

Amoxicillin/Metronidazole Dose Impact as an Adjunctive Therapy for Stage II - III Grade C Periodontitis (Aggressive Periodontitis) at 3- And 6-Month Follow-Ups: a Systematic Review and Meta-Analysis

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ABSTRACT

Objectives: This systematic review and meta-analysis study sought to review the efficacy of amoxicillin/metronidazole dose and duration time in the treatment of stage II - III grade C periodontitis (aggressive periodontitis) after current follow-up.

Material and Methods: An electronic search of the literature was performed in three main databases for relevant articles published until 31th of December 2021. According to the PRISMA statement, the extracted data from selected articles were pooled. The weighted mean difference (MD) and 95% confidence interval (CI) of clinical attachment level (CAL) gain and probing depth (PD) reduction at 3 and 6 months of follow-up were calculated. The heterogeneity of the data was evaluated by the I² test.

Results: The results of six randomized clinical trials revealed significant improvement of clinical parameters in moderate and severe pockets. Prescription of 400 to 500 mg metronidazole caused significant CAL gain changes just in moderate pockets (MD = 1.82; 95% CI = 1.11 to 2.53; P < 0.05).

Conclusions: Amoxicillin/metronidazole has positive short-term effects as an adjunct to scaling and root planning for treatment of stage II - III grade C periodontitis. Higher doses of metronidazole (400 to 500 mg) are required for optimal efficacy regarding clinical attachment level gain.

Keywords: aggressive periodontitis; amoxicillin; drug dose-response relationship; meta-analysis; metronidazole; dental scaling.

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INTRODUCTION

Aggressive periodontitis (AgP) has defined as an inflammatory, multi-factorial, complex type of periodontal disease in 1999 that generally affects healthy individuals younger than 30 years of age with rapid progression [1]. In the last world workshop on the classification of periodontal and peri-implant diseases, severity (stage II - III) or complexity and speed of progression were the basis of new classification, that grade C represent rapid rate of progression [2]. Due to the rapid rate of progression, high prevalence in some areas [3]. and predilection for young age and the risk of early edentulism in patients, immediate and meticulous treatment is required to eliminate as many pathogens as possible, which is challenging in the long-term [4,5].

Conventional scaling and root planning (SRP) is generally believed to be a successful approach for reduction of microbial count. However, this modality does not completely eliminate the microorganisms and cannot significantly affect the long-term clinical outcome [6-8], except in cases where modern technologies such as periodontal endoscopy have been used simultaneously [9]. Also, microorganisms can lodge in the furcation areas, infra-bony pockets, hard-to-reach areas (for instrumentation), the tongue, and the tonsils [10-13]. Therefore, despite the same susceptibility, patient responses to treatment often vary. Thus, researchers are in search of adjunctive treatments such as systemic antibiotic therapy along with SRP [14-16]. Evidence shows that adjunctive use of systemic antibiotics leads to more favourable clinical results with regard to probing depth (PD) and clinical attachment level (CAL) in AgP patients [17]. Systemic antibiotic therapy with correct choice of antibiotics can eliminate inaccessible pathogens. Thus, combined use of adjunctive antibiotic therapy and removal of periodontal biofilm by SRP is a suggested treatment protocol for these patients [18-21]. The suggested antibiotic regimen for this purpose includes azithromycin, doxycycline, tetracycline, moxifloxacin and amoxicillin/metronidazole (AMX/MET) [22-26]. Since combined use of multiple adjunctive antimicrobial agents may lead to higher stability of the microbiota [18], AMX/MET are the most commonly suggested antibiotics for this purpose since they have a broad-spectrum antibacterial activity [27,28]. Some certain biomarkers and clinical and radiographic evidence is used to assess the efficacy of different antibiotic regimens in the literature [29,30]. Assessment of clinical parameters such as PD and CAL is most commonly performed for

this purpose [26,31-34]. However, some previous studies [32,35,36] that compared the efficacy of SRP plus AMX/MET versus SRP alone for nonsurgical treatment of AgP by measurement of clinical parameters reported additional benefits for AMX/MET administration with respect to PD reduction and CAL gain especially in deep pockets. Regarding the CAL gain, less improvement was noted compared with PD reduction. Moreover, some substantial variations exist in the treatment protocols of previous studies that need to be addressed and standardized with respect to study design, duration of antibiotic therapy, antibiotic dosage, determining the severity of the disease based on a unique protocol, and meticulous assessment of the side effects of antibiotic therapy.

Some meta-analyses [16,26,37-39] generated a combined estimate based on the mean change in clinical results to compare the outcomes of systemic antibiotic therapy versus SRP. A recent study on the efficacy of systemic antibiotic therapy plus SRP for treatment of AgP showed that metronidazole and MET/AMX yielded more favourable outcomes compared with doxycycline regarding the CAL gain [26]. Also, they reported the positive effect and clinical safety of combined use of AMX/MET plus SRP versus SRP alone with respect to CAL gain, PD reduction, and improvement of gingival bleeding index, bleeding on probing, and visible plaque index. Also, the two modalities were the same regarding complications or adverse events [38]. It is clear that use of AMX/MET has positive clinical results for AgP treatment. However, some shortcomings exist in homogenizing the methodological approaches such as variations in administered doses of AMX/MET and duration of antibiotic therapy, and inadequate number of randomized clinical trials (RCTs) for different disease severities that impede achieving reliable results. A recent meta-analysis compared low- and high-dose AMX/MET plus full mouth SRP versus full mouth SRP alone for treatment of periodontitis and reported that higher doses had superior effects on clinical parameters at the 3-month follow-up [40]. However, since the pathogens involved in AP are different from those responsible for chronic periodontitis, the required antibiotic dosage would be different for a successful treatment in moderate and severe forms of disease. Since selection of antibiotic dosage (and its resultant efficacy) for cases with different levels of attachment loss is often performed empirically, this systematic review and meta-analysis sought to determine the most effective dose of AMX/MET as an adjunct to scaling and root planning in stage II - III grade C periodontitis (aggressive periodontitis) based on clinical parameters.

MATERIAL AND METHODS

The present systematic review and meta-analysis was prepared in line with the PRISMA [41] and Cochrane Collaboration and Check Review [42] checklists. The following clinical question was addressed: “What is the dose impact of AMX/MET as an adjunct to SRP in moderate and severe forms of AgP at 3 and 6 months of follow-up?”

Search strategy

An electronic search was conducted in PubMed, Cochrane, EMBASE, Scopus, and Science Direct databases by two reviewers (ZB, MK) for English articles published until 31th December 2021 (Figure 1). The literature was searched using a combination of the following Mesh terms and text words: “early-onset periodontitis” [MeSH] OR “aggressive periodontitis” [MeSH], OR “juvenile periodontitis”

AND “antibiotic therapy” [MeSH] OR “AMX/MET” OR “amoxicillin/metronidazole” OR amoxicillin AND “nonsurgical treatment” OR “scaling root planning” OR “periodontal debridement”.

Eligibility criteria

Inclusion criteria

The inclusion and exclusion criteria were applied by two masked reviewers (ZB, MK). Studies meeting the below-mentioned criteria were included in this meta-analysis:

- RCTs.
- Evaluation of AgP patients according to the American Academy of Periodontology [43].
- Having a test group undergoing SRP with antibiotic therapy (AMX/MET).
- SRP treatment for the control group.
- 3- or 6-month follow-ups.
- Reporting the mean PD and CAL.
- English language articles.

