Review

Effectiveness of Systemic Amoxicillin/Metronidazole as Adjunctive Therapy to Scaling and Root Planing in the Treatment of Chronic Periodontitis: A Systematic Review and Meta-Analysis

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Background: The combination of Amoxicillin and metronidazole (AMX/MET) as an adjunctive treatment to scaling root planing (SRP) has been proposed for the treatment of chronic periodontitis; however, its effectiveness and clinical safety remain to be defined. The purpose of the present meta-analysis is to assess the effectiveness of SRP + AMX/MET compared to SRP alone.

Methods: An electronic search of eight databases from their earliest records through October 8, 2011 and a hand search of international dental journals for the last 15 years were conducted. Gain in clinical attachment level (CAL), reduction in probing depth (PD), secondary outcomes, and adverse events were analyzed. A random-effect model was used to pool the extracted data. The weighted mean difference (WMD) with 95% confidence interval (CI) was calculated for continuous outcomes; heterogeneity was assessed with the Cochrane χ^2 and I^2 tests. The level of significance was set at $P<0.05$.

Results: After the selection process, four randomized clinical trials were included. Results of the meta-analysis showed significant CAL gain (WMD = 0.21; 95% CI = 0.02 to 0.4; $P<0.05$) and PD reduction (WMD = 0.43; 95% CI = 0.24 to 0.63; $P<0.05$) in favor of SRP + AMX/MET. No significant differences were found for bleeding on probing (WMD = 10.77; 95% CI = –3.43 to 24.97; $P>0.05$) or suppuration (WMD = 1.77; 95% CI = –1.7 to 5.24; $P>0.05$).

Conclusion: The findings of this meta-analysis seem to support the effectiveness of SRP + AMX/MET; however, future studies are needed to confirm these results. *J Periodontol 2012;83: 1257-1269.*

KEY WORDS

Amoxicillin; chronic periodontitis; meta-analysis; metronidazole; root planing.

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Chronic periodontitis (CP) is a complex disease that is mainly caused by intraoral biofilms harboring periodontal pathogenic microorganisms.[1] The main goal of therapy for CP includes reduction of the levels and proportions of periodontal pathogens and increasing of the proportions of beneficial species periodontal biofilms and pathogenic microorganism.[2] However, non-surgical and surgical mechanical therapies are ineffective at reducing the presence of periodontal pathogenic bacteria in non-dental intraoral habitats.[3] Consequently, recolonization of the subgingival area by pathogens is common after treatment.[4,5]

Other protocols have been proposed for the treatment of CP, with the aim of potentiating the effects of mechanical therapy.[6-8] Among these protocols, the use of systemic antibiotics has been proposed in addition to periodontal therapy. This treatment strategy could affect periodontal pathogens via multiple routes, such as through the saliva and gingival crevicular fluid. In addition, antimicrobials could reduce the microbial load at extracrevicular sites and at subgingival areas that are insufficiently treated by mechanical instrumentation.[1] Among the various antibiotics used in the treatment of CP, metronidazole (MTZ) in

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combination with amoxicillin (AMX) has been proposed.[9,10] AMX is a moderate-spectrum, bacteriolytic β-lactam antibiotic, whereas MTZ is a nitroimidazole that is particularly active against anaerobic bacteria characteristic of the main periodontal pathogens.[11]

Current treatment strategies that are applied in the initial phase of periodontal therapy primarily revolve around full-mouth scaling and root planing (SRP), which is associated with varying degrees of additional clinical and microbiological benefits.[12-15] The combined use of AMX + MET as an adjunctive treatment to SRP has been tested in several studies.[16-20] However, these studies have reported contrasting results in the improvement of clinical parameters, as well as contradictory microbiological findings with respect to the capability of adjunctive AMX + MET to reduce levels of the most involved periodontal pathogens, such as *Porphyromonas gingivalis*, *Treponema denticola*, and *Tannerella forsythius*.[1,8,10,18,20]

Several important issues related to combination AMX/MET + SRP therapy have yet to be clarified. There is no clear consensus on the mechanism of action or effectiveness of AMX/MET combined use. Notable variations in the study design, dosage, and duration of AMX/MET administration have been used in published studies.[7] Moreover, the possibility that AMX/MET combined treatment could induce antibiotic resistance in the periodontal microflora, suppress the microflora itself, or cause overgrowth by periodontal or opportunistic pathogens, as well as the risk of side effects and adverse events must be further analyzed.

Previous meta-analyses for the effectiveness of systemic antibiotics as adjunctive therapy to periodontal treatment have revealed a positive effect on clinical parameters.[6,7] However, to the best of our knowledge, no previous systematic review has been conducted on the adjunctive use of AMX/MET to SRP in the treatment of CP. Therefore, the primary aim of the present systematic review and meta-analysis is to address the effectiveness of SRP + AMX/MET compared to SRP alone. A secondary aim is to address the safety of the adjunctive AMX/MET combined therapy.

