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Review Article

Effect of locally delivered doxycycline as an adjunct to scaling and root planing in the treatment of periodontitis in smokers: A systematic review of randomized controlled trials with meta-analysis and trial sequential analysis

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ABSTRACT

Background: Scaling and root planing (SRP) for the treatment of periodontitis may be less effective in some patients. This study evaluated the effectiveness of local doxycycline as an adjunct to SRP among smokers with periodontitis compared to SRP alone in randomized controlled trials (RCTs).
Materials and Methods: For this systematic review and meta-analysis, PubMed and Scopus databases were searched till November 2018 for English publications. RCTs that compared the effect of local doxycycline adjunct to SRP among smokers with periodontitis were selected. Patient characteristics, disease characteristics, and outcome data on clinical attachment level (CAL) and periodontal probing depth at 1, 3- and 6-month follow-up was extracted. Quality of selected studies was assessed by the revised Cochrane Risk of Bias 2.0 tool. Random effects model and trial sequential analysis were performed. GRADE approach was used to assess the quality of evidence. $P > 0.05$ was considered as statistically significant.
Results: Five trials were included in the review. Local use of doxycycline as an adjunct to SRP was effective in gain of 1.1 mm (0.47–1.74, $P = 0.091$) in CAL at 6 months calculated from two studies. The evidence was of low quality, and at least a total of 866 patients are required for conclusiveness.
Conclusion: Local doxycycline as an adjunct to SRP significantly improved clinical attachment in smokers with periodontitis and can be recommended. Studies are required with long-term follow-up and patient-related outcome data.

Key Words: Dental scaling, doxycycline, periodontitis, root planing, smokers

INTRODUCTION

Periodontitis is a chronic inflammatory disease of the supporting structures of the periodontium caused by the interaction of pathogenic biofilm in a susceptible host.[1] The bacterial plaque triggers the host immune response resulting in disease progression and tissue destruction. The goal of nonsurgical

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periodontal therapy is the elimination of the suspected bacterial pathogen (s) to arrest the destruction of the periodontium.[2,3] The primary nonsurgical periodontal therapy involves mechanical therapy, i.e., scaling and root planing (SRP). However, SRP was found inadequate in some cases of periodontitis, especially in areas of furcation involvement and deep periodontal pocket.[4] In such cases, the use of anti-microbial agents as an adjunct to SRP may prove to be beneficial.

Smoking is an established risk factor for periodontal disease.[5] Smokers have been identified to have a poorer response to nonsurgical periodontal therapy than nonsmokers. Smoking has an immunosuppressive effect on the host by impairing the polymorphonuclear leukocyte motility, chemotaxis, and phagocytosis thus compromising the first-line defense against subgingival bacterial pathogens.[6] Smokers were found to be more likely infected with *Tannerella forsythia* and *Porphyromonas gingivalis*[7] and showed suppressed levels of protease inhibitor such as α-1-antitrypsin and α-2-macroglobulin in gingival crevicular fluid.[6] Thus, there is added difficulty in managing periodontitis among smokers. Antimicrobials have been used locally as an adjunct to provide additional benefit to SRP among smokers.[8]