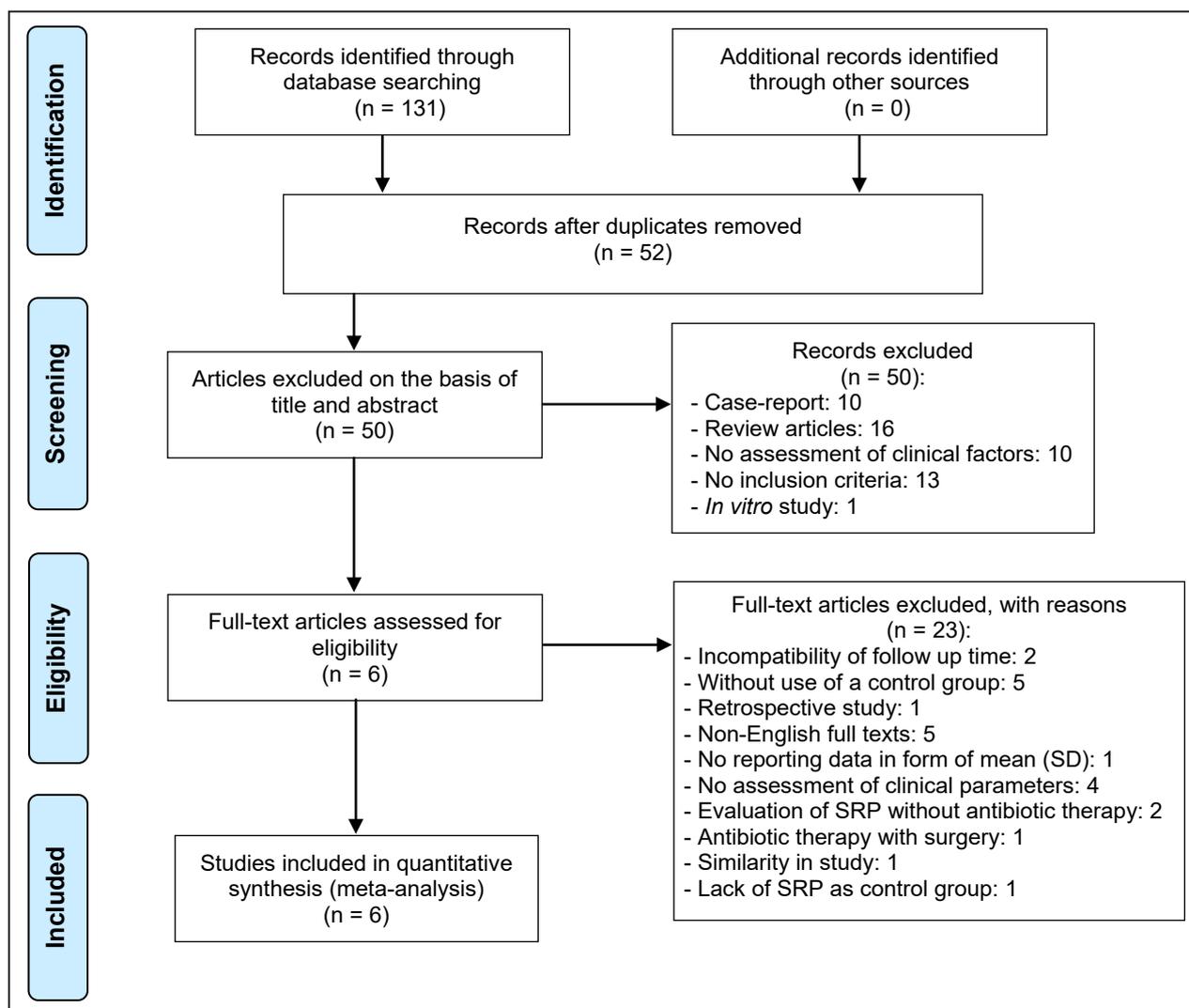


Figure 1. Flowchart of the search strategy according PRISMA guidelines.

Exclusion criteria

The exclusion criteria were:

- Patients with systemic diseases and those with a recent history of antibiotic intake.
- Smoker patients included in RCTs.
- Follow-up ≤ 3 months or ≥ 6 months.
- Duplicate studies.
- Case reports and review articles.
- Studies that only assessed patient radiographs or performed immunological assessments.
- Letter to editors.
- Studies on patients with chronic periodontitis.

Outcome measures

The mean change was recorded in CAL gain and PD reduction in millimetres (mm) between the baseline and the follow-up visits, in which the pre-intervention time corresponded to baseline and the post-intervention time to the end of 3 or 6 months of follow-up.

Data extraction

The retrieved articles were reviewed, and data extraction was performed by two independent reviewers (ZB, MK). The extracted data included the first author's name, year of publication, country, study design, number of patients per intervention group, male/female percentage, age, follow-up time, therapeutic regimen of AMX/MET, duration of AMX/MET prescription, and PD. Only the numerical data (in tables or text) were extracted. Disagreement in the extracted data was resolved by discussion until an agreement was reached.

Quality assessment

The quality assessment of the methodology of all included studies was performed according to the revised recommendation of the CONSORT (Consolidated Standards of Reporting Trials) statement for reporting RCTs (methods of randomization and allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other sources of bias) [44] by two independent blind reviewers. The quality assessment was based on the extracted full-text articles. Next, the overall risk of bias (low, moderate, or high) was estimated for all the enrolled articles. Low risk of bias was considered when all criteria were met. Doubt in one or more criteria and unavailability of one or more

were considered as unclear and high risk of bias, respectively [45].

Statistical analysis

The data regarding the administered dosage of AMX/MET for moderate and severe AgP in the form of mean and standard deviation (M [SD]) were extracted. Then, its efficacy at 3 and 6 months of follow-up were evaluated. The heterogeneity of the data was assessed by I^2 measurement and $P \leq 0.05$ was considered significant. Also, the mean difference in PD and CAL was calculated with 95% confidence interval (CI). Moreover, the effect size was assessed and reported by the mean difference (MD) with 95% CI. However, risk difference at 95% CI was utilized to pool the outcome of each treatment group for pairwise data. The data were pooled for meta-analysis by Review Manager (RevMan) version 5.0 software (The Cochrane Collaboration; Oxford, UK) and due to the observed heterogeneity in the MD of studies, a random effect model was used [46]. For visual detection and quantity analysis of the publication bias for each outcome, the funnel plot analysis [47] and the "Trim and Fill" method, were performed, respectively by STATA software version 16 (StataCorp LLC.; College Station, Texas, USA).

RESULTS

Study selection

A total of 131 potentially relevant titles were found by the electronic search of databases (Figure 1); 52 duplicate studies were removed and 50 records were excluded after screening the titles and abstracts. Therefore, 29 articles were eligible for full-text evaluation. During the last phase, 6 articles remained for quantitative synthesis [14,32,35,36,48,49]. In this stage, 23 articles were excluded because of incompatibility of the follow-up times [50,51] not having a control group [33,34,36,52,53] retrospective design [31], non-English full-texts [54-58], not reporting the data in the form of mean (SD) [59-61], not assessing the clinical parameters [62-65], evaluation of SRP without antibiotic therapy, antibiotic therapy with surgery [66], studies using the same data pools [20], and not performing SRP alone as the control group [15]. Thus, a total of 6 studies related to AMX/MET therapy plus SRP as non-surgical therapy for the management of AgP were evaluated and analysed for quality and heterogeneity assessment.

Description of studies

Only six RCTs were evaluated in this study. The characteristics of the included RCTs are summarized in Table 1. All parallel studies had two arms comparing AMX/MET + SRP versus SRP alone [14,32,35,36,48,49] at 3- and 6-month follow-ups from baseline. Four articles evaluated patients with moderate and severe pockets. One study performed two-session full-mouth debridement [36]; while, the remaining three studies treated the patients in one session. Since the administered doses of amoxicillin were almost the same in RCTs, the dosage of metronidazole was used as the basis for dose assessment. Two studies evaluated 250 mg [32-36] and over 250 mg [14,35] doses of metronidazole.

Quality assessment

The outcome quality assessment of included studies

is illustrated in Figure 2. Three studies met all the criteria. However, the remaining three revealed high risk of bias due to not reporting the randomization process and allocation concealment [14,48,49]. Also, two studies did not report the process of blinding of the participants and the outcome assessment criteria [14,48]. Only one RCT was not satisfactory regarding the performance and detection bias [49]. Thus, three of six included studies had low risk of bias [14,35,36], and three studies had high risk of bias [14,48,49] (Figure 2).

