Arabia	2014	doxycycline	35	33	68
Al-Zahrani et al. ¹⁷	Saudi Arabia	2009	doxycycline	14	15	29
Gaikwad et al. ¹⁸	India	2013	doxycycline	25	25	50
O'Connel et al. ¹⁹	Brazil	2008	doxycycline	15	15	30
Rodrigues et al. ²⁰	Brazil	2003	amoxicillin/clavulanic acid	15	15	30
Singh et al. ²¹	India	2008	doxycycline	15	15	30
Tsalikis et al. ²²	Greece	2014	doxycycline	31	35	66
Gupta et al. ²³	India	2008	doxycycline	30	30	60
Pandit et al. ²⁴	India	2013	metronidazole	20	20	40
Lie et al. ²⁵	China	1998	metronidazole	18	18	36
Eickholz et al. ²⁶	Germany	2002	doxycycline	110	110	220
Srirangarajan et al. ²⁷	India	2011	doxycycline	10	10	20
Kinane et al. ²⁸	UK	1999	metronidazole	19	20	39
Aimetti et al. ²⁹	Italy	2012	metronidazole/amoxicillin	19	20	39
Guerrero et al. ³⁰	USA	2005	metronidazole/amoxicillin	20	21	41
Xajigeorgiou et al. ³¹	Greece	2006	metronidazole/amoxicillin	10	11	21
Yek et al. ³²	Turkey	2010	metronidazole/amoxicillin	12	16	28
Mestnik et al. ³³	Brazil	2012	metronidazole/amoxicillin	15	15	30
Madi et al. ³⁴	Saudi Arabia	2018	doxycycline	15	15	30
Tamashiro et al. ³⁵	Brazil	2016	metronidazole/amoxicillin	29	27	56
Taiete et al. ³⁶	Brazil	2016	metronidazole/amoxicillin	21	18	39
Grossi et al. ³⁷	USA	1997	doxycycline	17	22	39

Table 2. Analysis results of all models

Model	Estimate	p-value	95% CI lower limit	95% CI upper limit	I ²	Begg's test	Egger's test
Systemic antimicrobial therapy impact on PPD reduction	0.79	0.006	0.225	1.356	91.45%	0.51	0.001
Subgroup 1 doxycycline	0.947	0.128	-0.273	2.167	96.56%	0.72	0.001
Subgroup 2 metronidazole/amoxicillin	0.796	<0.001	0.539	1.053	0%	1	0.808
Systemic antimicrobial therapy impacts on CAL	0.688	0.128	-0.197	1.573	96.5%	0.19	0.001
Subgroup 1 doxycycline	1.03	0.303	-0.929	2.987	98.61%	0.399	0.001
Subgroup 2 metronidazole/amoxicillin	0.482	<0.001	0.226	0.738	2.87%	0.562	0.665
Adjuvant topical antimicrobial agents' impact on PPD	0.363	<0.001	0.181	0.545	0%	0.548	0.708
Subgroup 1 doxycycline	0.442	0.002	0.165	0.719	23.8%	1.000	0.682
Subgroup 2 metronidazole	0.254	0.175	-0.113	0.622	0%	0.333	0.411

95% CI – 95% confidence interval; PPD – pocket probing depth; CAL – clinical attachment level.

Results

After reviewing 1,918 pertinent studies, 23 research papers from the period between 1997 and 2019, including 1,093 study participants with periodontal disease receiving non-surgical interventions, were selected for the meta-analysis.^{15–37} The results of these investigations are compiled in Tables 1,2. In addition, analysis models and publication bias were reported in Fig. 2–6.

Systemic antimicrobial therapy's impact on probing pocket depth reduction

Continuous analysis using the random-effects model of 16 clinical trials for evaluation of the impact of adjuvant antimicrobial therapy on non-surgical periodontal therapy regarding the PPD reduction (Fig. 2A). The outcomes of the analysis showed a significant ($p < 0.01$) beneficial impact of combining systemic antimicrobial therapy with