Local drug delivery (LDD) systems provide a higher concentration of the antimicrobial with a sustained release over a longer duration of time.[8] One of the most commonly used active agents for LDD is the tetracycline group of drugs.[8] Doxycycline is a third-generation tetracycline showing superior properties such as better absorption, protein binding, diffusion into tissue structure, and prolonged action when compared to tetracycline.[9] In addition to being antimicrobial, doxycycline possesses other properties such as inhibiting enzymes involved in connective tissue breakdown such as collagenase, matrix metalloproteinase 8, and elastase.[10] Studies have shown that smokers benefit from the use of locally delivered doxycycline in conjunction to nonsurgical therapy than when treated with SRP alone.[11-14] While other studies have failed to show any benefits of topically applied doxycycline.[10,15,16] Smiley *et al*.[17] in his review of 72 articles reported that adjunctive nonsurgical therapies such as systemic subantimicrobial-dose doxycycline, systemic antimicrobials, chlorhexidine chips, and photodynamic therapy with a diode laser were effective in improving clinical attachment level (CAL). Sgolastra *et al*.[18] reported the effectiveness of long-term adjunctive subantimicrobial dose doxycycline for the treatment of chronic periodontitis. A recent review by Chambrone *et al*.[19] showed the effectiveness of commonly used local antimicrobial therapy in smokers with periodontitis. All the previous reviews have evaluated the effectiveness of different adjuncts of nonsurgical therapy from various studies and were not exclusive to local doxycycline or smokers, and this would have limited the accuracy of information revealed due to the presence of heterogeneity. Our review was limited to the evaluation of the effectiveness of local doxycycline as an adjunct to SRP in treating periodontitis in smokers. Our research question aligned to PICOS was: "Does locally delivered doxycycline (I) as an adjunct to SRP, compared to SRP alone (C), result in better clinical attachment gain (O) in smokers with periodontitis (P) in randomized controlled trials (S)?"

MATERIALS AND METHODS

This systematic review was reported based on Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines[20] and *a priori* protocol of the review was registered in the PROSPERO database (CDR. No: CRD42017084686).

Study selection

Electronic databases of PubMed and Scopus were searched for published studies using the following search strategy: ((((smokers) OR smoking) OR cigarette)) AND ((((doxy) OR antibiotic)) AND ((((“scaling”) OR “root planing”) OR “periodontitis”) OR “periodontal disease”)) from inception to November 2018. Our search strategy was not restricted to only MeSH terms, which could result in less articles, and hence an exhaustive search using keywords was used. The search was supplemented in Clinical Trials Registry (clinicaltrials.gov) and Cochrane Clinical Registry (CENTRAL). A similar search strategy had been used for all the databases. The reference list of included studies, related reviews, and standard periodontology textbooks were searched for eligible studies. Studies in English language only were considered eligible for selection. The authors of selected studies were contacted for any missing information.

Inclusion and exclusion criteria

Randomized clinical controlled trials (RCTs) that evaluated the effect of locally delivered doxycycline

adjunct to SRP compared to SRP alone in patients who were smokers and diagnosed with periodontitis were selected. Trials were excluded if there was no follow-up data of at least 3 months. The inclusion criteria for being classified as a smoker were 10 cigarettes/day for a minimum of 5 years in most studies.[10,13,16,21]

Outcome variables

The primary outcome of measurement was the mean CAL gain at 6 months from baseline following periodontal treatment. The secondary outcomes were mean CAL gain at 3 months, mean periodontal probing depth (PPD) reduction at 3 months' and 6 months' follow-up.

Data extraction

Screening of the studies from the outlined search was done by two independent and standardized reviewers (SJP and SN). The same reviewers evaluated the selected studies for final inclusion in the review by full-text reading. Any disagreement in the selection of studies for final inclusion among the reviewers was resolved by team discussion. Data extraction was performed on *a priori* agreed extraction form by two independent, calibrated reviewers (SJP and SN) with disagreement being sorted by team discussion. The data extracted included the study characteristics, patients' characteristics, and primary and secondary outcome measures.

Risk of bias (quality) assessment

The included studies were appraised using the revised Cochrane Risk of Bias Tool (RoB 2.0)[22] by two independent reviewers (SJP and SN) with a resolution of any disagreement by team discussion.