Outcomes of meta-analysis

Probing depth of pockets

Overall, at the 3 and 6-month follow-ups, a total of 160 patients were compared in six studies for changes in the mean CAL and PD. Of these studies, only four reported moderate and severe pockets. The results showed significant mean difference in PD reduction

Table 1. Main characteristics of the antibiotic therapy studies

Study	Year of publication	Country	Study design	Sample	Age (years)	Male/female	Systemic disease	Intervention	Follow-up (months)	Assessed PPD (mm)
					Mean (SD)					
Guerrero et al. [14]	2005	UK	Parallel, double-blind, placebo-controlled, randomized	Test: 20	Test: 29.8 (6.45)	Test: 4/16	No	Test: SRP + 500 mg AMX/500 mg MET 7 days	6	Moderate (PD = 4 to 6); severe (PD ≥ 7)
				Control: 21	Control: 31.86 (5.22)	Control: 9/21				
Casarin et al. [32]	2012	Brazil	Parallel, masked, placebo-controlled randomized	Test: 12	Test: 28.8 (6.2)	Test: 3/9	No	Test: SRP + 375 mg; AMX/250 mg MET 7 days	3, 6	Moderate (PD = 5 to 6); severe (PD ≥ 7)
				Control: 12	Control: 28.3 (5.9)	Control: 5/7				
Mestnik et al. [35]	2010	Brazil	Parallel, double-blind, placebo-controlled, randomized	Test: 15	Test: 26.8 (3.9)	Test: 6/9	No	Test: SRP + 500 mg AMX/400 mg MET 14 days	3	Moderate (PD = 4 to 6); severe (PD ≥ 7)
				Control: 15	Control: 27.6 (3.5)	Control: 4/11				
Varela et al. [36]	2011	Brazil	Parallel, double-masked, placebo-controlled, randomized	Test: 18	Test: 33.1 (5.1)	Test: 8/10	No	Test: SRP + 500 mg AMX/250 mg MET 10 days	3, 6	Moderate (PD = 4 to 6); severe (PD ≥ 7)
				Control: 17	Control: 32.1 (3.9)	Control: 4/13				
Ercan et al. [48]	2015	Turkey	Parallel, placebo-controlled,	Test: 15	Test: 31.3	Test: 6/9	No	Test: SRP + 500 mg AMX/500 mg MET	3	PPD ≥ 3
				Control: 15	Control: 31.7	Control: 4/11				
Rodrigues et al. [49]	2012	Brazil	Parallel, randomized	Test: 15	Test: 27.73 (5.84)	Test: 11/4	No	Test: SRP + 500 mg AMX/400 mg MET 7 days	3, 6	PPD ≥ 3
				Control: 15	Control: 27.73 (5.84)	Control: 11/4				

SRP = scaling root planning; AMX = amoxicillin; MET = metronidazole; PPD = probing pocket depth; PD = probing depth.

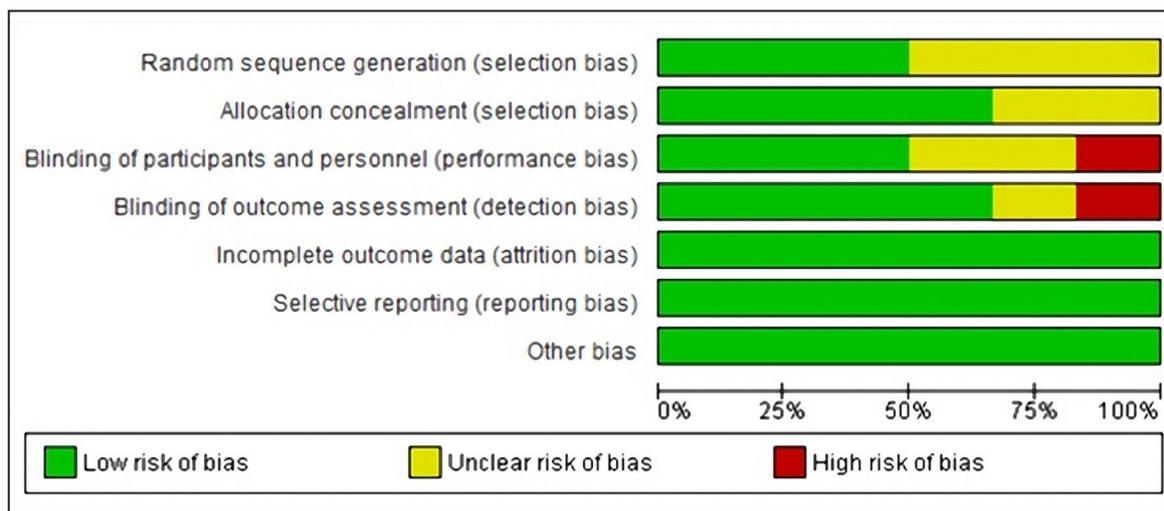


Figure 2A. Risk of bias graph.

MD = 0.42 mm (95% CI = 0.27 to 0.58; I² = 53%) (Figure 3A). Though CAL gain revealed MD = 1.04 mm (95% CI = 0.2 to 1.88; I² = 85%) (Figure 3B).

Analysis of moderate and severe pockets in 4 studies revealed significant results MD = 1.7 mm (95% CI = 0.61 to 2.8; I² = 85%; P = 0.002) (Figure 4A) and MD = 1.44 mm (95% CI = 0.55 to 2.33; I² = 80%; P = 0.002) (Figure 4B).

Similar to the results of PD reduction, the results of the mean CAL gain revealed a significant difference MD in moderate and severe attachment losses (Figure 5).

Metronidazole dosage

Four studies assessed moderate and sever pockets based on the dosage of metronidazole. There were two studies in each group of 250 mg [32,36] and over 250 mg (400 to 500 mg) metronidazole dosage [14,35]. A significant difference was noted in the metronidazole dosage (250 mg and over 250 mg) between the test and control groups in moderate cases of AgP MD = 0.3 (95% CI = 0.24 to 0.36; P ≤ 0.00001; I² = 0%) and MD = 0.5 (95% CI = 0.38 to 0.6; P ≤ 0.00001; I² = 0%) (Figure 6). But there was no significant reduction in PD of severe pockets in patients who took 250 mg metronidazole MD = 0.46 (95% CI = -0.25 to 1.17; P = 0.02; I² = 82%). However, in severe pockets, 400 to 500 mg metronidazole caused significant reduction of PD MD = 1.32 (95% CI = 1.06 to 1.58; P = 0.00001; I² = 0%) (Figure 6).

Regarding CAL, A statistically significance difference was noted just in moderate pockets in use of 400 to 500 mg metronidazole MD = 1.82 (95% CI = 1.11 to 2.53; P < 0.0001; I² = 36%). No statistically significant difference in the mean MD = 0.85 mm (95% CI = 1.08 to 2.78; I² = 0.39) showed that 250 mg metronidazole did not improve the outcome of

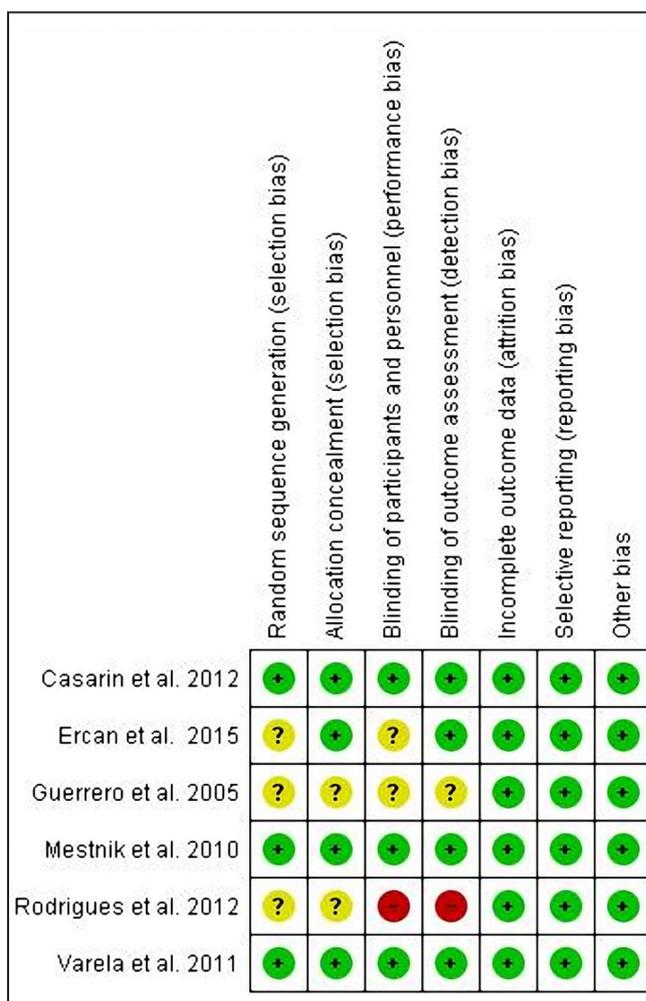


Figure 2B. Risk of bias summary.

treatment when used for moderate pocket. There was no statistically significant difference in any of the evaluated metronidazole doses in deep pockets MD = 2.2 (95% CI = 0.37 to 4.78; P = 0.09; I² = 94%), MD = 0.79 (95% CI = 0.21 to 1.79; P = 0.12; I² = 70%) (Figure 7).

