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ORIGINAL ARTICLE

The effect of drug dose and duration of adjuvant Amoxicillin-plus-Metronidazole to full-mouth scaling and root planing in periodontitis: a systematic review and meta-analysis

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Abstract

Objectives The aim is to explore the optimal drug dose and duration of adjunctive Amoxicillin-plus-Metronidazole (AMX/MET) to full-mouth scaling and planing (FMSRP) in periodontitis.

Methods An electronic search in four databases and manual search in four journals were conducted for randomised clinical trials comparing AMX/MET adjunct to FMSRP with FMSRP alone for at least 3 months.

Results Eleven studies were eligible and included. The primary outcome was clinical attachment level (CAL) gain, the secondary outcomes were periodontal pocket depth (PPD) reduction and adverse events. Our results showed a beneficial effect of adjunctive AMX/MET with higher drug dose to FMSRP for CAL gain and PPD reduction at 3 months, and the benefit remained stable at 6 months. However, minimal difference among three-seven-and ten-day drug duration was observed. In addition, the risk difference of adverse events was minimal between two groups.

Conclusion FMSRP adjunct to a high drug dose of 500/500 mg of AMX/MET showed a significant and stable improvement on 6-month follow-up period. No decision for drug duration could be made due to limited evidence.

Clinical relevance On 6-month follow-up, higher dose of AMX/MET adjunct to FMSRP could provide a stable clinical effect. No recommendation for drug duration could be made.

Keywords Periodontitis · Amoxicillin · Metronidazole · Root planing · Meta-analysis

Introduction

Periodontitis is a multifactorial inflammatory disease that is characterised by destruction of the dental supporting apparatus. Periodontitis occurrence and development are mainly caused by the imbalance between the microbial load within periodontal pockets and the local and systemic host immune mechanisms. Moreover, bacterial products and inflammatory mediators produced by periodontal pathogens could further affect systemic health. After scaling and root planing, subgingival microbial load could be reduced 1000-fold [1, 2]. Despite the great reduction of pathogens, bacteria can re-colonise the periodontal pocket in 3–7 days [3–5]. In non-surgical periodontal therapy (NSPT), quadrant scaling and root planing (QSRP) carries the risk of bacterial contamination from untreated sites to treated sites [6]. Full-mouth

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scaling and root planing (FMSRP) is considered as an alternative treatment for periodontitis. Full-mouth treatment was proposed by Quirynen in 1995, aiming to delay the re-infection that occurred after QSRP [7]. The strategy is usually implemented as FMSRP in 1–2 sessions within 24–48 hours with or without the use of antiseptics. Insufficient evidence supported that FMSRP was more effective than QSRP for CP treatment [8–10].A meta-analysis published in 2016 indicated that full-mouth debridement provided significantly greater improvement in clinical outcomes of moderate pockets in comparison to QSRP [10]. However, Sanz et al. recently reported that no substantial differences were observed between QSRP and FMSRP without using antiseptics [11]. Additional to clinical efficacy, FMSRP reduces treatment frequency and duration and increases cost-effectiveness [12, 13], which should be considered when selecting treatment modality.

Systemic use of antibiotics adjunct to FMSRP has frequently been applied in periodontal therapy, aiming to suppress multiple microbial species simultaneously and block transmission of residual periodontal pathogens, and to achieve maximum elimination of pathogenic bacteria. Various combinations of systemic antibiotics have been used, and strong data have indicated greater improvement in clinical outcomes in FMSRP combined with systemic antibiotics [14–19]. However, there is no evidence supporting a specific compound with optimal drug dose or duration [20, 21]. Amoxicillin-plus-Metronidazole (AMX/MET) has been reported to have an increased synergistic activity against gram-negative anaerobic bacteria [22]. Systematic reviews indicated an additional benefit for adjunctive AMX/MET in chronic periodontitis in clinical attachment level (CAL) gain and periodontal pocket depth (PPD) reduction [23, 24]. In addition, compared to other antibiotics, adjunctive AMX/MET to NSPT presented greater improvement than metronidazole alone and azithromycin [25–27] and a trend of better effectiveness than doxycycline in moderate and deep pockets [28]. A meta-analysis in 2018 reported no clinical difference between different doses or durations of AMX/MET at 3 months [29]. Despite a large amount of evidence reporting the clinical effect of AMX/MET adjunct to NSPT, there is lack of consensus on the optimal regimen of drugs and persuasive outcomes of long-term follow-up. The Council for Appropriate and Rational Antibiotic Therapy (CARAT) recommends appropriate aggressive short-course treatment to ensure clinical effect, patient adherence and control of drug resistance [30]. Given the increased concerns about antibiotic use, it is urgent to determine an optimal regimen of systemic adjunctive antibiotic use in terms of drug dose and duration.

This meta-analysis aimed to evaluate whether the drug dose and duration of adjunctive AMX/MET to FMSRP affect clinical outcomes in periodontitis and to explore an appropriate treatment combination for patients with periodontitis considering multiple aspects, including clinical efficacy, patient comfort and cost-effectiveness.

Materials and methods

The systemic review protocol was designed based on the PRISMA guidelines and conducted following recommendations from the Cochrane Collaboration.

Focus question

The focus question according to PICOS was: Do drug dose and duration of adjunctive AMX/MET to FMSRP affect the clinical efficacy at 3 and 6 months in patients with periodontitis?

Eligibility criteria

The following inclusion criteria were applied: (1) randomised clinical trials (RCTs), (2) FMSRP conducted in 1–2 sections within 48 h, (3) studies comparing the FMSRP and FMSRP + AMX/MET, (4) studies reporting on multiple antibiotic groups or different treatment modalities, the studies were included when the results of FMSRP and FMSRP + AMX/MET arm were reported, (5) a minimum of 3-month follow-up, (6) clear reporting on the dose and duration of AMX/MET and (7) publication in English language only. The following exclusion criteria were applied: (1) duplicate publication and (2) recruitment of patients with certain specific systemic diseases.

Search strategy

An electronic search was conducted using PubMed, Embase, and the Cochrane Library until May 31st, 2020. A search of the OpenGrey database was performed for unpublished trials, and a manual search was performed in the following journals for issues after 2004: *Journal of Dental Research*, *Journal of Periodontology*, *Journal of Clinical Periodontology*, and *Journal of Periodontal Research*. The authors of relevant articles were contacted by e-mail for obtaining raw data and clarifying the study methodology and potential inclusion.

The following terms were applied in PubMed (modified and adapted for the other databases):

(Periodontitis [MeSH Terms] OR Chronic Periodontitis [MeSH Terms] OR Aggressive Periodontitis [MeSH Terms]) AND (therapy OR treatment 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 remove OR calculus debridement OR dental debridement OR periodontal debridement OR ultrasonic OR periodontal disinfection OR Dental Scaling [MeSH Terms] OR Root Planing [MeSH

Terms]) AND (Amoxicillin [MeSH Terms] Metronidazole [MeSH Terms] 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)

Study selection

Included studies were identified independently through two selection stages by two blinded reviewers (H.Z. and JC.H.): (1) Title and abstract screening: Titles and abstracts were reviewed for eligibility. Studies that fulfilled the inclusion criteria or could not be confidently excluded were evaluated in the next stage, (2) Full-text review: Full-text studies were obtained and assessed. Reasons for exclusion were recorded. Any disagreements were resolved by discussion and voting until a consensus was reached. Agreement between reviewers was calculated using kappa statistics.