Statistical analysis

Data synthesis was performed to determine the pooled standardized mean difference (SMD) at 95% confidence by the random-effects model and heterogeneity assessed by the I^2 statistic (I^2 > 50% considered as significant heterogeneity) for outcome data at 1-month, 3 and 6 months. Subgroup meta-analysis on studies with split-mouth/parallel – study design and type of probing method used was done. A sensitivity analysis to evaluate the accuracy and robustness of the primary outcome was done on initially randomized group sizes. The meta −+* analysis was performed using STATA 15 software (StataCorp. 2017, Stata Statistical Software: Release 15. StataCorp LLC, College Station, TX, USA). For assessing the quality of the studies, the GRADE approach was done using GRADE proGDT software (GRADEpro GDT 2015, GRADEpro Guideline Development Tool, McMaster University, and Evidence Prime, Inc. available online https://gradepro.org/).[23,24] Trial sequential analysis (TSA) was performed to determine the adequacy of the data in evaluating the effectiveness of local doxycycline for the CAL outcome.[25]

RESULTS

The study selection process is shown in Figure 1. Five trials were included for the systematic review.[10-13,16] The characteristics of the five studies are shown in Table 1. All five studies[10-13,16] had enough data to provide summary measures of CAL gain and PPD reduction at 3 months, while two studies[13,16] were included for meta-analysis for summary measures at 6 months. A total of 297 patients contributed data at 3 months, while at 6 months, 169 patients were studied.

Summary measures from meta-analysis by the random-effects model at 1, 3, and 6 months' follow-up is given in Table 2. All the forest plots of primary and subgroup analysis for CAL gain and PPD reduction at 1, 3, and 6 months' follow-up is given as Supplementary Figures 1-4 (https://universityofadelaide.app.box.com/folder/113492413236). Meta-analysis showed statistically significant improvement (SMD 1.10; 0.46–1.74 mm, P = 0.091) present in CAL at 6 months by

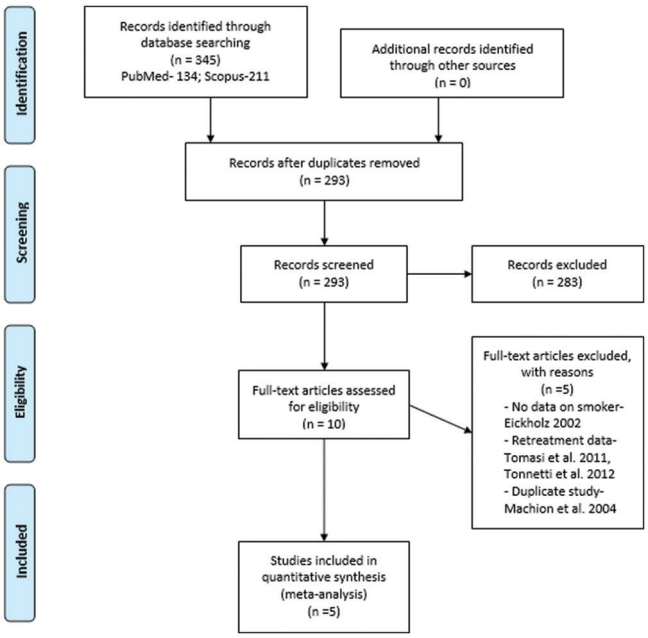

Figure 1: Flow diagram showing the study selection process.

the adjunct use of local doxycycline compared to SRP alone [Table 2]. The data for CAL gain at 6 months are represented in a forest plot [Figure 2]. There was an improvement of CAL at 3 months (SMD 0.61; 0.17–1.05 mm) [Supplementary Figure 2a], PPD at 3 months (SMD 0.67; 0.16–1.19 mm) [Supplementary Figure 2c] and PPD at 6 months (SMD 0.63; 0.29–0.97 mm) [Supplementary Figure 3b]. The heterogeneity (I^2 statistics) for 0, 3, and 6 months CAL gain was 0, 68.2, and 64.9 and for PPD reduction at 0, 3, and 6 months was 0, 76.7, 0 [Table 2].