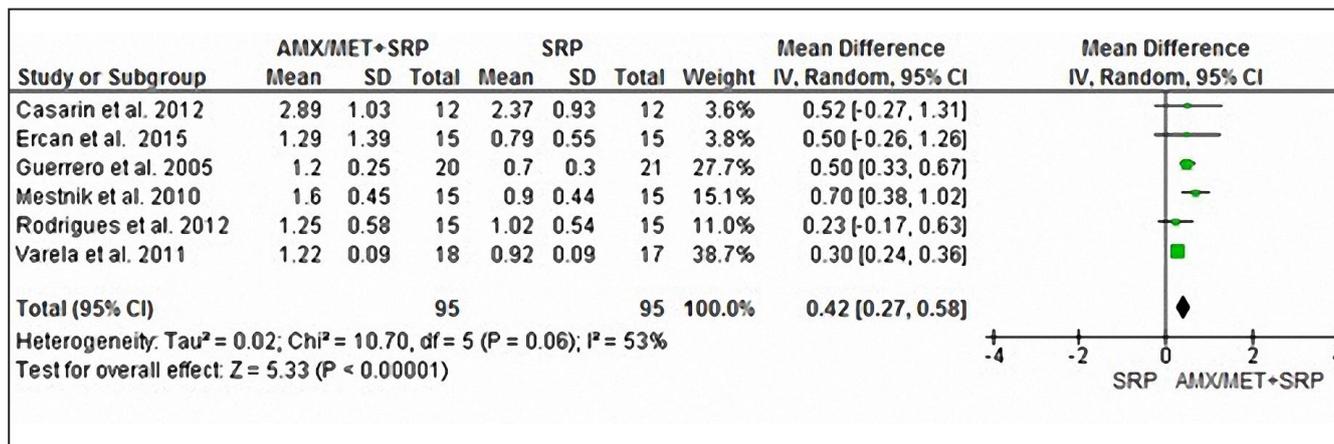


Figure 3A. Forest plot of probing pocket depth reduction (Review Manager [RevMan]).

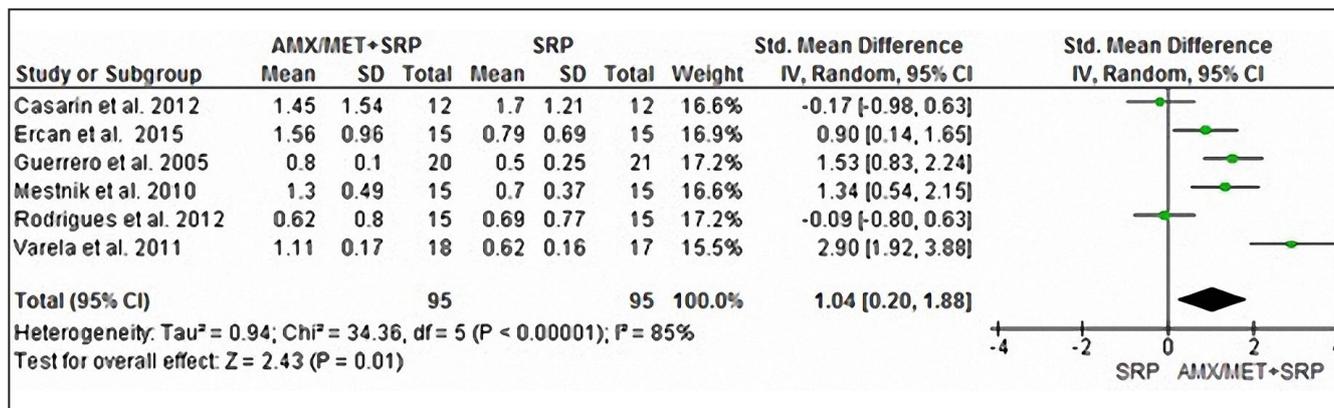


Figure 3B. Forest plot of clinical attachment level gain (Review Manager [RevMan]).

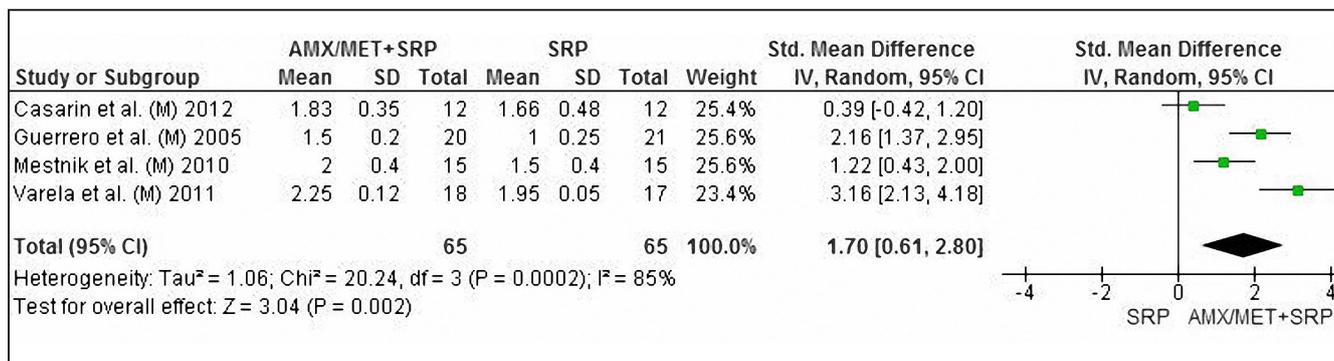


Figure 4A. Forest plot of probing pocket depth reduction in moderate pockets.

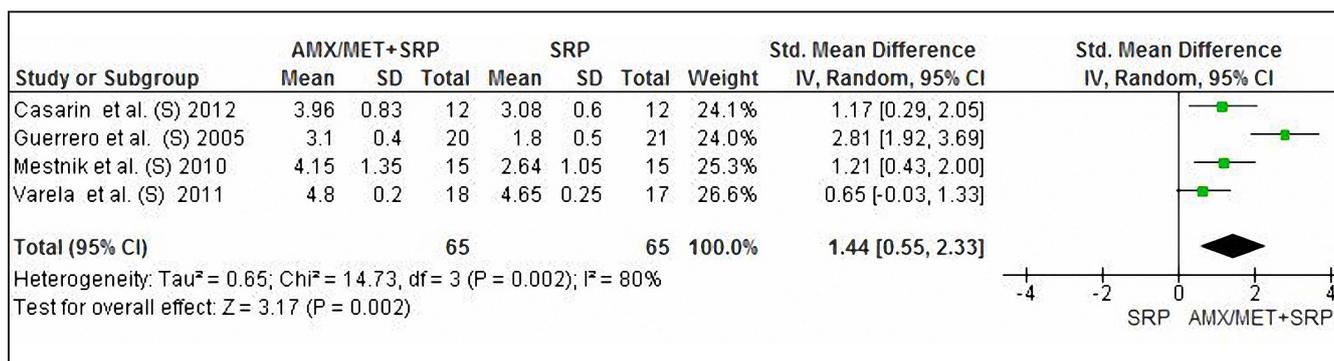


Figure 4B. Forest plot of probing pocket depth reduction in severe (B) pockets.