Assessment of risk of bias

The quality of each included study was assessed by two independent reviewers (H.Z. and JC.H.), using the revised risk of bias assessment tool from the Cochrane Collaboration's handbook, version 5.1.0 [31] based on the seven criteria: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other sources of bias. Each category was evaluated as low, high, or unclear. Low risk of bias was determined when all seven criteria were judged as 'low'; moderate risk of bias, when one or more criteria were judged as 'unclear'; and high risk of bias when one or more criteria were evaluated as 'high'.

Primary and secondary outcomes

Primary outcomes were clinical attachment level (CAL) gain at 3 and 6 months. Secondary outcomes were probing pocket depth (PPD) reduction at 3 and 6 months and adverse events.

Data collection/data items

A standardised data extraction form was used to record the following items in the included studies: types of periodontitis, antibiotic/placebo regimen (dose and duration), characteristics of participants, clinical methods, number of adverse events, length of follow-up, number of patients, and reported results.

Data synthesis

Meta-analyses were performed using RevMan version 5.3 (2014). Risk ratio and mean difference (MD) with 95% confidence intervals (95% CIs) were used for dichotomous and continuous data, respectively. The inverse-variance method and a random-effects model were used, considering the variable difference between studies (inclusion of smokers or not, type of full-mouth approach, adjunctive use of chlorhexidine, or not). Forest plots and funnel plots were generated, and the synthesised effect was defined as statistically significant if $p < 0.05$. I2 was used to determine statistical heterogeneity and categorised into four levels: 0%–25%, no heterogeneity; 25%–50%, low heterogeneity; 50%–75%, moderate heterogeneity; and 75%–100%, high heterogeneity [32].

Results

Study selection

A total of 998 studies were initially identified: 281 in PubMed, 546 in Embase, 160 in Cochrane Library database, 0 in OpenGrey, and 11 after manual search. After removal of the duplicates (n = 366), 632 publications were included for screening the titles and abstracts. The kappa value for inter-reviewer agreement for the title and abstract screening was 0.92. At the full-text screening stage, 47 studies were excluded for various reasons (Table S1), and 11 studies were included in the review and meta-analysis. The kappa value was 0.95. Fig. 1 illustrates the study identification flowchart based on PRISMA19.

Description of included studies

All 11 included articles were randomised, placebo-controlled clinical trials, and reported the primary or secondary outcomes. A total of 876 participants completed the entire follow-up period and were included. Six trials included patients with chronic periodontitis and four included those with aggressive periodontitis. One study did not report the type of periodontitis included. The model of treatment varied between FMSRP in one visit [15, 33–35], two sessions within 24 h [19, 36, 37], and two sessions within 48 h [16, 17, 38, 39]. The dose of AMX/MET was prescribed at 500/500 mg [19, 33, 35, 36], 500/400 mg [39], 500/375 mg [38], 375/500 mg [16, 17], 500/250 mg [37], and 375/250 mg [15, 34]. All doses were administered thrice daily. Antibiotics were administered for 7 days in eight studies. One trial prescribed antibiotics for a duration of 10 days [37]. Two studies had two test groups with two durations, either 3 or 7 days [19, 33]. One study divided patients into two groups based on the detection of Aa+ and Aa − bacteria at baseline [16]. These groups were included as

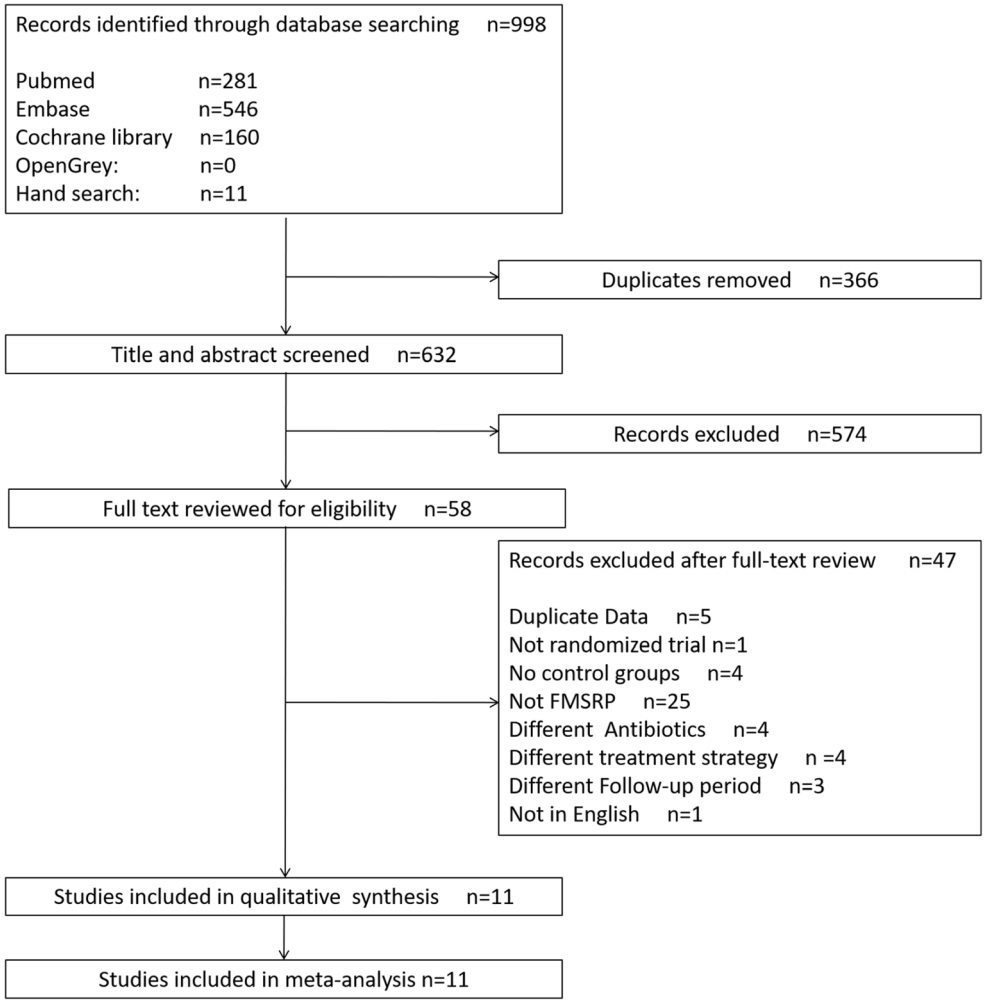

Fig. 1 Flowchart of the study identification with reasons for exclusion

separate data sets for the meta-analysis. Table 1 summarises the characteristics of the included studies.