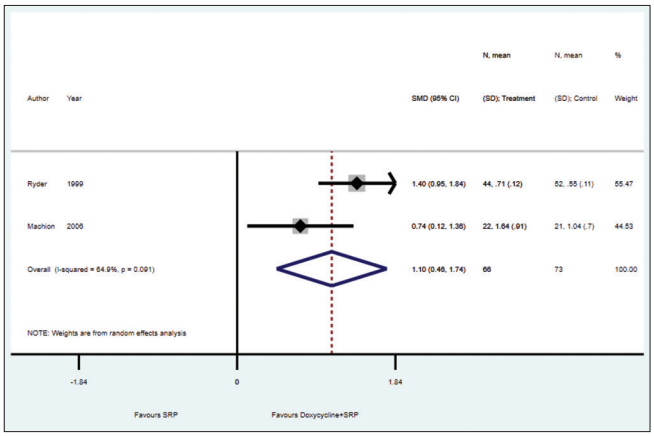

Figure 2: Forest plot of clinical attachment gain at 6 months, actually randomized groups.

The subgroup analysis for 3 months' data showed improvement in manual probing method studies than studies that used automated probing method [Supplementary Figure 4a and Table 3], whereas improvement in CAL and PPD in parallel studies compared to split-mouth studies [Table 3 and Supplementary Figure 4b, c].

RoB evaluation showed that only one trial[13] had low RoB while the rest had high RoB [Table 4]. Sensitivity meta-analysis using initially randomized group sizes did not detect any change in the direction of the effectiveness observed in primary analysis [Table 1]. TSA showed that there is a need for more studies

Table 1: Characteristics of included studies

Author (year) and country	Study design	Periodontitis classification	Product used with concentration (%)	Probing method	Pockets analyzed	Groups (male/female)	Mean age	Follow-up in months
Ryder (1999) America	Parallel	Periodontitis type not defined	Doxycycline hyclate in a polylactic acid-based polymer gel	UNC 15 manual probing, six sites	≥5 mm, ≥7 mm	Test (60) Control (61)	47	3, 6
Tomasi and Wennstrom (2005) Sweden	Parallel	Periodontitis type not defined	Doxycycline hyclate (8.5%)	UNC 15 manual probing	≥5 mm	Test (11 males/11 females) Control (6 males/14 females)	Test - 47.9, Control - 46.7	3
Machion (2006) Brazil	Parallel	Chronic Periodontitis	Doxycycline hyclate (10%)	Automated six sites	≥5 mm	Test (19 males, 24 females) Control (6 males, 14 females)	Test - 40.45±4.47 Control - 42.00±4.38	1, 3, 6, 12, 24
Hulami (2011) Saudi Arabia	Split Mouth	Chronic Periodontitis	Doxycycline hyclate in a polylactic acid-based polymer gel (10%)	Automated six sites	5-6 mm, ≥7 mm	Test Control (16 males)	39.43±8.15	1, 3
Sandhya (2011) India	Split Mouth	Chronic Periodontitis	Doxycycline hyclate in a polylactic acid-based polymer gel (10%)	Manual with stent	≥6 mm	Test and control (45)	25-50	1.3

NI: No information; UNC: University of North Carolina

Table 2: Meta-analysis summary measures comparing the effectiveness of doxycycline as an adjunct to scaling and root planing among smokers with periodontitis

Outcome description	Number of studies	Actual randomized			Initially randomized		
		Total patients	Effect size SMD (mm) (95% CI)	Heterogeneity (I^2 statistic) %	Total patients	Effect size SMD (mm) (95% CI) initially randomized	Heterogeneity (I^2 statistic) %
1-month CAL gain	3	157	0.13 (–0.18-0.45)	0	165	0.13 (–0.18-0.44)	0
3-month CAL gain	5	297	0.61 (0.17-1.05)	68.2	333	0.59 (0.16-1.03	70.9
6-month CAL gain	2	139	1.10 (0.46-1.74)	64.9	169	1.10 (0.47-1.74)	69.3
1-month PPD reduction	3	157	0.20 (–0.12-0.51)	0	165	0.19 (–0.11-0.49)	0
3-month PPD reduction	5	297	0.67 (0.16-1.19)	76.7	333	0.66 (0.15-1.17)	78.7
6-month PPD reduction	2	139	0.63 (0.29-0.97)	0	169	0.64 (0.33-0.95)	0