MATERIALS AND METHODS

The following meta-analysis was conducted in agreement with the recommendations of the Cochrane Collaboration[21] and the principles of the PRISMA (Preferred Reporting Items for Systemic Reviews and Meta-Analyses) statement.[22]

Focused Question

The focused question addressed in this study is "What is the effectiveness of combined AMX/MET therapy as an adjunct to SRP, when compared to SRP alone, in the treatment of CP?"

Search Strategy

The following databases were searched from their earliest records through October 8, 2011: MEDLINE, Cochrane Controlled Clinical Trial Register, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, CINAHL (Cumulative Index to Nursing and Allied Health Literature), Science Direct, Thomson Reuters Web of Science (formerly ISI Web of Knowledge), and Scopus. To minimize the potential for reviewer bias, screening was performed independently by two masked reviewers (FS and AP). Inter-reviewer reliability in the study selection process was determined by the Cohen κ test, assuming an acceptable threshold value of 0.61.[23,24] Discrepancies with regard to the inclusion or exclusion of studies were resolved by discussion between the reviewers who selected the studies (FS and AP).

Databases were searched with the following search algorithm, in which Boolean operators were used and the asterisk indicates truncation: ("Periodontitis"[Mesh] OR "Chronic Periodontitis"[MeSH] OR "Periodontal Diseases"[MeSH] OR "Periodontal Pocket"[MeSH] OR "Periodontal Attachment Loss"[MeSHh] OR "Tooth Mobility"[MeSH] OR periodontitis OR periodontal disease* OR periodontal pocket* OR attachment loss OR alveolar bone loss OR pocket depth OR clinical attachment level OR periodontal non surgical treatment OR periodontal non surgical therapy OR scaling root planing OR dental scaling OR periodontal treatment OR periodontal therapy OR calculus remov* OR calculus debridement OR dental debridement OR periodontal debridement OR "Dental Scaling"[MeSH] OR "Root Planing"[MeSH] OR "Dental Prophylaxis" [MeSH]) AND ("Amoxicillin"[MeSH] "Metronidazole" [MeSH] OR amoxicillin plus metronidazole OR amoxicillin metronidazole OR (amoxicillin and metronidazole) OR amoxicillin-metronidazole OR amoxicillin metronidazole combination OR amoxicillin metronidazole combined OR amoxicillin/metronidazole OR AMX/MTZ OR AMX MTZ combined OR AMX MTZ combination). The MeSH terms were not used in the CINAHL, Scopus, or Science Direct databases. No truncation or abbreviations were used in the Scopus or Science Direct databases.

In addition, a manual search was performed of issues from the past 15 years of the following journals: *Journal of Periodontology*, *International Journal of Periodontics and Restorative Dentistry*, *Journal of Clinical Periodontology*, *Journal of Dental Research*, *Journal of Periodontal Research*, *Periodontology 2000*, *Journal of Dentistry*, *Journal of the American Dental Association*, *Journal of Clinical Dentistry*, and *Clinical Oral Investigations*. To avoid selection bias, no restrictions were applied with regard to language or year; additionally, the references of all selected full-text articles and related reviews were

scanned. The corresponding authors were contacted to find unpublished material, obtain missing data, or clarify paramount methodological issues.

Study Inclusion and Exclusion Criteria

The study selection process was performed by two masked reviewers (FS and RG) in two phases. In the first phase, studies were analyzed according to inclusion criteria A: 1) randomized clinical trials (RCTs) with parallel design; 2) studies comparing SRP with SRP + AMX/MET; 3) patients with diagnosed CP; 4) and studies involving human adults (age >18 years).

Only studies that met all inclusion criteria A were admitted to the second phase, which consisted of analysis of the preselected studies according to exclusion criteria B: 1) studies not reporting numerical full-mouth clinical attachment level (CAL) or probing depth (PD); 2) patients with systemic disease or who, within the past 6 months, had taken antibiotics or medications that are assumed or known to affect periodontal tissue or treatment; 3) follow-up of <3 months; 4) duplicate studies; and 5) primary outcome of interest not analyzed.

Outcome Variables

Primary outcomes of interest. The primary outcomes were changes in full-mouth CAL gain (in millimeters), full-mouth PD reduction (in millimeters), as well as CAL gain and PD reduction stratified according to baseline PD.

Secondary outcomes of interest. Secondary outcomes were changes at study sites in the following: bleeding on probing (BOP) (expressed as the percentage of sites with BOP), suppuration (SUPP) (expressed as the percentage of sites with SUPP), microbiological changes, adverse events, compliance of patients to AMX/MET administration, and costs/benefits ratio. All outcome variables were analyzed as pre-intervention (baseline) and postintervention (end of follow-up period).

Data Extraction

Data were collected by two independent reviewers (FS and AM). The following data were extracted from the included studies: year of publication, country, study design, demographic characteristics of participants, number of patients per intervention group, dosage of AMX/MET administration, therapeutic regimen of AMX/MET, frequency and type of AMX/MET-related adverse events, microbiological outcomes, and length of follow-up. Disagreements were resolved by discussion until consensus was reached.

Quality Assessment

Quality assessment of the methodologies of all included studies (Table 1) was performed independently

Table 1.