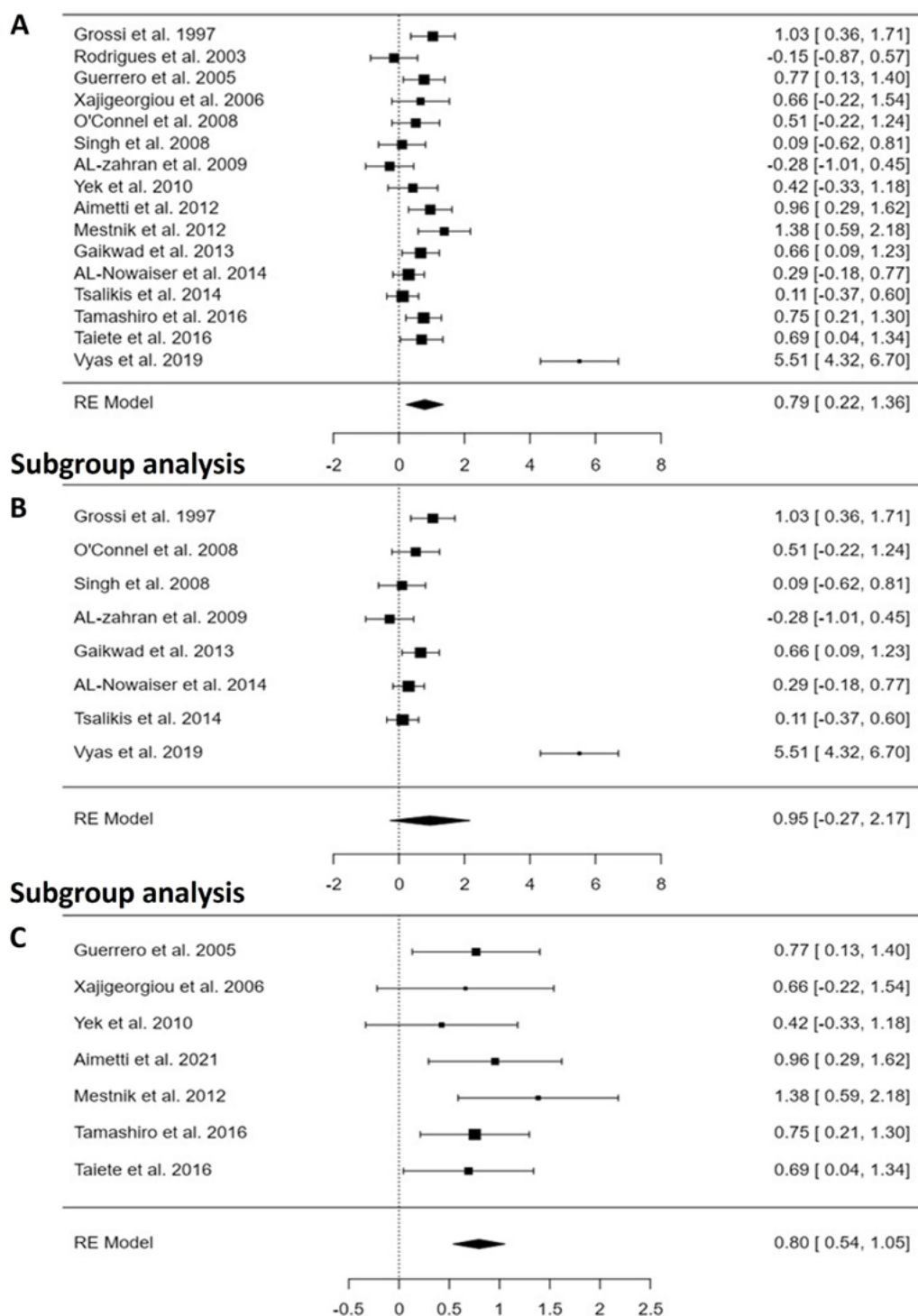


Fig. 2. Forest plot for the analysis of the impact of systemic adjuvant antimicrobial therapy on non-surgical periodontal therapy regarding pocket depth reduction (PPD) (A), subgroup analysis including doxycycline (B) and subgroup analysis including the metronidazole/amoxicillin combination (C)

SRP compared to controls (MD = 0.79, 95% CI: [0.22–1.36], $I^2 = 91.4\%$). A single study (Vyas et al.) may be deemed unduly influential based on Cook's distances.¹⁵