PPD: Pocket probing depth; CAL: Clinical attachment level; SMD: Standard mean difference; CI: Confidence interval

to reach a sample size of 866 patients [Figure 3] to conclusively determine the effectiveness of local doxycycline in achieving a clinical gain of at least 2 mm in 6 months. GRADE analysis assessed the evidence of the outcome for CAL at 3 and 6 months and PPD at 3 months to be of low quality due to inadequate randomization, no examiner blinding and heterogeneity among studies while the other outcome of PPD at 6 months was of moderate quality evidence [Figure 4].

DISCUSSION

Tobacco smoking is an important risk factor for periodontitis.[5,26] Periodontal treatment for smokers tends to have a less favorable therapeutic response to nonsurgical therapy than nonsmokers.[27,28] Studies have shown that current smokers show less significant improvements in clinical response such as reduction in PPD and gain in CAL after SRP than nonsmokers or past smokers.[27,28] The levels of *P. gingivalis, T. forsythia, and Treponema denticola* were equally prevalent among current, past, and never smokers before SRP and were shown reduced in all the groups post SRP except for the current smokers.[27] The use of antimicrobials as an adjunct to SRP for the treatment of periodontitis among smokers can be important for successful treatment. There have been studies among smokers which have shown improvement[11-14] of the periodontal disease with adjunct antimicrobials while others have shown no improvement.[10,15,16] This systematic review and meta-analysis were designed with the aim to assess the efficacy of LDD of doxycycline as an adjunct to SRP compared to SRP alone among smokers by synthesizing evidence from various studies.

In the present review, the majority of studies selected had used doxycycline hyclate 8.5% and 10.[10-13] Two studies did not specify the type of periodontitis patients included[12,16] while the rest of the studies were on chronic periodontitis patients. Al Hulami *et al.*[10] and Sandhya *et al.*[11] used the split-mouth study design while the other studies used parallel study groups.

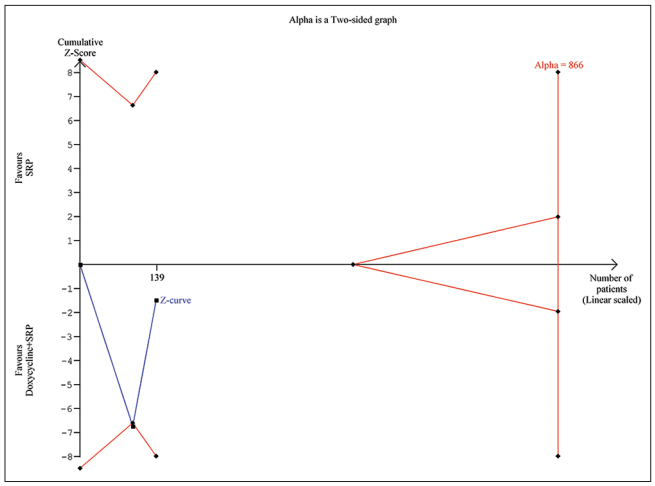

Figure 3: Trial sequential analysis to determine the required sample size for conclusive evidence.

Certainty assessment							No. of patients		Effect	Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	local doxycycline with SRP	SRP alone	Absolute (95% CI)		
3CAL (follow up: 3 months; Scale from: 0 to 10)											
5	randomised trials	serious [a,b]	serious [c]	not serious	not serious	none	149	148	SMD **0.61 SD higher** (0.17 higher to 1.05 higher)	⊕⊕◯◯ LOW	IMPORTANT
3PPD (follow up: 3 months; Scale from: 0 to 10)											
5	randomized trials	serious [a,b]	serious [c]	not serious	not serious	none	149	148	SMD **0.67 SD higher** (0.16 higher to 1.19 higher)	⊕⊕◯◯ LOW	IMPORTANT
6CAL (follow up: 6 months)											
2	randomized trials	serious [a,b]	serious	not serious [c]	not serious	none	84	85	SMD **1.1 SD higher** (0.47 higher to 1.74 higher)	⊕⊕◯◯ LOW	IMPORTANT
6PPD (follow up: 6 months; Scale from: 0 to 10)											
2	randomized trials	serious [a,b]	not serious	not serious	not serious	none	84	85	SMD **0.63 SD higher** (0.29 higher to 0.97 higher)	⊕⊕⊕◯ MODERATE	IMPORTANT