Categories Used to Assess the Quality of Selected Studies

Category	Description	Grading
A	Sample size calculation, estimating the minimum number of participants required to detect a significant difference among compared groups	0 = did not exist/not mentioned/not clear 1 = reported but not confirmed 2 = reported and confirmed
B	Randomization and allocation concealment methods	0 = clearly inadequate 1 = possibly adequate 2 = clearly adequate
C	Clear definition of inclusion and/or exclusion criteria	0 = no 1 = yes
D	Completeness of follow-up (specified reasons for withdrawals and dropouts in each study group)	0 = no/not mentioned/not clear 1 = yes/no withdrawals or dropouts occurred
E	Experimental and control groups comparable at study baseline for important prognostic factors	0 = no 1 = unclear/possibly not comparable for ≥1 important prognostic factors 2 = clearly adequate
F	Presence of masking	0 = no 1 = unclear/not complete 2 = yes
G	Appropriate statistical analysis	0 = no 1 = unclear/possibly not the best method applied 2 = yes

by two masked reviewers (FS and GM) according to the revised recommendations of the CONSORT (Consolidated Standards of Reporting Trials) statement.[25] The level of agreement between reviewers was calculated as reported above. Quality assessment was performed in two phases. During the first phase, quality assessment was based on the published full-text articles; in the second phase, all studies were reconsidered according to the additional information provided by the corresponding authors. After determining the scores at the conclusion of the second phase of quality assessment, the overall plausible risk of bias (low, moderate, or high) was estimated for each selected study. A low risk of bias was estimated when all of the criteria were met, a moderate risk was estimated when one or more criteria were partially met, and a high risk of bias was estimated when one or more criteria were not met.[21]

Statistical Analyses

Data were combined for meta-analysis with a statistical software package.† Heterogeneity was assessed by using the χ^2-based Q-statistic method and I^2 measurement, with significance indicated by $P<0.1$. However, because of the moderate insensitivity of the Q statistic,[26] only an I^2 value of 0% was considered reliable to detect the absence of heterogeneity.[27] The effect size was estimated and reported as the mean difference (MD), and the 95% confidence interval (CI) was calculated. Because of the expected inter-study heterogeneity, a random-effect model[28] was used. The level of significant was assumed to be $P<0.05$. Forest plots for each meta-analysis were used to present the raw data (means, standard deviations, and sample sizes) for each arm of the study. The publication bias was investigated for each outcome of interest by using two methods. Visual detection was used to analyze the funnel plot.[29] Quantitative analysis was performed with the regression asymmetry test[30] and the trim-and-fill method.[31] Publication bias was assessed with an additional statistical software package.‡

RESULTS

Study Selection

During the electronic and manual searches, a total of 517 abstracts were found (Table 2). In the first step of the study selection process, 481 publications were excluded based on an evaluation of titles and abstracts ($\kappa = 0.70$). During the second phase, the complete full-text articles of the remaining 36 publications[1,6-11,16-20,32-55] were thoroughly evaluated. A total of 24 articles[6,7,9,11,32-39,41-52] were excluded in this phase, because they did not fulfill the inclusion criteria A ($\kappa = 0.81$). Eight full-texts articles[16-19,40,53-55] of the remaining 12 publications were excluded because they met one or more of the exclusion criteria B ($\kappa = 0.73$) (Table 3). Four studies[1,8,10,20] fulfilled the required selection criteria of both phases and were included in the present systematic review. A flowchart for the study-selection process is shown in Figure 1. The main characteristics of the four included studies are summarized in Table 4.

Table 2.

Abstracts Retrieved by Electronic, Manual, and Reference Searching

Database	Overall Number of Search Outcomes	Number of Search Outcomes Without Overlap
PubMed (Basis)	200	200
Science Direct	30	30
Cochrane Controlled Clinical Trials Register	45	3
Cochrane Database of Systematic Reviews	7	0
CINAHL	50	22
Thomson Reuters Web of Science	159	26
Scopus	26	16
Hand search	0	0
Reference review articles	0	0
Reference selected articles	0	0

Description of Studies

The four included RCTs compared SRP + AMX/MET to SRP alone in the treatment of patients with CP. All of the studies used a parallel design, and three studies[8,10,20] were double-masked and placebo-controlled. The follow-up varied from 3 to 24 months. All studies reported full-mouth PD reduction, and full-mouth CAL gain was reported by three studies.[8,10,20] Two studies[8,20] analyzed gingival bleeding, BOP, SUPP, and visible plaque, and one study[10] reported bleeding index and full-mouth plaque index. Two studies[1,10] included both non-smoking and smoking patients and did not report significant differences between smokers and non-smokers in clinical parameters, one study[8] included only smoking patients, and one study[20] did not include smoking patients. SRP was accomplished in one to six sessions.

† Review Manager (RevMan) version 5, 2008, The Nordic Cochrane Center, The Cochrane Collaboration, Copenhagen, Denmark.
‡ Stata IC version 10.1, StataCorp, College Station, TX.

Table 3.