Synthesis of results

Ten studies were included in the meta-analysis of CAL gain and PPD reduction. Two subgroup analyses were conducted to evaluate the effect size of different drug doses and durations. Generally, antibiotic prescription should be based on patient weight. However, all included studies used systemic antibiotics according to the routine regimen. Owing to the insufficient data for assessing each dose regimen separately, we grouped the data into high and low doses, which was consistent with the systematic review of McGowan published in 2018. The doses of 500/250 mg, 500/375 mg, 375/500 mg, and 375/250 mg were classified as low dose, while 500/500 mg were classified as high dose. For drug duration, the included studies were divided into three subgroups of 3, 7, and 10 days.

Primary outcomes

Seven studies were included in the quantitative analysis of CAL gain. Compared with the control group, significant improvement was observed in FMSRP plus AMX/MET at 3 months with no heterogeneity (MD: 0.33 [95% CI: 0.23–0.44]; $p < 0.00001$, I2 = 5%). Additionally, the statistically beneficial effect of FMSRP plus antibiotics was also observed at 6 months post-treatment with moderate heterogeneity (CAL: MD: 0.37 [95% CI: 0.22–0.52]; $p < 0.00001$, I2 = 69%) (Fig. 2).

Subgroup analysis

Effect of antibiotic dose At 3 months, the meta-analysis revealed a significant improvement in CAL gain compared to baseline for FMSRP with both higher and lower drug doses (high dose: MD: 0.27 [95% CI: 0.12–0.42]; $p = 0.0003$, I2 = 0%]; low dose: MD: 0.36 [95% CI: 0.07–0.64]; $p = 0.01$, I2 = 75%) (Fig. 3a). At 6 months, compared with the control group, a greater benefit of CAL gain was also observed in

Table 1 Summary of the characteristics of included studies

Study		Type	Regimen		Participants			Adverse events				Methodology		Follow-up			N in analysis		Reported results
			A/M(mg/mg)	Duration	T	C	Sm	T	Inc (%)	C	Inc (%)	Treatment approach	CHX	3m	6m	1-2y	T	C	
1	Boia et al. (2019) 3 days	CP	500/500, tid	3	16	14	Yes	0	0	0	0	OSFMD in one visit	Yes	X			16	14	PPD, CAL,FMPS and FMBS, the number of deep pockets (PPD ≥6 mm) and the corresponding CAL and PPD of sites with a PPD ≥6 mm
	Boia et al. (2019) 7 days		500/500, tid	7	16		Yes	0	0			OSFMD in one visit	Yes	X			16		
2	Cosgarea et al. (2016) 3 days	CP	500/500, tid	3	34	34	Yes	7	0.2333	9	0.3	FMD within 2 consecutive days	Yes	X	X	X	30	30	GBI, FMPS, PPD, CAL and BOP, PPD and CAL of sites with PPD 4–6mm and PPD>7 mm, No. PPD ≥6, No. PPD ≥5
	Cosgarea et al. (2016) 7 days		500/500, tid	7	34		Yes	6	0.1935				Yes	X	X	X	31		
3	Harks et al. (2015)	CP	500/400, tid	7	251	255	Yes	43	0.2087	39	0.195	FMSRP in 2 consecutive days	No			X	206	200	PSAL, PPD, clinical attachment level, BOP and supragingival plaque
4	Almaghlouth et al. (2014)	CP and AgP	500/375, tid	7	19	21	Yes	4	0.2105	6	0.2857	FMSRP within 48 hours	Yes	X			19	21	GI, PPD and REC,BOP or suppuration on six sites of each tooth with a pocket of >4 mm at baseline tooth
5	Mombelli et al. (2013) Aa+	CP	375/500, tid	7	22	19	Yes	10	0.7045	10	0.5789	FMD within 48 hours	Yes	X			22	19	GI, PPD,REC,BOP, PS and suppuration; mean pockets with PPD>4 plus BOP+
	Mombelli et al. (2013) Aa-		375/500, tid	7	22	19	Yes	21		12		FMD within 48 hours	Yes	X			22	19	
6	Cionca et al. (2009)	CP	375/500, tid	7	25	26	Yes	13	0.5652	19	0.7917	FMD within 48 hours	Yes	X	X		23	24	GI, PPD,REC,BOP and PS; mean pockets with PPD>4 plus BOP+
7	Del Peloso Ribeiro et al. (2009)	CP	375/250, tid	7	14	14	No	4	0.3077	3	0.25	OSFMUD	No	X	X		13	12	VPI, GBI, BOP, PGM, PPD and RAL; PGM, PPD and RAL of sites with PPD 5–6 mm and PPD≥7 mm.
8	Casarin et al. (2012)	AgP	375/250, tid	7	13	12	No	3	0.25	2	0.1667	One session of FMUD within 45 minutes	No	X	X		12	12	FMPI,FMBS, PPD, relative CAL and relative GMP; PPD and RAL of sites with PPD 5–-6 mm and PPD≥7 mm; Percentage of Residual Pockets (PD≥5 mm plus BOP)
9	Aimetti et al. (2012)	AgP	500/500, tid	7	19	20	No	3	0.1579	0	0	OSFMD	Yes	X	X		19	20	PI(FMPS), BOP(FMBS),PPD, CAL;PPD and CAL of sites with PPD 4–-5 mm and PPD≥6 mm.
10	Varela et al. (2011)	AgP	500/250, tid	10	18	17	Yes	35		35		FMD in two visits within 24 hours	Yes	X	X		18	17	Supragingival biofilm, gingival bleeding,PPD,CAL,BOP, PS and suppuration;mean PPD of pockets with PPD≤3 mm, 4-6 mm, ≥7 mm amd mean CAL of sites with CAL≤3 mm, 4–6 mm, ≥7 mm; sites with ≥ 2 mm PD Reduction/CAL Gain with no residual PD≤4 mm, and Sites With ≥ 2 mm PD Increase/CAL Loss or no change resulting in residual PD >4 mm
11	Guerrero et al. (2005)	AgP	500/500, tid	7	20	21	Yes	13	0.65	5	0.2381	FMSRP in two visits within 24 hours	Yes		X		20	21	PPD, CAL,FMPS and FMBS (BOP), the number of deep pockets (PPD ≥5 mm), mean PPD and

Table 1 (continued)

Study	Type	Regimen		Participants			Adverse events			Methodology		Follow-up		N in analysis		Reported results
		A/M(mg/mg)	Duration	T	C	Sm	T	Inc (%)	C Inc (%)	Treatment approach	CHX	3m	6m	1-2y	T	C
																CAL of sites with PPD≤3 mm, 4–6 mm, ≥7 mm
Total				523	472		162		140						467	409

There was a large variation in the dose and duration of amoxicillin and metronidazole prescribed. Studies varied according to the inclusion or exclusion of smokers, type of full mouth scaling and root planing and with or without adjunct use of chlorhexidine after therapy. Adverse events and the final number of patients completing the entire follow-up period (excluding drop-out number) were recorded. *A/M*, amoxicillin/metronidazole; *tid*, three times daily; *n*, number; *T*, test group; *C*, control group; *CP*, chronic periodontitis; *AgP*, aggressive periodontitis; *OSFMD*, one stage full-mouth disinfection; *FMD*, full-mouth disinfection; *FMSRP*, full-mouth scaling and root planing; *FMUD*, full-mouth ultrasonic debridement; *CHX*, chlorhexidine; *FMPI*, full-mouth plaque index; *FMBS*, full-mouth bleeding score; *FMPS*, full-mouth plaque score; *GI*, gingival index; *BOP*, bleeding on probing; *PPD*, periodontal pocket depth; *CAL*, clinical attachment loss; *REC*, recession; *VPI*, visible plaque index; *GBI*, gingival bleeding index; *PGM*, position of the gingival margin; *RAL*, relative attachment level; *PSAL*, proportion of sites with new clinical attachment loss; *Sm*, smoker; *Inc*, incidence

FMSRP with higher drug dose of 500 mg/500 mg (MD: 0.42 [95% CI: 0.25–0.59]; $p < 0.00001$, I2 = 53%), whereas no additional effect of CAL gain was observed for FMSRP combined with low dose (MD: 0.25 [95% CI: −0.17–0.68]; $p = 0.24$, I2 = 85%) and high heterogeneity was detected (Fig. 3b).