Systemic doxycycline impact on probing pocket depth reduction

Subgroup continuous analysis using the random-effects model of 8 clinical trials for evaluation of the impact of adjuvant doxycycline therapy on non-surgical periodontal

therapy regarding the PPD reduction (Fig. 2B). The outcomes of the analysis showed a non-significant ($p < 0.13$) impact of combining systemic antimicrobial therapy with SCP compared with controls (MD = 0.95, 95% CI: -0.27–2.17, $I^2 = 96.5\%$). One study (Vyas et al.) had a value larger than ± 2.73 , suggesting that it might be an outlier in the context of this model, according to an analysis of the studentized residuals. By excluding this outlier study, the finding showed a significant ($p = 0.01$) beneficial difference in favor of doxycycline intervention.¹⁵

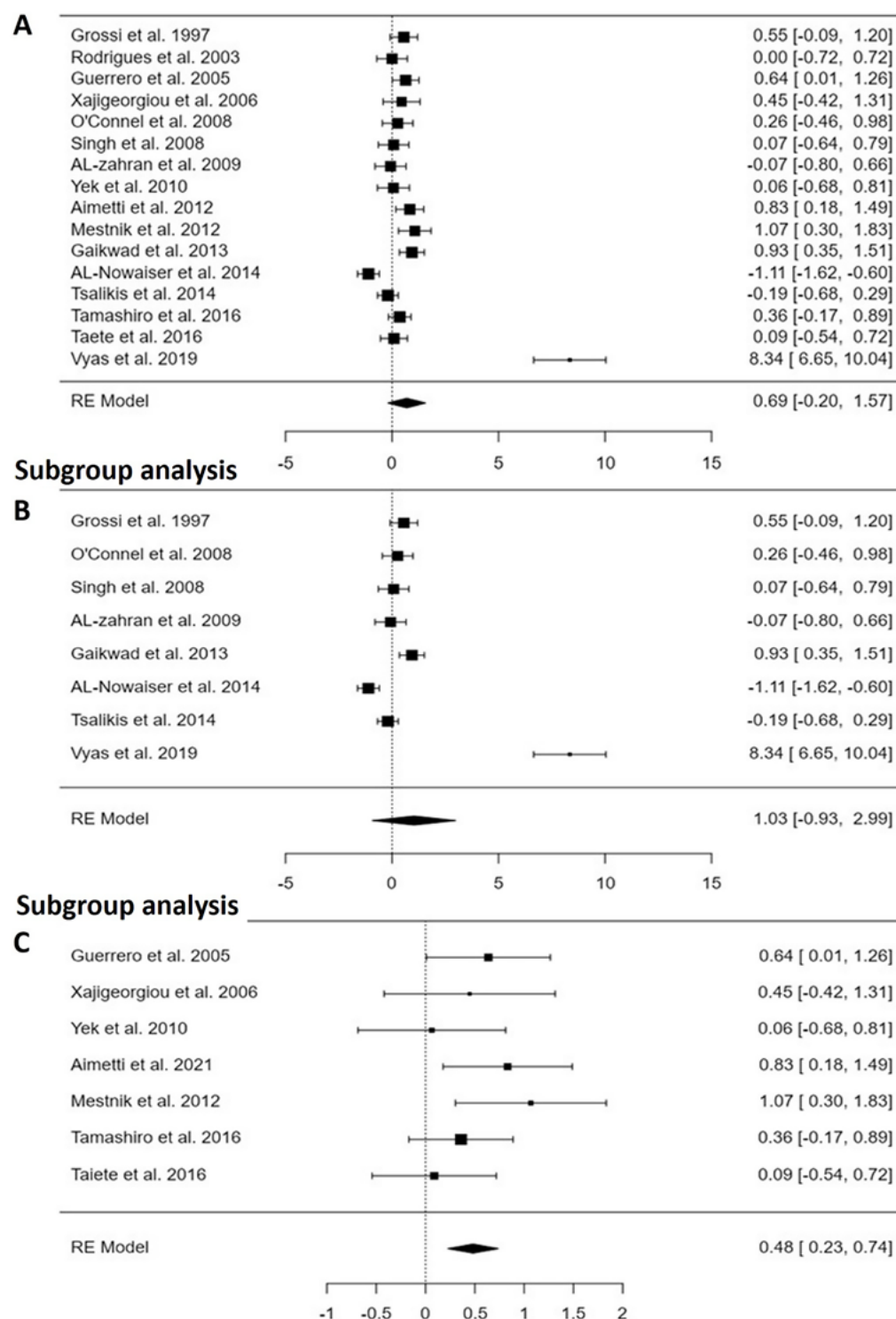


Fig. 3. Forest plot for the analysis of the impact of systemic adjuvant antimicrobial therapy on non-surgical periodontal therapy regarding clinical attachment level (CAL) (A), subgroup analysis including doxycycline (B) and subgroup analysis including the metronidazole/amoxicillin combination (C)