CI: Confidence interval; **SMD:** Standardized mean difference

Explanations

a. Blinding of outcome assessors was not reported

b. Randomization and allocation concealment not reported adequately.

c. Significant heterogeneity among studies.

Figure 4: GRADE analysis on the quality of evidence.

Table 3: Subgroup meta-analysis by probing method and study type on the effectiveness of doxycycline as an adjunct to scaling and root planing among smokers with periodontitis

Criteria for grouping	Groups by	Outcome measurement	Number of studies	Effect size SMD (mm) (95% CI)	Heterogeneity (I^2 statistic) %
Probing method	Automated	3-month CAL gain	2	0.26 (−0.22-1.36)	0
	Manual		3	0.81 (0.25-1.36)	74.3
	Automated	3-month PPD reduction	2	0.31 (-0.38,1.00)	48.2
	Manual		3	0.89 (0.20-1.58)	83.1
Study type	Parallel	3-month CAL gain	3	0.52 (0.22-0.81)	0
	Split-mouth		2	0.69 (−0.67-2.05)	88.6
	Parallel	3-month PPD reduction	3	0.56 (0.26-0.85)	0
	Split-mouth		2	0.76 (−0.85-2.38)	91.7

PPD: Pocket probing depth; CAL: Clinical attachment level; SMD: Standard mean difference; CI: Confidence interval

Table 4: Risk of bias assessment for included studies

Author, year	Randomization process	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported result	Overall bias
Ryder *et al.*, 1999	?[a]	+	+	-[b]	+	-
Tomasi *et al.*, 2004	?[a]	+	+	-[b]	+	-
Machion *et al.*, 2006	+	+	+	+	+	+
Hulami *et al.*, 2011	+	+	+	-[b]	+	--
Sandhya *et al.*, 2011	?[a]	+	+	-[b]	+	-

[a]No information on randomization process or allocation concealment, [b]No examiner blinding. +: Low risk of bias; ?: Some concerns; -: High risk of bias

The results of our study showed that there was a significant gain in attachment level and probing depth reduction at 3 and 6 months when locally delivered doxycycline was used as an adjunct to SRP than SRP alone among smokers. Albandar[29] and Angaji *et al.*,[30] in their two SRs found no evidence for advocating the use of adjunctive antibiotics during NSPT. The SRs had included one study on local doxycycline while other studies included had evaluated different types of antibiotics. The presence of heterogeneity due to different antibiotics used in the studies and more studies with high RoB precluded any meta-analysis in their reviews. Matesanz-Pérez *et al.*[31] in a systematic review on local antimicrobials found effective PPD reduction for doxycycline based on seven studies not restricted on smokers while the CAL improvement was not found significant.[9] Chambrone *et al.*[19] in their SR found that adjunctive use of antimicrobials in smokers with chronic periodontitis was beneficial in sites with PPD greater than 5 mm. Smiley *et al.*,[32] in an SR on various adjuncts to SRP for the treatment of periodontitis, found that local doxycycline was not superior as an adjunct when compared to SRP alone. The review included three trials irrespective of the smoking status of participants.