Effect of drug duration At 3 months, 7- and 10-day drug durations demonstrated significant CAL gain compared to control groups (7 days: MD: 0.28 [95% CI: 0.13–0.42]; $p = 0.0002$, I2 = 0%); 10 days: MD: 0.49 [95% CI: 0.32–0.66]); $p < 0.00001$, heterogeneity not applicable), whereas no significance was found for 3-day drug durations (3 days: MD: 0.19 [95% CI: −0.05–0.42]; $p = 0.12$, I2 = 0%) (Fig. 4a). At 6 months, all subgroups showed significant improvement in CAL gain (3 days: MD: 0.55 [95% CI: 0.22–0.88]; $p = 0.001$, heterogeneity not applicable); 7 days: MD: 0.30 [95% CI: 0.12–0.49]; $p = 0.002$, I2 = 65%; 10 days: MD: 0.52 [95% CI: 0.35–0.69]; $p < 0.00001$, heterogeneity not applicable) (Fig. 4b).

Secondary outcomes

Probing pocket depth reduction Compared with FMSRP+ placebo, a significant improvement of PPD was observed in FMSRP+AMX/MET at both 3 and 6 months. (3 months: MD: 0.31 [95% CI: 0.20–0.42]; $p < 0.00001$, I2 = 22%); 6 months:MD: 0.47[95% CI: 0.29–0.64]; $p < 0.00001$, I2 = 84%) (Fig. 5).

At 3 months, both high and low doses provided significant PPD reduction compared to control groups (high dose: MD: 0.42 [95% CI: 0.27–0.57]; $p < 0.00001$, I2 = 0%; low dose: MD: 0.24[95% CI: 0.12–0.36]; $p < 0.0001$, I2 = 13%) (Fig. 6a). At 6 months, compared to control groups, a significant improvement in PPD was observed for FMSRP with higher drug dose of 500 mg/500 mg (MD: 0.56 [95% CI: 0.40–0.71]; $p < 0.0001$, I2 = 45%) with low heterogeneity, no significant difference was observed for lower dose of drugs (MD: 0.34 [95% CI: 0.01–0.67]; $p = 0.05$, I2 = 88%) with high heterogeneity (Fig. 6b). For drug duration, at both 3 and 6 months of follow-up, all subgroups of 3-, 7- and 10-day drug durations showed significant PPD reduction compared to control (at 3 months: 3 days: MD: 0.35 [95% CI: 0.07–0.63]; $p = 0.01$, I2 = 25%); 7 days: MD: 0.33 [95% CI: 0.12–0.54)]; $p = 0.002$, I2 = 42%; 10 days: MD: 0.30 [95% CI: 0.20–0.40]; $p < 0.00001$, heterogeneity not applicable) (Fig. 7a); at 6 months: (3 days: MD: 0.64 [95% CI: 0.31–0.97]; $p = 0.0002$, heterogeneity not applicable); 7 days: MD: 0.49 [95% CI: 0.22–0.76)]; $p = 0.0003$, I2 = 87%; 10 days: MD: 0.30 [95% CI: 0.20–0.40]; $p < 0.00001$, heterogeneity not applicable) (Fig. 7b).

Adverse event In the test group, of the 467 patients included, adverse events occurred in 162 patients. In the control group, 140 reported adverse events out of the

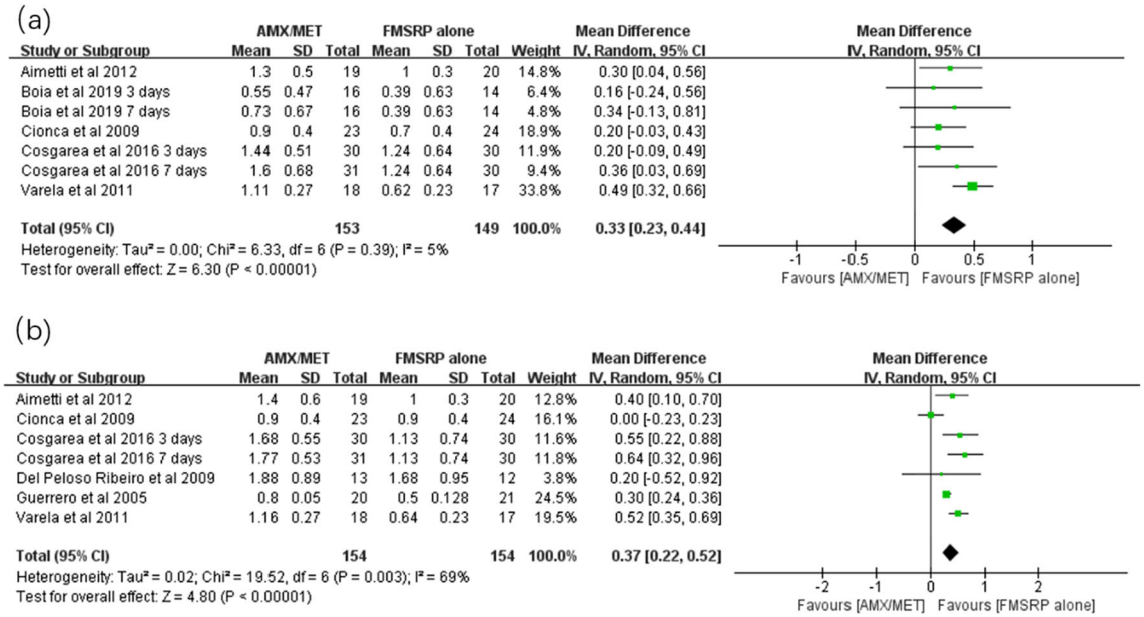

Fig. 2 Forest plots of the outcomes of CAL gain between AMX/MET adjunctive to FMSRP and FMSRP alone: (**a**) at 3 months, (**b**) at 6 months