Systemic metronidazole/amoxicillin impact on probing pocket depth reduction

Subgroup analysis using the random-effects continuous analysis model for 7 clinical trials for evaluation of the impact of adjuvant metronidazole/amoxicillin on non-surgical periodontal therapy regarding the PPD reduction (Fig. 2C). The outcomes of the analysis showed a significant ($p < 0.001$), beneficial impact of combining systemic

antimicrobial therapy with SRP compared to control (MD = 0.80, 95% CI: 0.54–1.05, $I^2 = 0\%$).

Systemic antimicrobial therapy impacts on clinical attachment level

In contrast to the analysis of 16 studies for PPD, analysis of the impact of systemic administration of adjuvant antimicrobial therapy on CAL (Fig. 3A) using 16 studies

revealed that the addition of antimicrobial drugs did not result in significant ($p = 0.13$) changes in CAL compared to controls (MD = 0.69, 95% CI: -0.20–1.57, $I^2 = 96.5\%$).

Systemic doxycycline impact on clinical attachment level

Regarding subgroup analysis of the impact of systemic administration of adjuvant antimicrobial therapy on CAL (Fig. 3B), results from the analysis of 8 studies revealed that the addition of doxycycline did not result in significant ($p = 0.3$) changes in the CAL compared to controls (MD = 1.03, 95% CI: -0.93–2.99, $I^2 = 98.6\%$).

Systemic metronidazole/amoxicillin impact on clinical attachment level

Concerning subgroup analysis of the impact of systemic administration of adjuvant antimicrobial therapy on CAL (Fig. 3C), results from the analysis of 7 studies revealed that the addition of systemic metronidazole/amoxicillin resulted in significant ($p < 0.001$) changes in the CAL compared to controls, represented as a higher CAL (MD = 0.48, 95% CI: 0.23–0.74, $I^2 = 2.87\%$).

Adjuvant topical antimicrobial agents impact on probing pocket depth

Regarding topical administration of adjuvant antimicrobial therapy (doxycycline or metronidazole) on PPD, results from the analysis of 8 studies revealed that the addition of topical antimicrobial agents to non-surgical periodontal therapy resulted in significant ($p < 0.001$) changes in PPD compared to controls, represented as a higher PPD level (MD = 0.36, 95% CI: 0.18–0.55, $I^2 = 0\%$). Among the 8 studies, 5 studies demonstrated the impact of topical doxycycline and 3 papers demonstrated the role of metronidazole. Subgroup analysis according to the type of topical antimicrobial agent showed a different result for doxycycline compared to metronidazole. Doxycycline showed a significantly ($p = 0.002$) higher impact on PPD compared to controls, while metronidazole did not ($p = 0.17$). The heterogeneity level for both subgroup analyses was 0% (Fig. 4).

Publication bias

Analysis of publication bias using Begg's and Egger's tests, in addition to the visual evaluation of funnel plots, showed differences between groups regarding the level of publication bias, as shown in Table 2 and Fig. 5,6. Groups that showed low levels or no publication bias were metronidazole/amoxicillin therapy's impact on PPD reduction (Begg's test = 1, Egger's test = 0.808), metronidazole/amoxicillin therapy's impact on PPD (Begg's test = 0.56, Egger's test = 0.66) and models for analysis of topical antimicrobial therapy's impact on PPD (Table 2, Fig. 6).

However, it is important to note that some of the analyzed groups contain sample size less than 10; in these cases, the Begg's and Egger's tests may not have the necessary power to identify bias.

Discussion

Twenty-three randomized clinical trials published between the period of 1997 to 2019, including 1,093 subjects with periodontal disease receiving non-surgical intervention, were selected for the current meta-analysis.^{15–36}

The addition of a systemic antibiotic to a non-surgical intervention resulted in a significant improvement in terms of the reduction in the PPD. On the other hand, metronidazole/amoxicillin demonstrated a significant impact on the CAL and PPD, whereas doxycycline did not demonstrate any significant impact on the CAL. The use of topical antimicrobial drugs had a substantial favorable impact in reducing pocket depth (PD) in relation to doxycycline; however, the effect connected to metronidazole was not significant.