Studies Excluded and Reason for Exclusion

Study	Criteria for Exclusion	Type of Study
Haffajee et al.[6]	A.1	Systematic review
Herrera et al.[7]	A.1	Systematic review
Berglundh et al.[9]	A.1	RCT
Mombelli et al.[11]	A.1	Review
Cionca et al.[16]	B.5	RCT
Ribeiro et al.[17]	B.1	RCT
Moeintaghavi et al.[18]	B.1	RCT
Rooney et al.[19]	B.1	RCT
Walter et al.[32]	A.1	In vitro study
Mombelli et al.[33]	A.1	Comment
Ardila et al.[34]	A.1	In vitro study
Ardila et al.[35]	A.1	In vitro study
Buchmann et al.[36]	A.3	RCT
Bono and Brunotto[37]	A.1	Systematic review
van Winkelhoff and Winkel[38]	A.1	Review
Colombo et al.[39]	A.1	In vitro study
Cionca et al.[40]	B.2	RCT
Dannewitz et al.[41]	A.1	RCT
Pahkla et al.[42]	A.1	Clinical trial
Mombelli[43]	A.1	Comment
López et al.[44]	A.2	RCT
Page[45]	A.1	Review
Bonito et al.[46]	A.1	Systematic review
Slots[47]	A.1	Review
Feres et al.[48]	A.1	Clinical trial
López et al.[49]	A.2	RCT
Winkel et al.[50]	A.1	Clinical trial
van Winkelhoff et al.[51]	A.1	Clinical trial
Pavicić et al.[52]	A.1	Clinical trial
Flemmig et al.[53]	B.1	RCT
Flemmig et al.[54]	B.5	RCT
van Winkelhoff et al.[55]	A.1	Clinical trial

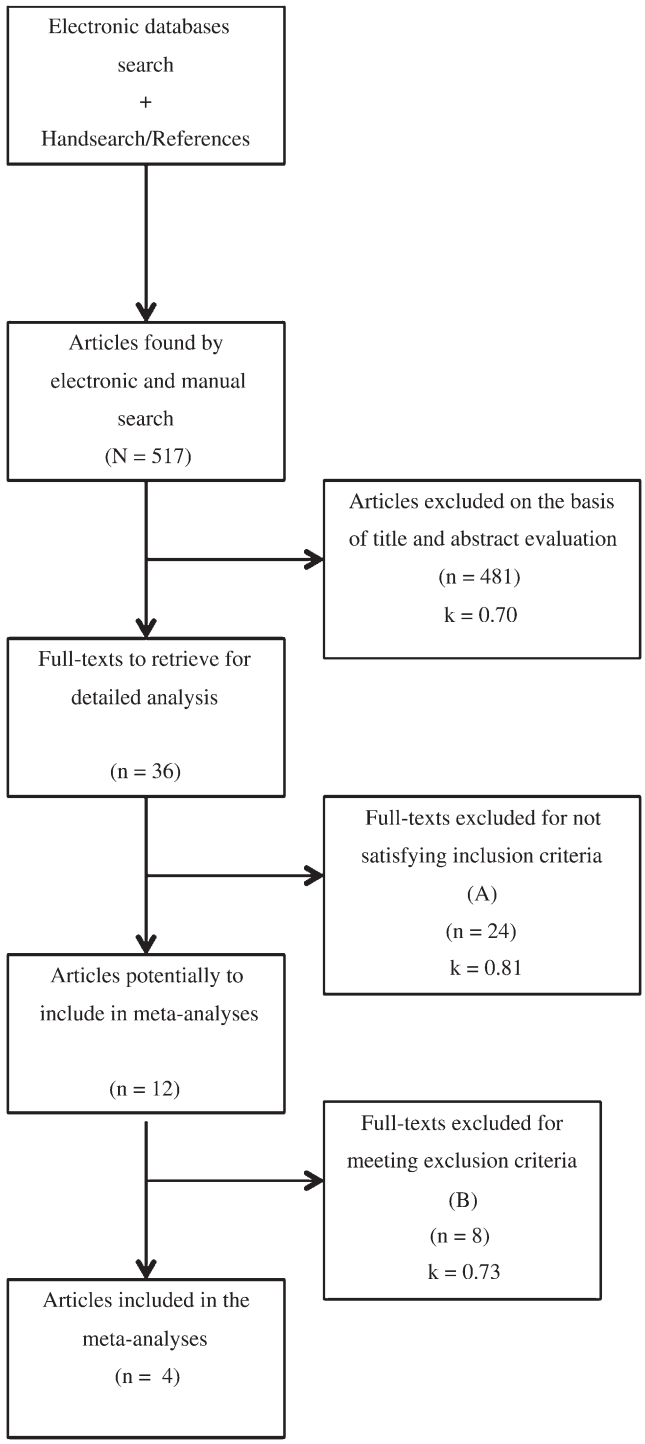

Figure 1.
Flowchart of the search strategy.

Table 4.