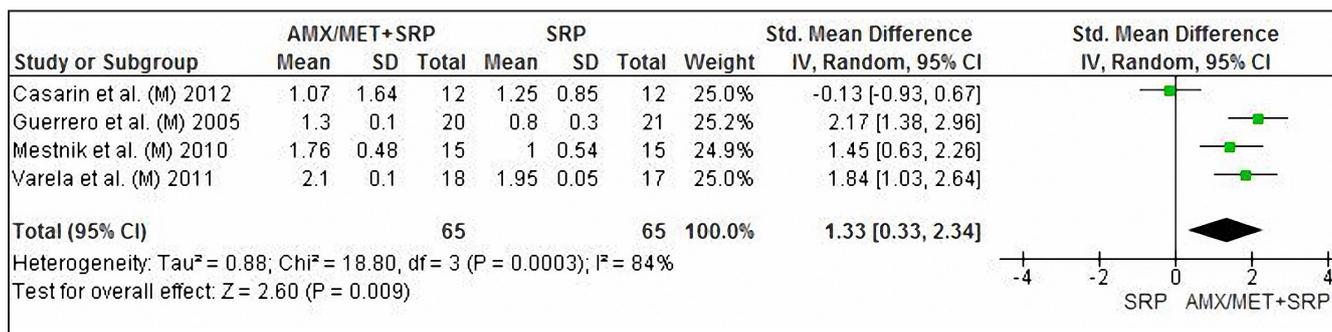


Figure 5A. Forest plots of clinical attachment level gain in moderate pockets.

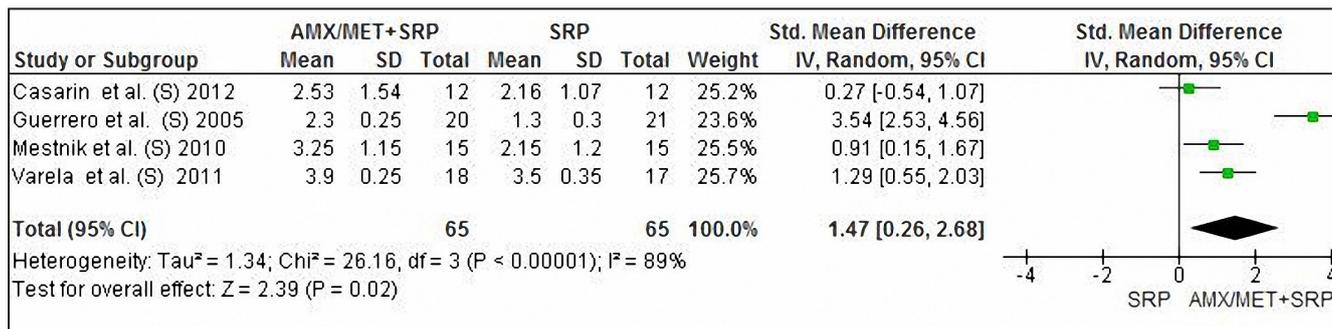


Figure 5B. Forest plots of clinical attachment level gain in severe pockets.

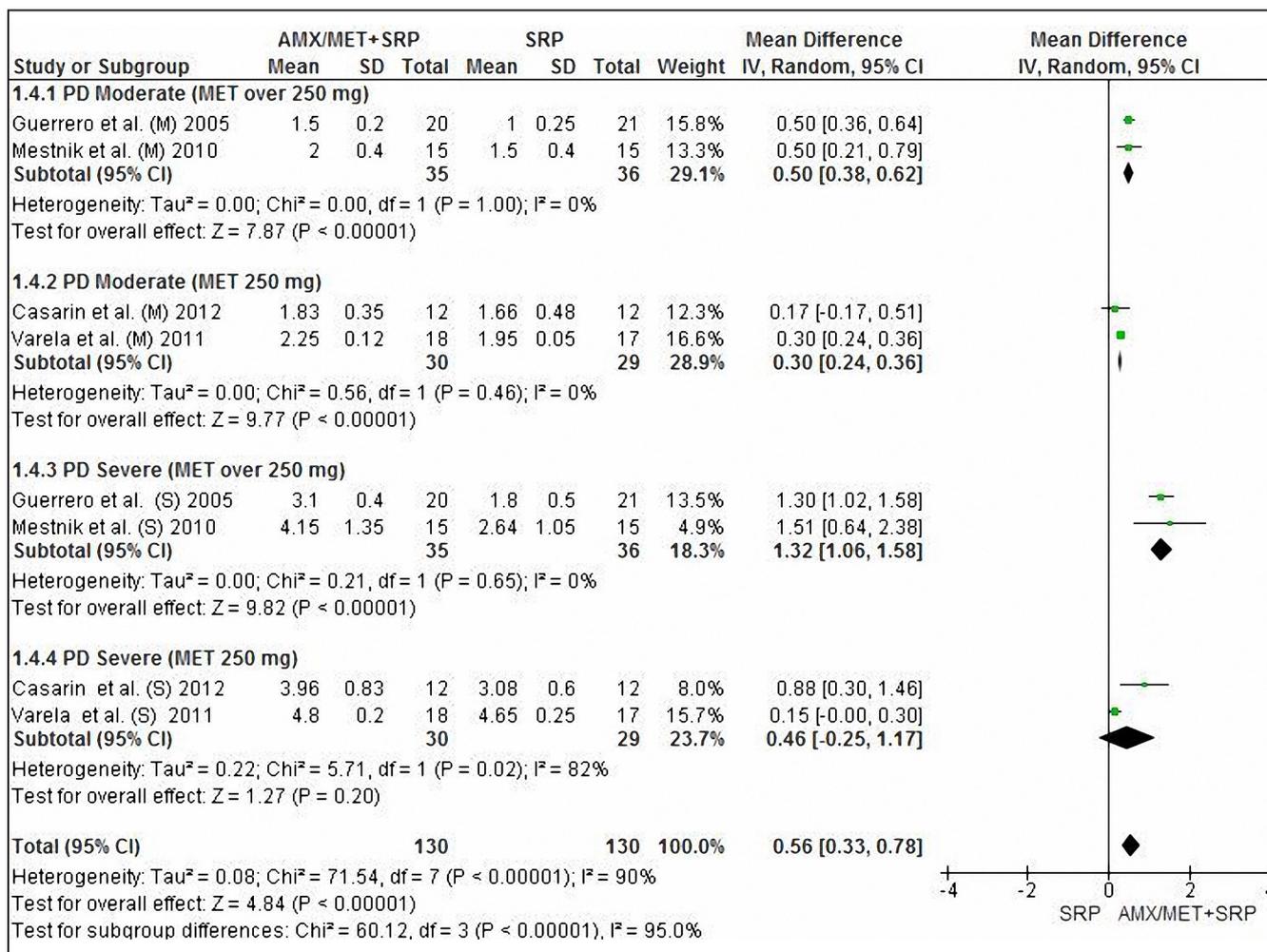


Figure 6. Forest plots of probing pocket depth reduction based on metronidazole dose in moderate and sever pockets.