Three recent systematic reviews have examined the effects of a specific combination of antibiotics, metronidazole plus amoxicillin, in treating chronic periodontitis (ChP), AgP or both. Systematic reviews previously conducted^{6,38,39} have shown that using this antibiotic protocol as an adjunct to treatment provides significant benefits. The prevailing method employed in these investigations involved producing aggregated estimations by utilizing the average alterations from the initial state to various time periods after therapy in clinical outcomes resulting from SRP alone or in conjunction with systemic antibiotics. A previous study by Teughels et al. indicated that systemic antimicrobials, when used as an adjuvant in periodontal therapy, produced statistically significant improvements in clinical outcomes, while the intervention groups that received systemic antimicrobials experienced more frequent side effects compared to controls.⁴⁰ In contrast, when compared to surgical therapy alone, the use of systemic or local antimicrobials during surgical therapy does not appear to increase the clinical efficacy in patients with peri-implantitis.⁴¹ While another study demonstrated the influence of topical antimicrobial agents showing that the PPD decreased and the CAL gained with statistically significant effects when the adjunctive was locally applied to subgingival antimicrobials.⁴² During surgical periodontal therapy, locally given antibiotics lead to longer-lasting post-surgical improvements for CAL, PPD and bleeding on probing (≤ 6 months).⁴³

Typically, when comparing the effectiveness of different antibiotics (as the experimental group) with conventional therapy (SRP as the control group), the studies are combined using a pairwise meta-analysis.^{44,45} However, a traditional pairwise meta-analysis is unable to directly compare 3 or more treatment regimens at the same time.