Characteristics of the Included Studies for SRP + AMX/MET and SRP Arms

Study	Population	Female/Male Age (years)	Design	Intervention	Follow-Up	Adverse Events	Microbiological Changes
Ehmke et al.[1]	35 patients with moderate-to-severe CP, Würzburg, Germany	11/7 (48.9 ± 11) 8/9 (53.2 ± 9.9)	Parallel, single-mask	Test = SRP + 8 days 350 mg MET/250 mg AMX (three times daily) Control = SRP	3, 6, 9, 12, 18, and 24 months from baseline	Not analyzed	No significant differences between test and control groups
Matarazzo et al.[8]	29 patients with CP, Guarulhos, Saõ Paulo, Brazil	6/8 (42.8 ± 7.1) 7/8 (40.5 ± 8.2)	Parallel, double-mask, placebo-controlled	Test = SRP + 14 days 400 mg MET/500 mg AMX (three times daily) Control = SRP + 14 days placebos (three times daily)	3 months after therapy	No statistical analysis	Significant reduction of red complex species and increasing of host-compatible species in favor of SRP + MET/AMX group
Silva et al.[20]	34 patients with generalized CP, Guarulhos, Saõ Paulo, Brazil	9/8 (45.5 ± 9.6) 10/7 (48.9 ± 12.4)	Parallel, double-mask, placebo-controlled	Test = SRP + 14 days 400 mg MET/500 mg AMX (three times daily) Control = SRP + 14 days placebos (three times daily)	3 months after therapy	No statistical analysis	Significant reduction of the orange complex and increase in *Actinomyces* species in favor of SRP + MET/AMX group
Winkel et al.[10]	49 patients with CP, Amsterdam, the Netherlands	12/11 (45; 32 to 63) 16/10 (40;28 to 55)	Parallel, double-mask, placebo-controlled	Test = SRP + 7 days 250 mg MET/350 mg AMX (three times daily) Control = SRP + 7 days placebos (three times daily)	3 months after therapy	No statistical analysis	Significant reduction of number of patients positive for *P. gingivalis*, *T. forsythensis*, and *P. micra* in favor of SRP + MET/AMX group

Quality Assessment

Quality assessment revealed that two[8,20] of the four RCTs were at low risk of bias (κ = 1.0), whereas the other twostudies[1,10] were at a high risk of bias since they did not report a sample size calculation (criteria A) or the method of randomization (criteria B) (κ = 1.0) (Table 5). After contacting the authors, no additional information was provided.

Microbiological Outcomes

All four studies analyzed microbiological outcomes (Table 4): two studies[8,20] used deoxyribonucleic acid (DNA)–DNA hybridization, one study[1] used polymerase chain reaction, and one study[10] reported identification by analysis of Gram stain, colony morphology, and production of specific enzymes. Significant reduction in favor of SRP + AMX/MET for the proportions of red complex microbes was reported in only one study.[8] Another study[10] reported a significant reduction in favor of SRP + AMX/MET in the number of patients positive for *P. gingivalis*, *T. forsythensis*, and *P. micra*. One study[1] did not report any significant differences from baseline to the end of follow-up in microbiological outcomes between SRP + AMX/MET and SRP. Only one study[20] observed a significant reduction in the proportion of orange complex species and a significant increase in the proportion of blue complex species in favor of SRP + AMX/MET.

Compliance and Adverse Events

All four studies analyzed compliance by counting the number of tablets provided to patients. Two studies[1,20] did not report the outcomes of the compliance analysis. One study[8] reported full adherence and one study[10] reported that only one patient was not compliant.

Three studies[8,10,20] analyzed adverse events. All three of these studies reported the variable occurrence of adverse events in the SRP + AMX/MET and SRP groups, with the exception of one study[8] that did not observe adverse events in the SRP group. However, none of the studies[8,10,20] performed a statistical analysis for the adverse events.

Meta-Analyses

Primary outcomes. Results of the meta-analyses revealed that patients who received SRP + AMX/MET showed a significant full-mouth CAL gain (MD = 0.21; 95% CI = 0.02 to 0.4; P <0.05) (Fig. 2) and full-mouth PD reduction (MD = 0.43; 95% CI = 0.24 to 0.63; P <0.05) (Fig. 3) from baseline to the end of follow-up compared to patients who received SRP alone. No significant heterogeneity was retrieved for either outcome (χ^2 = 0.67, I^2 = 0%, P = 0.88 and χ^2 = 0.22, I^2 = 0%, P = 0.90, respectively).

Secondary outcomes. No significant differences between SRP + AMX/MET and SRP were found for BOP changes (MD = 10.77; 95% CI = –3.43 to 24.97; P >0.05) (Fig. 4) or SUPP changes (MD = 1.77; 95% CI = –1.7 to 5.24; P >0.05) (Fig. 5). A meta-analysis of the microbiological changes was not performed because the data were not suitable for pooling.

Publication bias. Funnel plots for CAL gain did not show asymmetry (Fig. 6). Trim-and-fill analysis did not indicate missing studies for the full-mouth CAL. The PD funnel plot and the regression asymmetry test did not suggest publication biases (Table 6). For secondary outcomes, the trim-and-fill analysis showed one missing study for SUPP changes and no missing studies for BOP changes; however, because only two studies[8,20] were included in the meta-analyses of secondary outcomes, no regression asymmetry test could be performed. The difference between the original estimate and the adjusted effect was not significant for primary outcomes (Fig. 7).