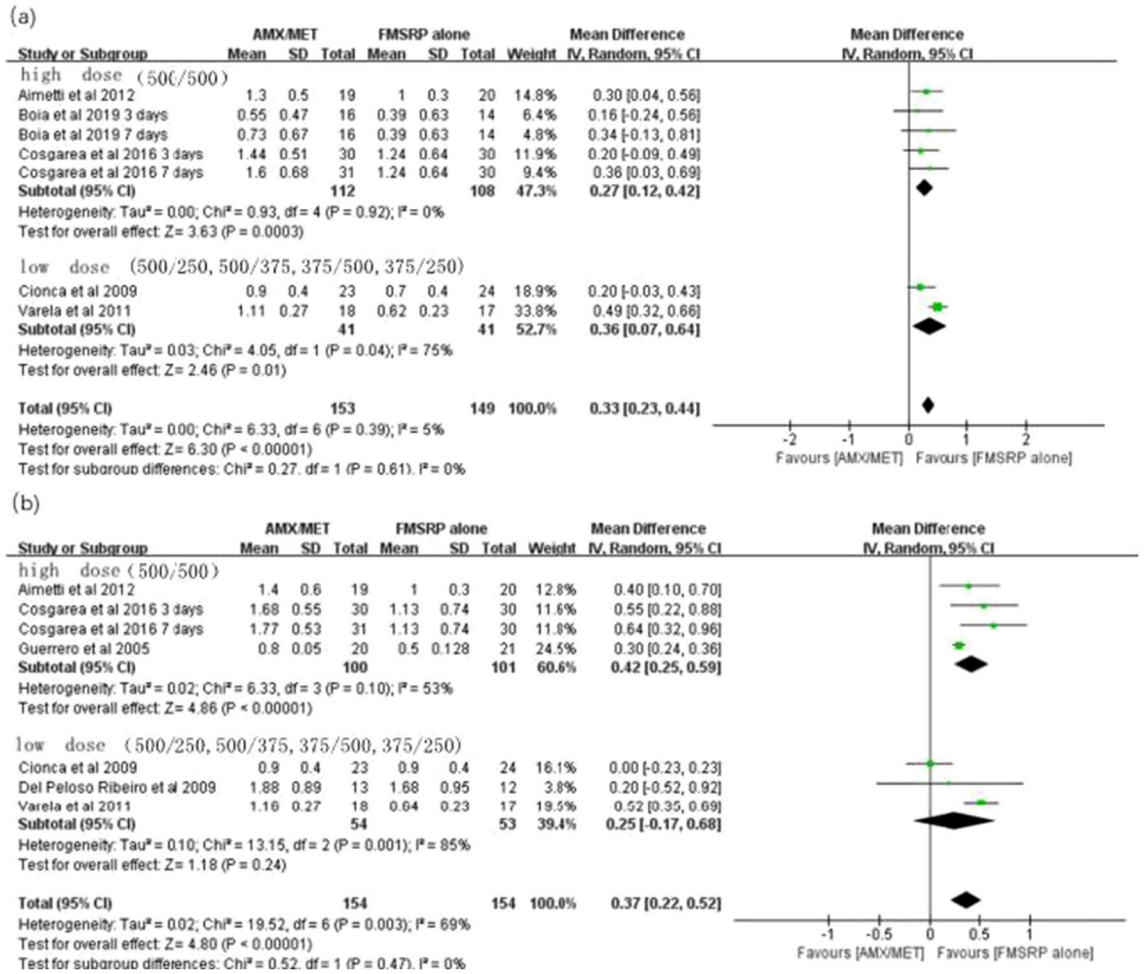

Fig. 3 Forest plots for subgroup analysis of CAL gain between AMX/MET adjunctive to FMSRP and FMSRP alone between high and low dose: (**a**) at 3 months, (**b**) at 6 months

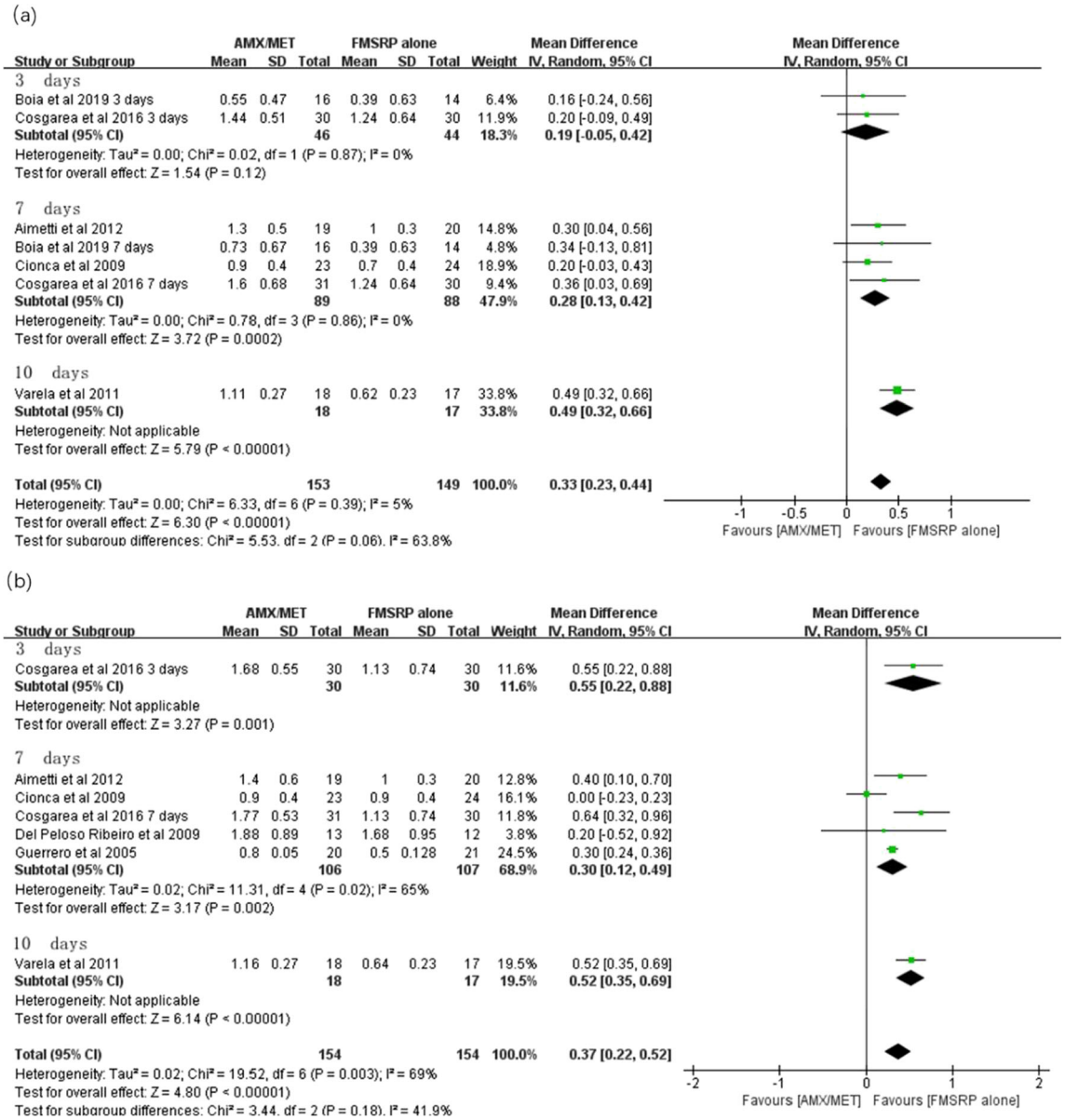

Fig. 4 Forest plots for subgroup analysis of CAL gain between AMX/MET adjunctive to FMSRP and FMSRP alone among different durations: (**a**) at 3 months, (**b**) at 6 months

409 patients included. Additionally, the incidence of adverse events in the test group ranged from 0% to 70.45%, while that in the control group was between 0% and 79.17% (Table 1).