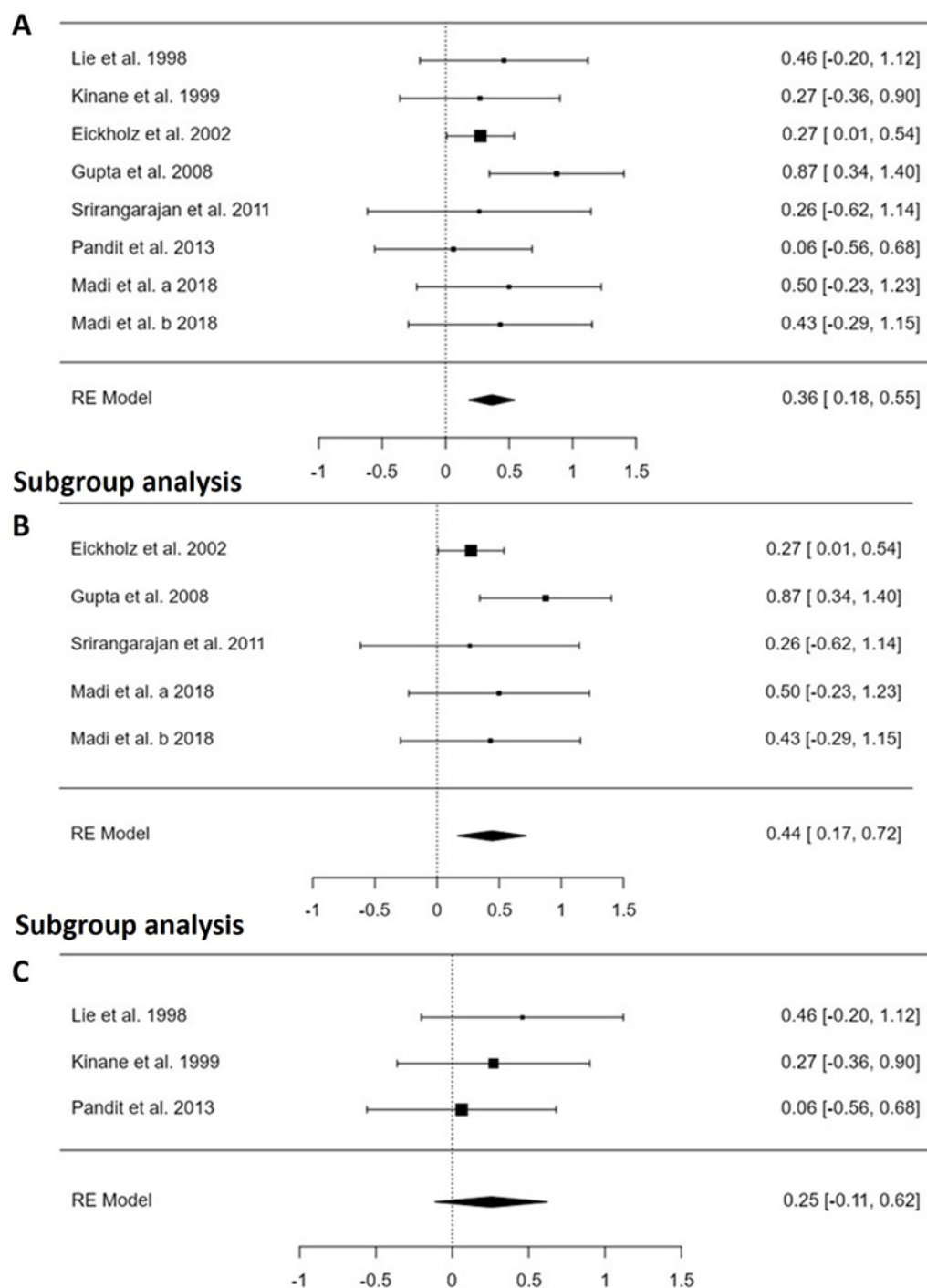


Fig. 4. Forest plot for the analysis of the impact of topical adjuvant antimicrobial therapy on non-surgical periodontal therapy regarding pocket depth reduction (PPD) (A), subgroup analysis including topical doxycycline (B) and subgroup analysis including topical metronidazole (C)

To evaluate the impact of various treatments, it is necessary to do several pairwise analyses for each outcome measured. These analyses are based on studies^{46–48} employing a Bayesian network meta-analysis to address this limitation. Instead of doing numerous individual comparisons, this form of meta-analysis evaluates all existing treatment regimens under a single statistical model.^{46,49,50}

The results of this meta-analysis align with previous systematic reviews^{51–53} that have suggested the clinical effectiveness of systemic antibiotics, particularly metronidazole + amoxicillin, in treating individuals with AgP.^{38,45} Nevertheless, a noteworthy outcome of the current study,

worth considering, was the substantial therapeutic advantage shown when utilizing additive metronidazole to treat patients with AgP. This pairwise meta-analysis has shown that the combination of SRP and metronidazole resulted in a statistically significant increase in CAL and a decrease in probing depth by 1.08 mm and 1.05 mm, respectively, compared to 0.45 mm and 0.53 mm for the combination of SRP, metronidazole and amoxicillin. It is crucial to highlight that the increased gain in CAL and reduction in PPD seen in the SRP + metronidazole group compared to the SRP + metronidazole/amoxicillin group may be attributed to the severe periodontal damage