DISCUSSION

Adjunctive antimicrobial therapy has been widely investigated in terms of its ability to confer additional clinical benefit to non-surgical periodontal therapy[56] and to reduce the long-term need for periodontal surgery.[57] The present meta-analysis assessed the use of combined AMX/MET therapy with SRP in the treatment of patients with CP. The results seem to support its adjunctive clinical benefits. This finding is consistent

Table 5.

Quality Assessment of Selected Studies Before and After Contact (parentheses) With Corresponding Authors

Study	A (0 to 2)*	B (0 to 2)*	C (0 to 1)*	D (0 to 1)*	E (0 to 2)*	F (0 to 2)*	G (0 to 2)*	Estimated Risk of Bias
Ehmke et al.[1]	0 (0)	0 (0)	1 (1)	1 (1)	2 (2)	2 (2)	2 (2)	High (High)
Matarazzo et al.[8]	2 (2)	2 (2)	1 (1)	1 (1)	2 (2)	2 (2)	2 (2)	Low (Low)
Silva et al.[20]	2 (2)	2 (2)	1 (1)	1 (1)	2 (2)	2 (2)	2 (2)	Low (Low)
Winkel et al.[10]	0 (0)	0 (0)	1 (1)	1 (1)	2 (2)	2 (2)	2 (2)	High (High)

* Letters refer to categories of quality assessment defned in Table 1.

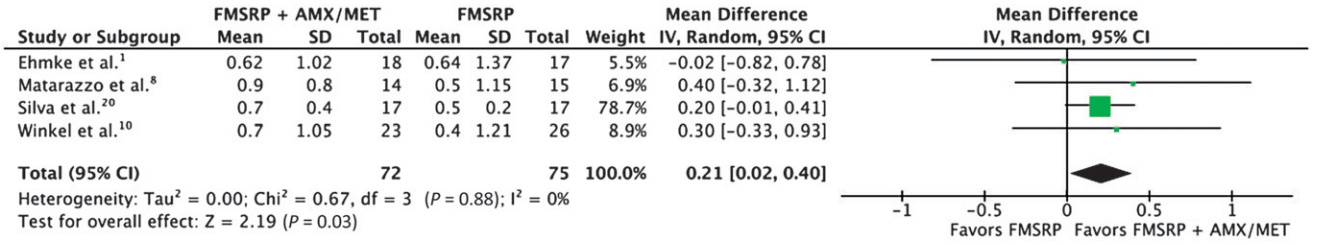

Figure 2.
Forest plot of CAL gain.

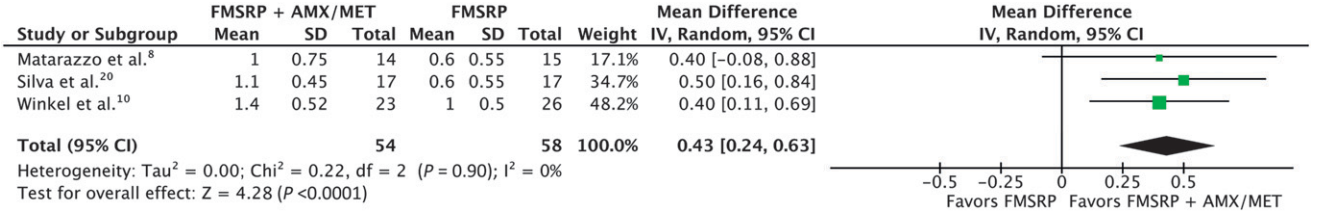

Figure 3.
Forest plot of PD reduction.

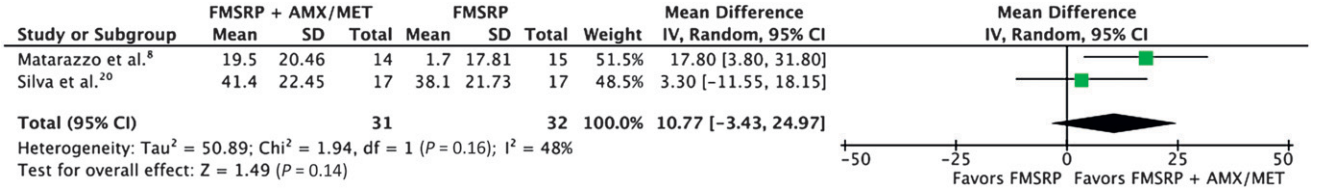

Figure 4.
Forest plot of changes in BOP.