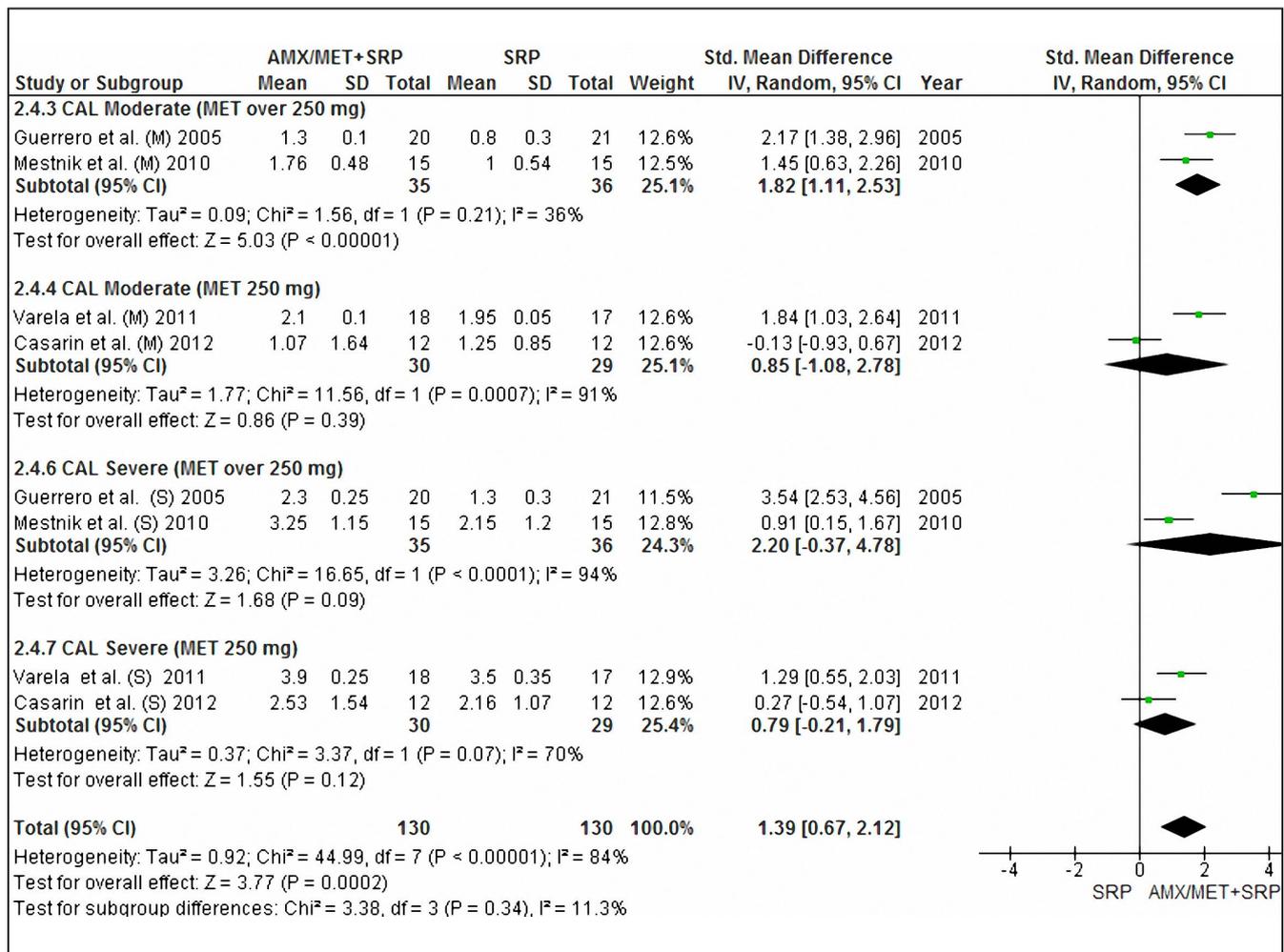


Figure 7. Forest plots of clinical attachment level gain based on metronidazole dose in moderate and severe pockets.

Duration of treatment

The recommended duration of treatment (7 or 10 to 14 days) is another factor that affected the results regarding CAL gain. AMX/MET + SRP resulted in significant CAL gain in moderate and severe attachment losses when used for 7 days MD = 0.49 (95% CI = 0.35 to 0.62; P < 0.00001; I² = 37%), MD = 0.98 (95% CI = 0.82 to 1.15; P < 0.00001; I² = 24%) and 10 to 14 days MD = 0.16 (95% CI = 0.11 to 0.21; P < 0.00001; I² = 90%), MD = 0.44 (95% CI = 0.24 to 0.64; P < 0.0001; I² = 60%) (Figure 8).

Three- and six-month follow-ups

A total of 190 patients in 6 studies were analysed. Systemic AMX/MET + SRP were compared with SRP alone. Five studies assessed the outcomes at 3 months, and 4 studies assessed the results at 6 months. Comparison of the total follow-up time between the test and control groups showed a significant MD in PD reduction 1.3 mm (95% CI = 0.58 to 2.02; heterogeneity I² = 86%) in favour of the systemic

use of AMX/MET. A total of 144 patients across 5 studies were evaluated at 3 months and 130 patients across 4 articles were evaluated at 6 months. The difference in CAL gain was found to be significant in the total follow-up time between the test and control groups MD = 0.96 (95% CI = 0.33 to 1.6; P = 0.003; I² = 83%). Significant improvement of CAL was observed at both 3 months MD = 1.01 (95% CI = 0.25 to 1.76; P = 0.009; I² = 78%) and 6 months MD = 0.91 (95% CI = -0.3 to 2.13; P < 0.00001; I² = 90%) (Figure 9).

Publication bias

The funnel plots were used to assess the publication bias. Totally, the outcomes of CAL gain in the funnel plots (Figure 10) showed no asymmetry. Moreover, the trim and fill analysis demonstrated no missed study in PD and CAL funnel plots in moderate and severe pockets of AgP patients. Also, the regression asymmetry test did not reveal any publication bias in the results (Table 2).

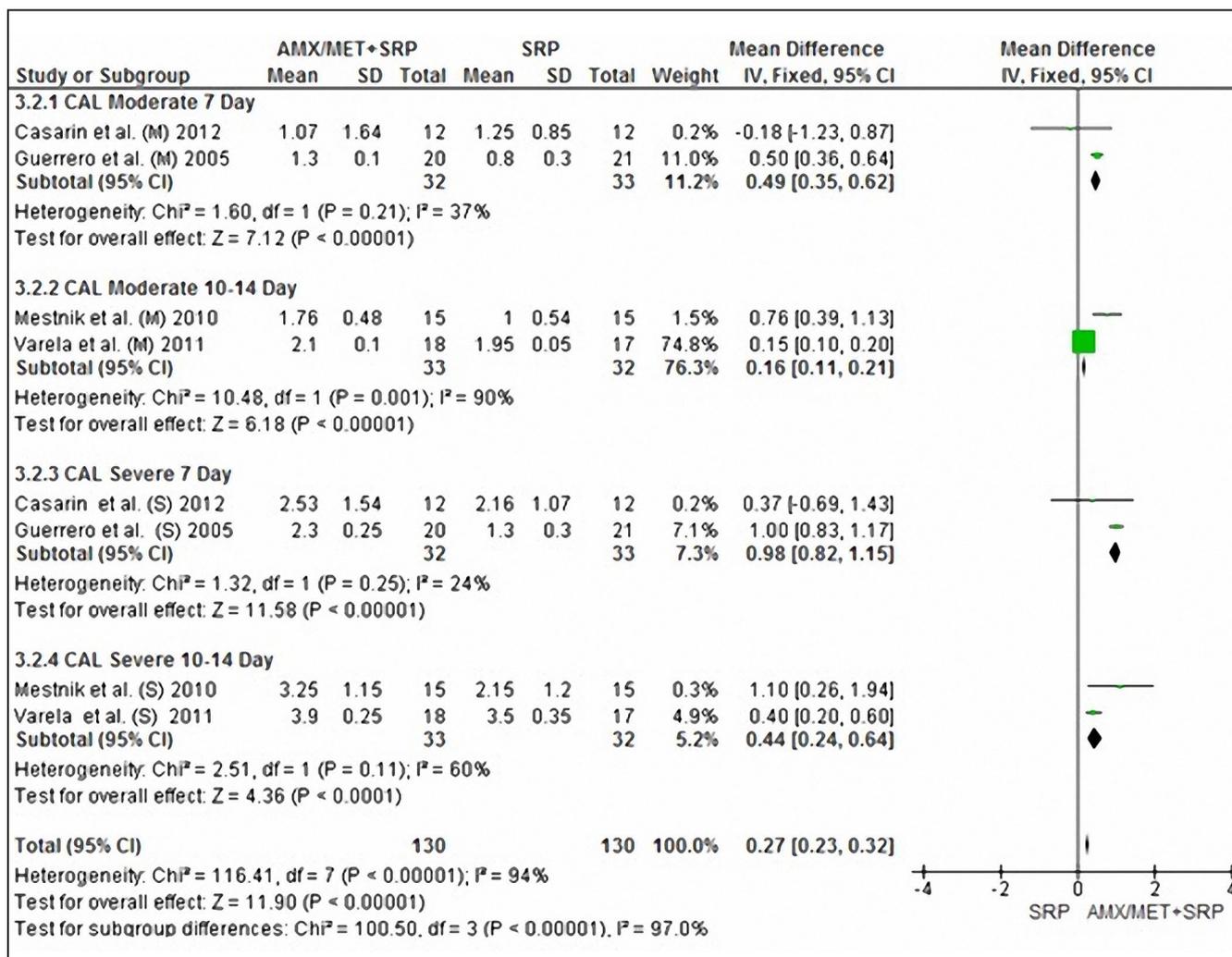


Figure 8. Forest plot of clinical attachment level gain in different duration times