Risk of bias assessment

All 11 studies described the randomisation and blinding methods clearly. Additionally, five studies did not report drug medication compliance data. The risk of bias is demonstrated in Table 2.

Discussion

The diagnosis and corresponding treatment plan for periodontitis have incessantly developed in recent decades. CAL is the gold standard for the diagnosis of periodontitis. In the 2017 World Workshop, a new classification for periodontal and peri-implant diseases and conditions was adopted [40]. Owing to the difficulty of using PPD for the discrimination of periodontal health, gingivitis, and periodontitis, the new classification highlighted the need to establish CAL as the primary definition of periodontitis. Therefore, the improvement of CAL gain plays a key role in indicating the prognosis

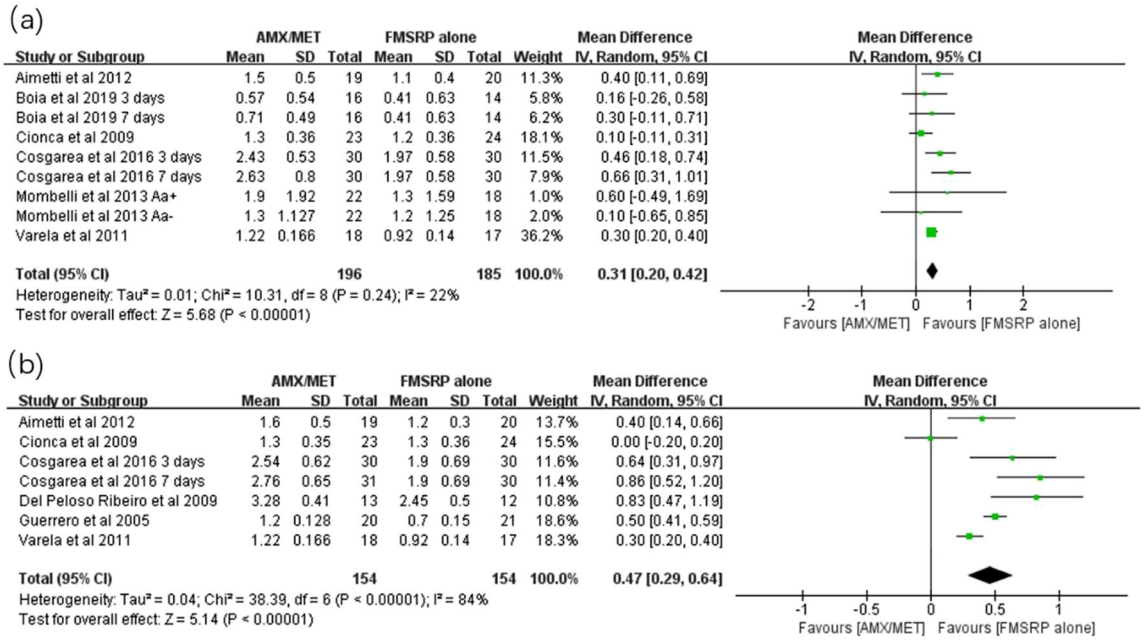

Fig. 5 Forest plots of the outcomes of PPD reduction between AMX/MET adjunctive to FMSRP and FMSRP alone: (**a**) at 3 months, (**b**) at 6 months

of periodontitis treatment. As the primary outcome of this meta-analysis, the results showed that adjunctive AMX/MET treatment had significant clinical improvement in terms of CAL gain at both 3 and 6 months compared to FMSRP alone. For the subgroup analysis of drug dose and duration, the results showed an additional benefit of CAL gain with FMSRP plus low drug dose at 3 months with a mean MD of 0.36 mm; however, this improvement was not significant at 6 months with a mean MD of 0.25 mm. In contrast, the high drug dose presented a stable beneficial effect, with mean MD of 0.27 mm and 0.42 mm at 3 and 6 months, respectively. Additionally, compared with the control group, the CAL gain was slightly greater in the 3-day drug duration and significant in the 7- and 10-day groups at 3 months. It is noteworthy that the improvement of CAL gain was maintained and slightly improved in all three drug-duration subgroups at 6 months than 3 months. PPD is also an important clinical parameter for periodontitis, which could present the change of inflammation and the development of the disease, often indicating the need for periodontal treatment. As secondary outcomes, our meta-analysis showed significant improvement of PPD in the adjunctive AMX/MET groups at both 3 and 6 months, and a high drug dose of 500 mg/500 mg showed stable improvement at both the 3-month and 6-month follow-up, with mean MD of 0.42 mm and 0.56 mm, respectively. Among the three drug duration subgroups, no difference was observed.

The results supported that adjunctive AMX/MET could improve the clinical benefit of clinical parameters, as demonstrated by other meta-analyses and studies [24, 29]. However, no consensus has been reached on the dosage and duration of adjunctive antibiotics, which may influence the treatment efficacy of FMSRP. The variable regimen of AMX/MET has previously been reported, with significantly better outcomes of clinical parameters [41–45]. The dose varied from 250 mg to 500 mg, and the treatment course was normally between 7 and 14 days. Evidence supports the idea that new resistant strains or resistance factors in the bacterial population may appear, particularly when a low dose of drugs is prescribed. Furthermore, antibiotic-resistant species in the subgingival plaque in chronic periodontitis detected before drug therapy, rapidly increase during drug administration and return to baseline 90 days after therapy [46]. This study did not show any difference in antibiotic-resistant isolates at time points of day 3, day 7, and day 14, and indicated that 'antimicrobial agents might have contributed to the elimination or prevented growth of cells of the most sensitive species, giving rise to an overgrowth of different resistant species' [46]. This finding was confirmed by a study from Boia in 2019, which did not find significant differences in bacterial resistance between 3-day and 7-day courses of antibiotic therapy [33]. In the meta-analysis, two included studies [19, 33] have reported the adjunctive AMX/MET with a 3-day duration in comparison with 7 days. The results demonstrated that higher doses of 500 mg/500 mg plus either 3- or 7-day duration resulted in a significant benefit of clinical parameters. The difference in the effect size between the durations was not convincing. However, in the study from Boia in 2019, baseline CAL and PPD in the control group were significantly lower than the two test groups. In addition, only two studies included for 3-day drug duration. In view of these facts, the power of the result for 3-day drug duration was weak. Moreover, only a single included study reported the outcomes