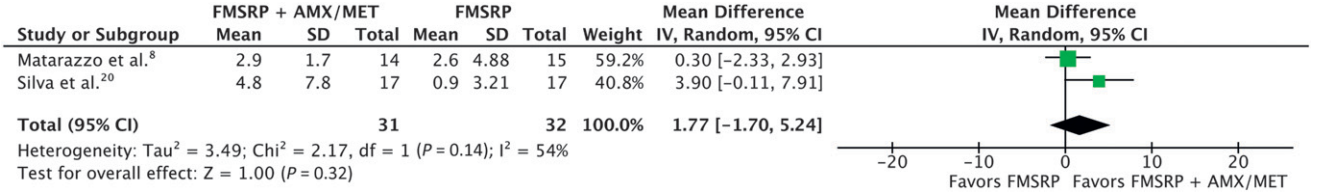

Figure 5.
Forest plot of changes in SUPP.

with the results of the included studies, which all reported a significant difference in favor of SRP + AMX/MET for PD reduction and CAL gain. Furthermore, two[1,10] of the studies reported that patients who received adjunctive AMX/MET treatment showed significant differences in the percentage of sites exhibiting a CAL gain ≥ 2 mm; these results also seem to support the clinical significance[58] of adjunctive AMX/MET. Although no additional benefit was found in the reduction of the percentage of sites with BOP and SUPP, these outcomes were analyzed by pooling only two studies. Therefore, the lack of significant differences could be attributable to the small number of studies analyzed, and future studies should include those clinical parameters.

Contrasting results were found for the effect of combined AMX/MET therapy on the microbial profile

of CP patients. Only one study[8] reported a significant reduction, in patients receiving AMX/MET, of the red complex species that are particularly involved in CP progression.[59] These discrepancies could be attributable to the use of different elements, such as antibiotic dosage, regimen and compliance, follow-up times, or susceptibility of the microbes to AMX and MET. Interestingly, none of the studies performed a preliminary analysis of microbial resistance, nor did any study consider this issue in the interpretation of the results. Many factors could negatively influence the effectiveness of systemic antimicrobial therapy, including resistance of periodontal pathogens to one or more antibiotic agents[60] and decreased antibiotic diffusion in the biofilm.[61] These issues also should be considered in future studies.

Compliance was reported in all of the included studies. Only one study[8] reported that all patients fully adhered to the dosage and regimen of the treatment protocol. However, the method used to assess patient compliance in all of the studies (tablet counting) has not been verified as objective and reliable;[49,62] in particular, use of this method can lead to overestimation of patient adherence to the treatment protocol.[63] Adverse events were analyzed by three[8,10,20] of the four studies, none of which reported the occurrence of serious adverse events. However, none of the studies compared adverse events between the SRP and SRP + AMX/MET groups. Therefore, it is not possible to state whether adjunctive AMX/MET therapy could be considered as a safe treatment. Furthermore, because the occurrence of adverse events could negatively influence compliance and clinical outcomes,[64] this issue and its influence on compliance should be reported in future studies.

A cost/effectiveness analysis could not be performed because it was not reported by any of the included studies. The addition of adjunctive AMX/MET to non-surgical periodontal therapy is thought to be much more effective than non-surgical therapy alone or in combination with local antimicrobials, with little additional cost.[56] Assessments of the cost/effectiveness ratio should include the risk of antimicrobial resistance, as well as the long-term prognosis and future need for periodontal surgery of patients treated by SRP + AMX/MET.

It is well known that smoking can reduce the response to periodontal therapy.[65-67] Thus, there is a growing interest in defining a more effective treatment strategy for smoking patients.[8] Among the four studies in the meta-analysis, one study[20] did not include smoking patients. One study[1] reported that, after assessing the influence of smoking on clinical results, the inclusion of smoking patients did not lead to changes in the clinical results. Another study,[10] which performed a separate analysis according to smoking status, found a greater, but non-significant, clinical benefit of adjunctive AMX/MET combined

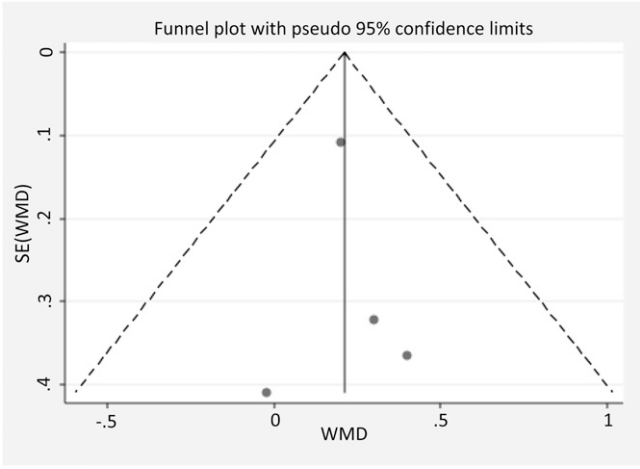

Figure 6.
Funnel plot for CAL gain. SE = standard error. WMB = weighted mean difference.

Table 6.

Quantitative Analysis for Publication Bias Assessments

	Original Meta-Analysis		Trim-And-Fill Analysis		
Outcome	MD (95% CI)	*P*	MD (95% CI)	Studies Trimmed/ Total Studies	Egger Regression *P*
CAL gain	0.21 (0.02 to 0.40)	0.03	0.21 (0.02 to 0.39)	0/4	0.84
PD reduction	0.43 (0.24 to 0.63)	<0.0001	0.43 (0.23 to 0.63)	0/3	0.99
BOP changes	10.77 (–3.43 to 24.97)	0.14	10.77 (–3.43 to 24.97)	0/2	
SUPP changes	1.77 (–1.7 to 5.24)	0.32	0.3 (–3.27 to 3.87)	1/2	