DISCUSSION

Addition of antibiotic therapy to conventional periodontal therapy is a challenging topic for many dental clinicians in management of AgP. According to the results of the available RCTs, AMX/MET is the most effective adjunct to SRP for PD reduction and CAL gain [18,67]. PD and CAL are the most frequently evaluated clinical parameters for assessment of periodontal status in RCTs [68]. The 0.85 mm (95% CI = -1.08 to 2.78; I² = 91%) finding supported the adjunctive use of AMX/MET since it caused a substantial improvement in clinical parameters of moderate and severe 0.85 mm (95% CI = -1.08 to 2.78; I² = 91%), pockets in AgP, except in one RCT [36] which is probably due to the conduction of full-mouth debridement in this particular study. They performed full-mouth ultrasonic debridement under local anaesthesia in two sessions and prescribed 0.2% chlorhexidine gel during a 24-hour period. Thus, they could not precisely

detect the anti-inflammatory effect of antibiotic therapy.

Comparison of the efficacy of AMX/MET at 3- and 6-month follow-ups revealed considerable improvement of PD and CAL at the 3-month follow-up. Nevertheless, no significant change occurred after the 3-month follow-up (until 6 months), which indicates deceleration or discontinuation of the healing process. This finding indicates the greatest impact of AMX/MET on clinical parameters in the first 3 months after treatment. The effect of antibiotic therapy after this time period is questionable unless another interfering factor improves the clinical parameters. This reduction in healing process is inconsistent with the results of a RCT [32] which may be due to reinforcement of oral hygiene protocol and full-mouth supragingival debridement in the respective study. Therefore, it appears that antibiotic therapy with AMX/MET as an adjunct to SRP has a short-term effect on clinical parameters [69].

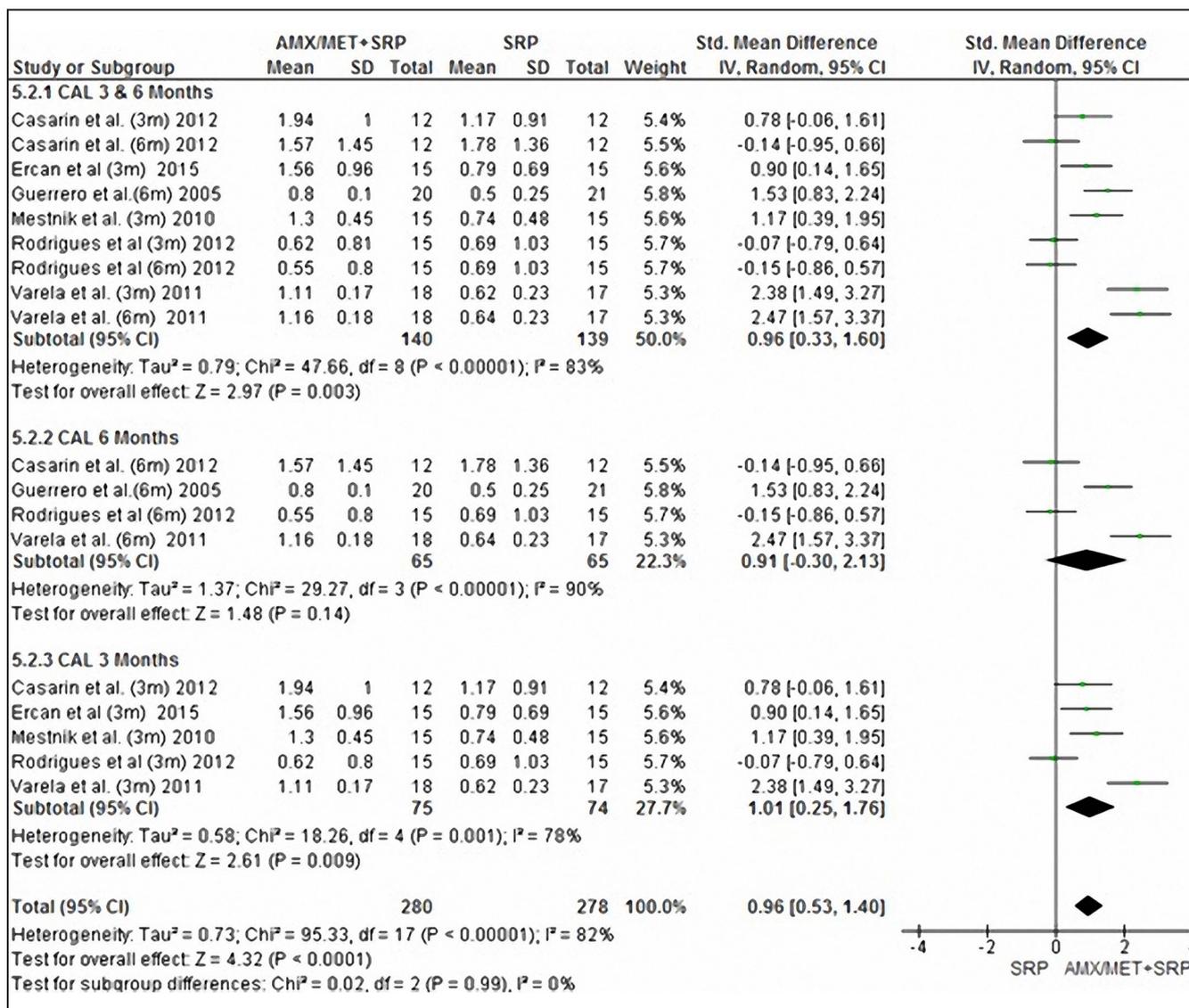


Figure 9. Forest plot of clinical attachment level gain at 3 and 6 month follow-up (Review Manager [RevMan]).

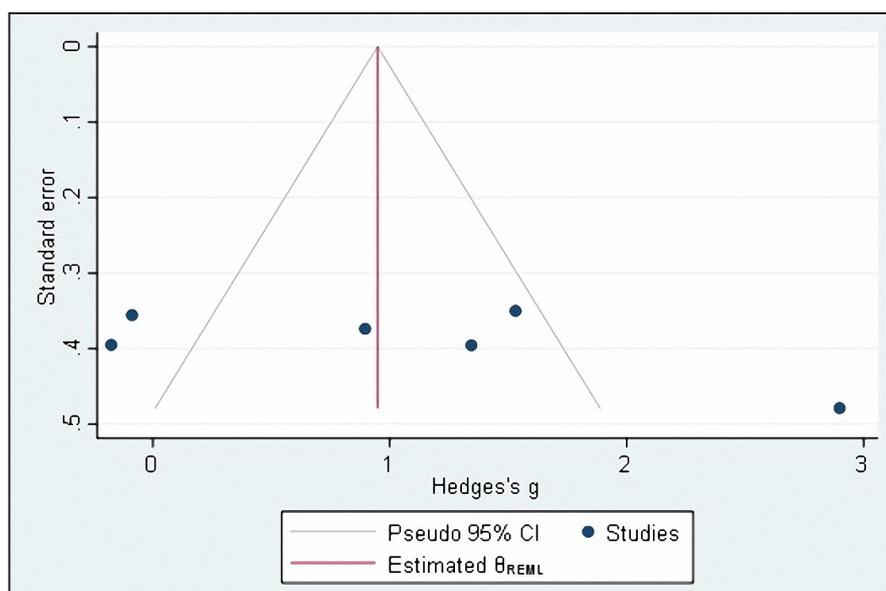


Figure 10. Funnel-plots for clinical attachment level gain adjusted with Trim and Fill method (all included studies) (STATA software).