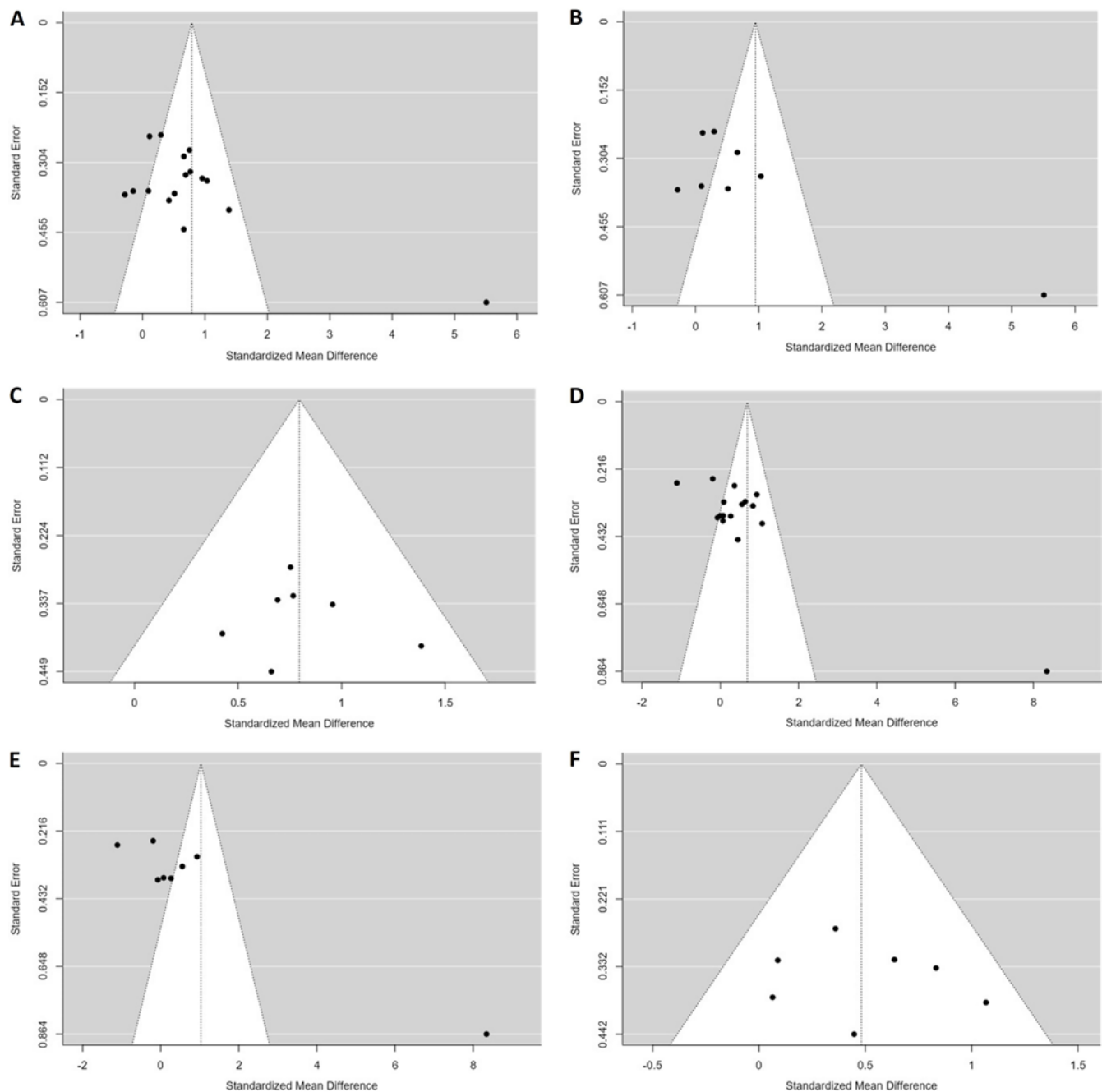


Fig. 5. Funnel plot showing the possibility of publication bias for studies included for the analysis models of the impact of systemic adjuvant antimicrobial therapy to non-surgical periodontal therapy regarding pocket depth reduction (PPD) (A), subgroup analysis of doxycycline (B), subgroup analysis of the metronidazole/amoxicillin combination (C), the impact of systemic adjuvant antimicrobial therapy to non-surgical periodontal therapy regarding clinical attachment level (CAL) (D), subgroup analysis including doxycycline (E), and subgroup analysis including the metronidazole/amoxicillin combination (F)

present in the study population of one of the research studies investigating the effects of metronidazole.³⁹ The average PD and CAL values at the beginning of the trial were 5.8 mm and 6.2 mm, respectively, when measured across all teeth in the mouth. By comparison, the groups examined in the 5 trials that evaluated the impact of SRP + metronidazole/amoxicillin had average initial PD values ranging from 4.1 mm to 4.63 mm and CAL values from 4.5 mm to 4.97 mm. Therefore, these initial clinical variations may have had a role in the more significant level of recovery

seen in participants who were treated with metronidazole compared to those who received metronidazole and amoxicillin. Furthermore, it is crucial to acknowledge that the favorable outcomes found for metronidazole were derived solely from the analysis of data from 2 randomized controlled trials.^{31,39} Hence, the data regarding the significant advantages of metronidazole in treating AgP, as seen in the current study, should be approached with caution, especially when compared to the benefits observed for metronidazole + amoxicillin.