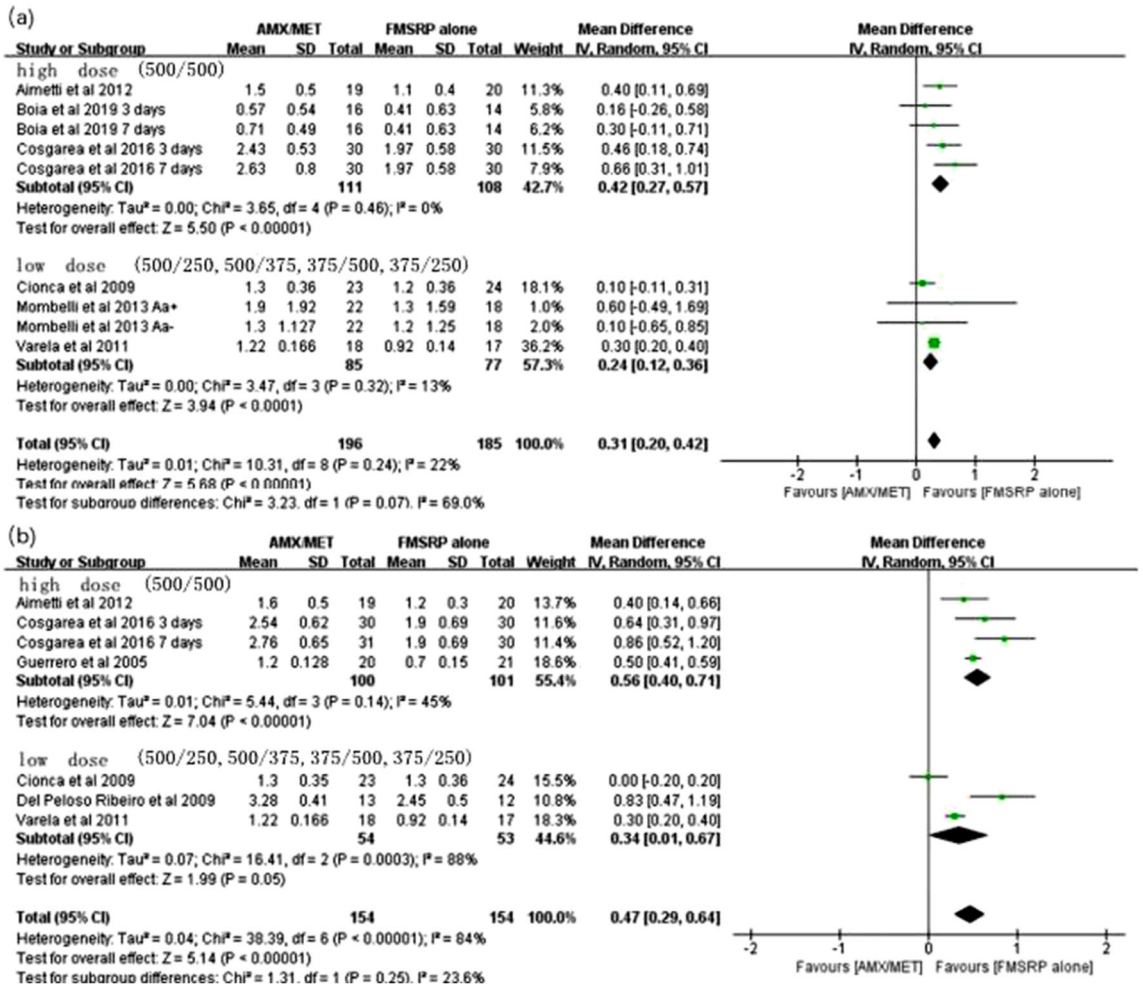

Fig. 6 Forest plots for subgroup analysis of PPD reduction between AMX/MET adjunctive to FMSRP and FMSRP alone between high and low dose: (**a**) at 3 months, (**b**) at 6 months

for a 10-day drug duration in this meta-analysis. According to these findings, compared to low dose of adjunctive AMX/MET, a higher drug dose of 500 mg/500 mg provided a more stable improvement on 6-month follow-up period; however, owing to multiple impact factors, no decision of optimal drug duration could be made.

The optimal regimen of antibiotics must balance the potential benefits with possible adverse events [47], which could negatively affect treatment outcomes and increase the risk of incompliance and antibiotic resistance [48]. When we calculated the incidence of adverse events, the difference was 1.07 (0.80, 1.42) (Fig. S1), indicating no significant difference between adjunctive AMX/MET to FMSRP and FMSRP alone, which was in line with a previous systematic review [23]. However, a recent meta-analysis in 2018 reported a higher incidence of adverse events in the SRP group combined with antibiotics, and risk differences in the higher dose and longer duration groups were minimally greater [29]. Additionally, the occurrence of adverse events in individual studies showed a wide range (0–79%), which indicated that certain factors such as individual differences in patients may influence the outcomes. For adequately addressing this issue, a more rational design of RCTs is needed in the future, and more factors, such as analysis of adverse events at different durations (3/7/10 days) and drug regimen based on patient weight, should be considered.

Heterogeneity analysis

High heterogeneity was observed in the subgroup analysis at 6 months. Variable factors had a great influence on the results and further led to bias. A small number of studies in subgroups at 6 months were included, such as only one study was included for 3- and 10-day drug duration, which could largely limit the power of the results. Additionally, initial disease severity should be considered; the mean CAL varied from 3.47 mm to 8.22 mm, and the mean PPD at baseline from 3.11 mm to 6.4 mm. The large baseline value change interval may lead to a large variation in the statistical results, which indicate that different disease severities at baseline may have influenced the degree of treatment efficacy. Various meta-analyses and