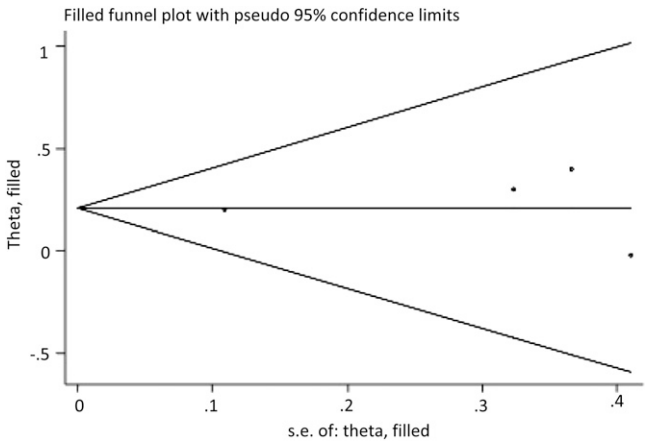

Figure 7.
Funnel plot for CAL gain, adjusted with the trim-and-fill method.

therapy in smokers compared to non-smoking patients. The final study[8] included only smoking patients and reported significant differences in clinical parameters in favor of SRP + AMX/MET. However, because the results in clinical parameters were not stratified according to smoking status and studies with smokers were included in the meta-analysis, the influence of smoking on the outcomes of the meta-analysis could not be assessed. Although it has been speculated that smoking may be a discriminating element in the decision to treat severe CP patients with systemic antibiotics, future studies with large sample sizes are needed.

An important issue that has been suggested to subtend the differences in clinical results between the studies is the dosage and administration regimens of adjunctive AMX/MET therapy. In the present meta-analysis, the administration regimen was three times per day in all of the d studies, although the dosages varied with only two studies[8,20] reporting the same dosage. Considering the small number of patients, the influence of dosage on clinical outcomes could not be assessed. Although there is no general consensus on the optimal dosage of AMX/MET,[8] recent studies[68] based on the knowledge that lower antibiotic dosages may limit the clinical and microbiological effects of systemically administered agents recommend the adjunctive use of 1,500 mg twice daily AMX and 1,200 mg twice daily MET.. Only two[8,20] of the four studies used this suggested dosage; the other two studies[1,10] used lower dosages of both AMX and MET. Because dosage is paramount in determining the microbiological and clinical outcomes of adjunctive systemic antimicrobial therapy, future studies are needed to assess the optimal dosage, relative to the occurrence of adverse events and patient adherence to the treatment protocol.

Despite consistent differences in terms of follow-up times, antimicrobial dosage, and smoking habits, no evidence of heterogeneity was detected for the primary and secondary outcomes of interest among the present studies. This homogeneity could be attributable to the use of strict eligibility criteria in the selection of the studies. Although the results of the present meta-analysis are consistent with those of a previous meta-analysis,[7] the present study adopted a rigorous methodological design, based on recommendations of the Cochrane Collaboration[21] and on the principles of the PRISMA statement,[22] with a CONSORT-based quality assessment of RCTs.[25] Furthermore, a quantitative and qualitative analysis was used to detect publication bias. Although no evidence of publication bias was observed, we cannot exclude the possibility of publication bias because only a small number of studies were included in the meta-analysis.

The results of meta-analysis showed that adjunctive AMX/MET therapy could provide additional benefits in terms of CAL gain and PD reduction. These findings should be interpreted with caution because the meta-analysis had important limitations. Only four studies were eligible for inclusion in the meta-analysis, which included a total of 147 patients for CAL gain and 112 for PD reduction. Furthermore, only two[8,20] of the studies reported the calculation of the minimum sample size necessary to detect significant differences between groups. Quality assessment revealed that two studies[1,10] were at high risk of bias, due to lack of sample size calculation and inadequate randomization. Finally, differences in the clinical parameters were extracted based on the baseline to end of follow-up, and this range varied from 3 to 24 months. Time-related changes in clinical parameters could have influenced the results of the meta-analysis. Future well-designed RCTs with an adequate sample size and longitudinal data are needed to confirm these results. Such studies should also analyze the effect of adjunctive AMX/MET therapy on the profile of periodontal pathogens that are involved in the pathogenesis of CP, the possibility of acquiring antimicrobial resistance, the occurrence of adverse events, and the influence of smoking on the outcomes, and should also include a cost/effectiveness analysis.

CONCLUSIONS

General Conclusion

The results of the meta-analysis seem to support overall effectiveness of AMX/MET as an adjunct therapy to SRP, compared to SRP alone, in the treatment of CP. However, given the small number of included studies, additional large RCTs are needed to confirm these findings.

Implications for Research

Several important issues, which relate to AMX/MET dosage, to its effects on periodontal pathogens, as well as to the influence of smoking on clinical results and to the occurrence of adverse events, are highlighted in this systematic review. Future studies should clarify these issues.

Implications for Practice

The present systematic review reveal that adjunctive AMX/MET therapy could provide additional benefit to SRP. However, until the paramount issues that were mentioned above are addressed, we consider that it is not appropriate to give specific recommendations for the use of AMX/MET combined therapy.

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