Table 2. Quantitative analysis of publication bias evaluation

Outcome	Original meta-analysis		Trim and fill analysis		
	Mean difference 95% CI	P-value	Mean difference 95% CI	Studies trimmed/ total studies	Egger regression P-level
PD reduction (total)	0.42 (0.27; 0.58)	< 0.00001	0.42 (0.27; 0.58)	0/6	0.5
PD reduction (moderate)	1.07 (0.61; 2.8)	0.002	1.07 (0.61; 2.8)	0/4	0.1
PD reduction (sever)	1.44 (0.55; 2.33)	0.002	1.44 (0.55; 2.33)	0/4	0.1
CAL gain (total)	1.04 (0.2; 1.88)	0.01	1.04 (0.2; 1.88)	0/6	0.07
CAL gain (moderate)	1.33 (0.33; 2.34)	0.009	1.33 (0.33; 2.34)	0/4	0.7
CAL gain (sever)	1.47 (0.26; 2.68)	0.02	1.47 (0.29; 2.68)	0/4	0.01
CAL gain (Sgolastra et al. [27])	0.42 (0.23; 0.61)	< 0.0001	0.37 (0.19; 0.54)	1/6	0.72

PD = probing depth; CAL = clinical attachment level; CI = confidence interval.

Although assessment of clinical parameters at 3 and 6 months showed satisfactory results, the effect of antibiotic dosage on improvement of clinical parameters is undeniable. To date, no comparative data are available regarding the most effective dosage of AMX/MET, and since the amoxicillin dosage was almost the same in all RCTs, only the metronidazole dosage was selected as the comparison criterion. Accordingly, there were two articles that prescribed 250 mg metronidazole [32,36], and four studied treated patients with 400 to 500 mg metronidazole plus amoxicillin [14,35,48,49]. The findings of CAL gain indicated significant improvement of moderate attachment loss in AgP after prescription of 400 to 500 mg metronidazole while in severe attachment losses wasn't effective, significantly. Also, the effect of 250 mg metronidazole on moderate and severe attachment loss was not significant. It appears that 250 mg metronidazole is not sufficient to efficiently eliminate the pathogens in moderate and severe attachment losses, which was similar to the findings of a recent study [40] on periodontitis that reported beneficial effect of adjunctive AMX/MET at a higher dosage. Also, Metronidazole dose increasing cannot improve the severe attachment losses, effectively. It is noteworthy that although increasing the dosage increases the frequency of adverse side effects, increasing the dosage of metronidazole up to 500 mg for treatment of periodontitis did not increase the side effects in the reviewed studies [38,40]. Therefore, the commonly prescribed dosage of metronidazole (250 mg or 400 to 500 mg) combined with amoxicillin is safe with respect to side effects.

Aside from the antibiotic dosage, duration of antibiotic therapy is another important factor that plays a role in development of adverse effects. Limited studies and high heterogeneity regarding the duration of antibiotic intake in the included studies

decreased the sensitivity of the analysis of the effect of different durations of AMX/MET intake on improvement of AgP. Considering these limitations, the variations in duration of antibiotic therapy showed insignificant effect on improvement of clinical parameters in the present study.

In addition to clinical parameters, some authors assessed other parameters such as the microbial count, microbial sampling [35], gingival bleeding [16], and level of prostaglandin E2 and pro-inflammatory cytokines in gingival crevicular fluid [70,71]. For example, a previous study showed a significant reduction in the mean microbial count of red and orange complexes (which would directly indicate the efficacy of antibiotic therapy) at the 3-month follow-up following the consumption of AMX/MET [35]. Similarly, Xajigeorgiou et al. [4] indicated that *Aggregatibacter actinomycetem comitans* count did not significantly decrease at 6 weeks after AMX/MET consumption. However, all microorganisms that are believed to be involved in AgP decreased at the 6-month follow-up. In the present study, improvement of both PD and CAL was noted at 3 months. However, the results of studies varied regarding the continuation of healing process until 6 months. Thus, the data collected from microbiological, clinical and immunological evaluations confirmed the short-term effects of AMX/MET for treatment of AgP; however, its long-term effects are controversial. To assess the short-term effects of AMX/MET in treatment of AgP, the effect size and publication bias of the included studies were evaluated (Figure 11). In the present study, the effect size of the mean PD reduction and CAL gain variations showed almost 10 to 30% reduction in PD and 50 to 70% CAL gain, compared with other studies. Such differences are due to the various methodologies of RCTs included in the meta-analysis. Also, all included studies after the performance of trim and fill analysis were the same

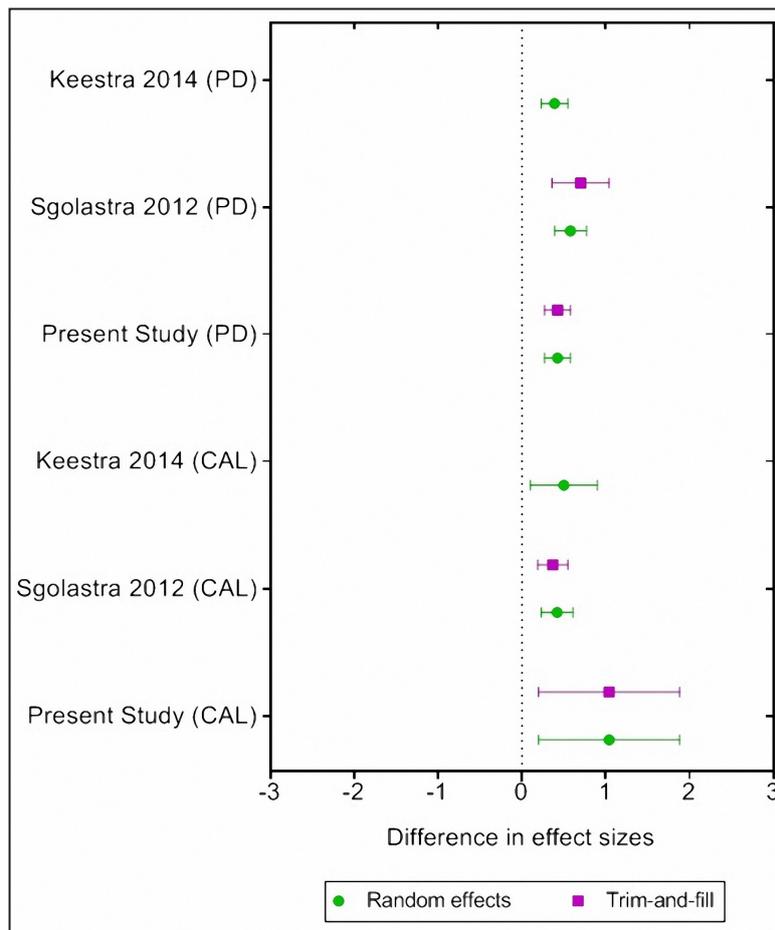


Figure 11. Results comparison of different meta-analysis studies.

in the meta-analysis, except for one article, that was omitted. This analysis showed that the heterogeneity was acceptable and can indicate the positive effect of AMX/MET on AgP with regard to both CAL gain and PD reduction. Thus, antibiotic therapy appears to be cost-effective and valuable for treatment of AgP, which has been confirmed by other studies as well [14,26,68,72].

However, in addition to the parameters addressed in previous studies [38,73,74], this meta-analysis focused on evaluation of the prescribed dosage and duration of AMX/MET therapy on moderate and severe pockets in AgP. Moreover, despite the presence of differences in RCTs, the findings showed no asymmetry in the funnel plot analysis of the reviewed articles. Also, according to the adjusted effect size based on the “trim and fill method”, no study was missed in this analysis. Nevertheless, due to the small number of included articles, the results regarding the effect of AMX/MET dosage, duration of usage, adverse events, and bacterial resistance of antibiotics should be interpreted with caution. Finally, well-designed studies with long-term follow-ups and larger sample size are required to address these limitations.

CONCLUSIONS

This meta-analysis confirmed the positive short-term effects of amoxicillin/metronidazole as an adjunct to scaling and root planning for treatment of stage II - III grade C periodontitis (aggressive periodontitis). Furthermore, higher dosage (400 to 500 mg) of metronidazole in amoxicillin/metronidazole combination can improve the clinical parameters with no concern regarding side effects. Increasing the duration of intake did not significantly improve the outcome. However, well-designed randomized clinical trials with larger sample size and standard dosage and duration of antibiotic administration are required to obtain more accurate results regarding the treatment of stage II - III grade C periodontitis (aggressive periodontitis).

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