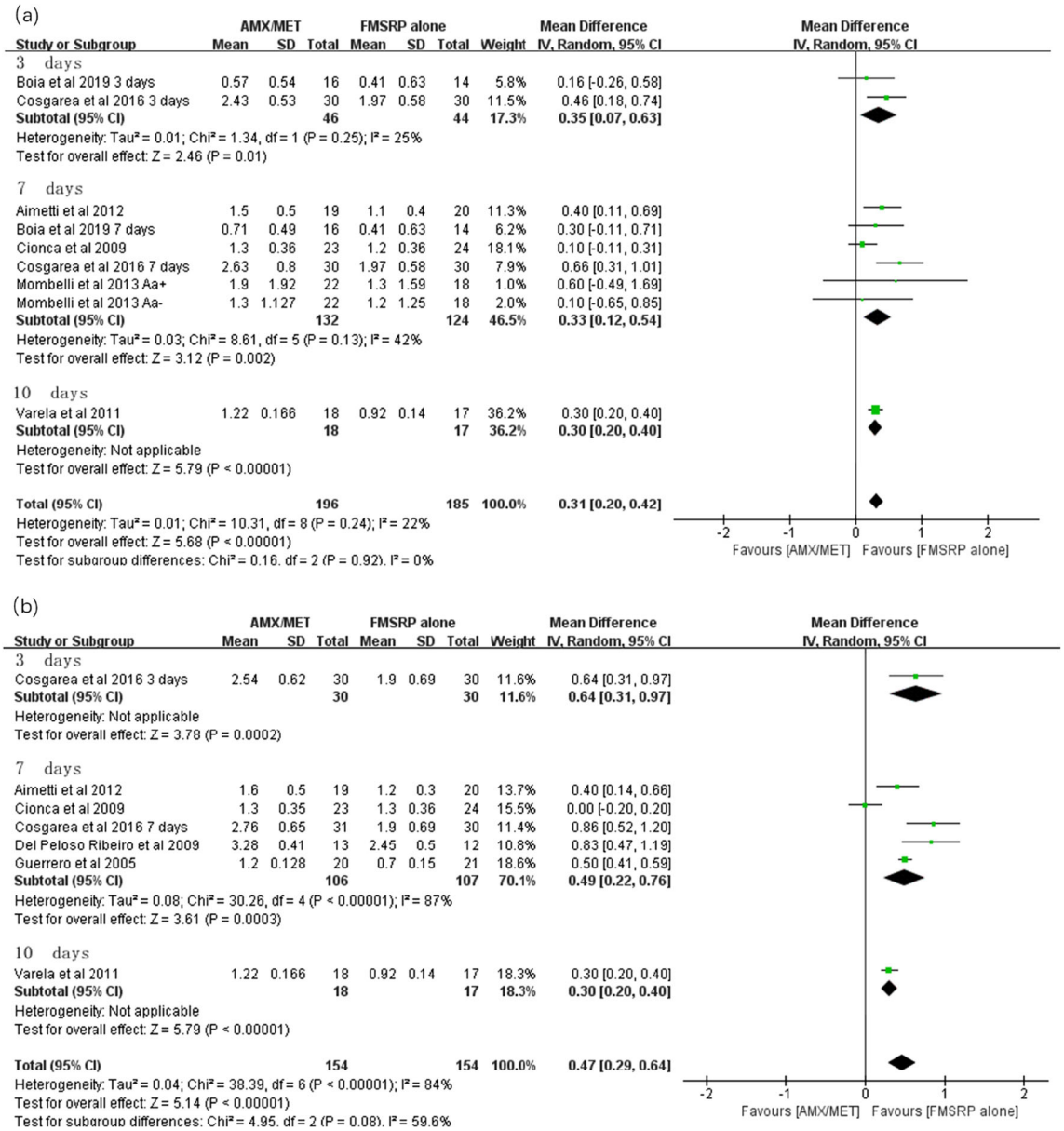

Fig. 7 Forest plots for subgroup analysis of PPD reduction between AMX/MET adjunctive to FMSRP and FMSRP alone among different durations: (**a**) at 3 months, (**b**) at 6 months

studies indicated that initially deep pockets showed greater improvement with AMX/MET compared to shallow sites [28, 42, 49–51]. The results indicate that other factors, such as disease severity, maybe more powerful and convincing when deciding on a regimen of adjunctive antibiotics. However, owing to the lack of studies and the different evaluation standards of the diversity of disease, these lack sufficient evidence.

Limitation

The new classification in the 2017 World Workshop highlighted the need to establish CAL as the primary definition of periodontitis. When CAL > 5 mm, the diagnosis of periodontitis stage directly reaches stage III or IV. This is very different from the previous version using PPD as a major measurement for periodontitis staging. Therefore, RCTs according to the new grading standard of periodontitis are needed for clarifying the relationship between disease severity and the treatment effect of adjunctive antibiotics.

Additionally, all included studies in this systematic analysis did not prescribe systemic antibiotics according to the patient's weight. To date, clinical studies have commonly used conventional drug prescription in periodontal treatment, which requires further discussion. When the patient weight is considered for the use of adjunctive systemic antibiotics to

Table 2 Risk of bias of included studies

Number	Author (year)	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
1	Boia et al. (2019)	Low	Low	Low	Low	Low	Unclear	Low
2	Cosgarea et al. (2016)	Low	Low	Low	Low	Low	Low	Low
3	Harks et al. (2015)	Low	Low	Low	Low	Low	Low	Low
4	Almaghlouth et al. (2014)	Low	Low	Low	Low	Low	Unclear	Low
5	Mombelli et al. (2013)	Low	Low	Low	Low	Low	Unclear	Low
6	Casarin et al. (2012)	Low	Low	Low	Low	Low	Unclear	Low
7	Aimetti et al. (2012)	Low	Low	Low	Low	Low	Low	Low
8	Varela et al. (2011)	Low	Low	Low	Low	Low	Low	Low
9	Cionca et al. (2009)	Low	Low	Low	Low	Low	Unclear	Low
10	Del Peloso Ribeiro et al. (2009)	Low	Low	Low	Low	Low	Low	Low
11	Guerrero et al. (2005)	Low	Low	Low	Low	Low	Low	Low

NSPT, the outcomes of clinical effect and incidence of adverse events may be different.

The abuse of systemic antibiotics is a critical issue in treatment. Therefore, we believe that the adjunctive use of antibiotics should not be regarded as a blanket therapy for periodontal treatment. Individualised treatment plans play a key role. There is no strong evidence that systemic antibiotics as an adjunct to NSPT could improve the therapeutic effects in specific populations such as patients with diabetes [52]. Moreover, no additional benefit of adjunctive systemic antibiotics was observed in smokers with chronic periodontitis [53]. In the European Federation of Periodontology guidelines of 2020, Sanz et al. indicated that "the adjunctive use of specific systemic antibiotics may be considered for specific patient categories" [11]. Based on this evidence, systemic antibiotics may not be effective for any population. The specific populations more appropriate for adjuvant antibiotic therapy require further analysis and evidence support. More detailed groupings and discussions should be carried out to further clarify the indications for the use of adjunctive systemic antibiotics in periodontal treatment.

A variety of antibiotics are used in NSPT, such as tetracycline and azithromycin. Network meta-analysis could be designed for analysing conditions with multiple interventions and combinations of direct or indirect interactions. When we need to analyse different drug formulations or combinations, or even different doses of the same drug, network analysis shows obvious advantages. This systematic review focused on the adjunctive use of AMX/MET with different drug doses and durations; no network meta-analysis was conducted, thus lacking a comprehensive analysis for the use of multiple antibiotics.

Conclusions

Based on the findings of this meta-analysis, adjunctive use of AMX/MET to FMSRP could provide additional clinical benefits in patients with periodontitis at 3 and 6 months after treatment. FMSRP adjunctive to AMX/MET with high dose of 500 mg/500 mg could provide a stable and significant improvement in CAL gain during both the 3-month and 6-month follow-up. However, based on the small number of included studies and limited evidence, no recommendation could be made regarding drug duration. Considering the limitations of this meta-analysis, based on the new classification of periodontal diseases, multicentre studies with more rational designs are required to clarify the indication of treatment with adjunctive use of systemic antibiotics, and to determine the optimal drug use duration of adjunctive AMX/MET to FMSRP without compromising the clinical effect.

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Declarations

Ethics approval and consent to participate This article does not contain any studies with human participants or animals performed by any of the authors. For this type of study, formal consent is not required. Informed consent was obtained from all individual participants included in the study.

Conflict of interest Author Han Zhao declares that he has no conflict of interest. Author Jingchao Hu declares that he has no conflict of interest. Author Li Zhao declares that he has no conflict of interest.

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