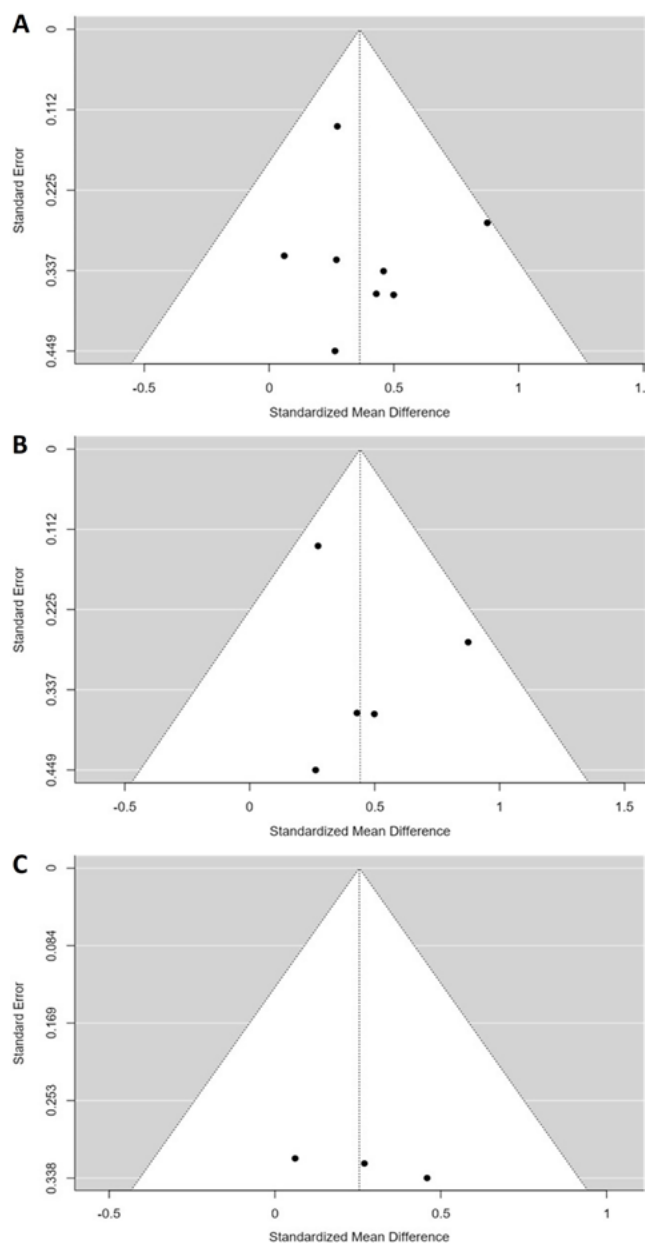


Fig. 6. Funnel plot for the analysis of the publication bias for models used for assessing the impact of topical adjuvant antimicrobial therapy on non-surgical periodontal therapy regarding pocket depth reduction (PPD) (A), subgroup analysis including topical doxycycline (B) and subgroup analysis including topical metronidazole (C)

The primary constraints associated with the utilization of locally administered supplementary treatment are the gel's stability within the defect, the amount of active medication accessible at the site and the duration of drug release. Local antimicrobials used as an adjuvant increased the effectiveness of non-surgical periodontal therapy in lowering PPD and raising CAL at sites where the PD present was ≥ 5 mm prior to treatment. The available data does not support comparable benefits when systemic antibiotics or antimicrobials are combined with SRP as part of therapy.⁵⁴ Various hydrogels, including chitosan, xanthan and hyaluronic acid, have been examined. However,

these hydrogels lack long-term stability of their 3-dimensional (3D) shape when compared to in-situ forming gel.⁵⁵ No control group was utilized for the duration of contact when topical antimicrobial gels were injected into the periodontal pocket in the experiments included. Thus, in multiple investigations, the application of gel was repeated at a 1-week interval on multiple occasions. This could be perceived as an inconvenience due to the time requirement and patient compliance needed for successful treatment. Furthermore, the majority of the studies included a follow-up period ranging from 3 months to 1 year. This follow-up period aligns with the duration required to achieve a state of stable healing. It is worth noting that the study did not evaluate pocket closure as a primary outcome. Enabling an objective comparison of trials and accurately evaluating the clinical efficacy of the tested treatment would be a highly useful measure. The majority of the papers analyzed exhibited significant heterogeneity, underscoring the necessity for additional verification of these findings.

Limitations

The absence of large multicenter studies and studies with large sample sizes are considered limitations of this analysis. Comparing different doses and therapy durations should be taken into consideration in further studies as most of the analyzed trials did not compare the impact of drug dose and duration.

Conclusions

When combined with non-surgical periodontal care, adjuvant systemic and topical antimicrobial medicines demonstrated a favorable influence on PPD reduction and CAL in cases of periodontal disease (metronidazole/amoxicillin). In addition, the application of doxycycline as a topical treatment has shown a positive impact on the decrease in PPD. Further multicenter randomized studies are needed to evaluate the influence of different medication doses on clinical outcomes.

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