Subgroup analysis showed that the split-mouth studies did not show any significant improvement with local doxycycline.[10,11] Both studies did not use a cross over design with a wash-out period and simultaneously treated the test and control sites in the patients. There is a possibility of contamination of test agent to the control sites.[33] Matesanz-Pérez *et al.*,[31] in their systematic review, found improvement in CAL measures to be present among parallel designed studies. Smiley *et al.*[32] also found among studies on doxycycline gel as an adjunct to SRP, split-mouth studies contributed to greater heterogeneity in the overall meta-analysis. The dose of smoking based on the frequency of smoking in a day and the duration in years will affect the improvement of NSPT. Our review was limited in evaluating the role of smoking dose as insufficient information was available among the studies. Most studies had considered 10 cigarettes/day for a minimum of 5 years as the inclusion criteria for smokers.[10,11,13] Our review found that studies using the automated probing method did not show any improvement with the adjunctive use of doxycycline. Automated and manual probing has been found to be reliable, and no significant difference has been found in their measurement.[34] However, the presence of inflammation could affect the periodontal measures.[35] Further studies need to be done to understand the heterogeneity between the two methods.

In our study, random-effects model was used. Fixed model is to be used when the true effect size is

assumed to be similar in all the studies selected. However, this was not possible as there was an inherent heterogeneity due to different populations, environment, and other factors. Hence, it is preferable to use random-effects model.[36]

RoB evaluates the study process to determine whether any bias would have occurred that could affect the quality of results. Five domains are assessed and include bias on randomization and allocation concealment, intended interventions, missing data, outcome measurement, and selection of results. The absence of examiner blinding was a major concern in most studies, while the inadequate process in randomization and allocation concealment was also identified. Data from inadequate sample size or repeated significance testing can lead to spurious results in the traditional frequentist meta-analysis. TSA calculates the required sample size referred as required information size that gives the number of patients needed to get results that are conclusive and reliable. It was calculated that the number of patients from two studies was way short of the required sample size of 866 patients for a CAL improvement of 2 mm at 6 months. This also provides us a rationale for the need of future studies before we can determine the usefulness of adjunct local doxycycline. GRADE assessment objectively evaluates the evidence from the systematic review and categorizes as good, moderate, or low-quality evidence. The quality of evidence from the results of our review was moderate-to-low and was downgraded primarily due to the assessment of bias in the selected studies and due to statistical heterogeneity among studies.

Only mean values of CAL and PPD from treated sites were considered in summary measures. The effect of improvement is more pronounced in sites with severe attachment loss compared to milder forms of destruction. This comparison was not possible due to the non-availability of similar data across selected studies. Our review could not evaluate the difference in the effectiveness of local doxycycline in chronic and aggressive periodontitis as the definition provided in the selected studies was insufficient to make the distinction and due to the limited overall number of studies. The assessment of publication bias was not possible on funnel plot generation due to few numbers of studies. Another limitation was except PubMed and Scopus databases, all other databases and publications in other languages were not included, and hence this could lead to publication bias.

Local use of doxycycline as an adjunct to SRP is effective in gain of attachment at 6 months by 1.1 mm compared to SRP alone. However, the relevance of this information translating into a clinical benefit is debatable and needs to factor patient-related outcome factors.[37] The review by Assem *et al*.[38] also failed to report the presence of any clinical relevance in recommending the use of systemic antimicrobials even in the presence of statistical evidence. Our review would be limited to recommend that local use of doxycycline can be considered for clinical attachment gain in smokers with periodontitis.

CONCLUSION

Within the limits of the present systematic review, the results of our study showed that there was a significant gain in attachment level and probing depth reduction at 3 and 6 months when locally delivered doxycycline was used as an adjunct to SRP than SRP alone among smokers. The quality of this evidence was low-to-moderate. There is a need for good RCTs (high quality) to conclusively assess the effectiveness of the use of local doxycycline as an adjunct to SRP for periodontitis in smokers. Future studies on local doxycycline are needed for reliable, accurate evidence regarding the effectiveness in smokers with periodontitis. Local doxycycline should be compared with other antimicrobial adjunct therapies to rank its effectiveness against others for a good clinical decision making.

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Conflicts of interest

The authors of this manuscript declare that they have no conflicts of interest, real or perceived, financial or nonfinancial in this article.

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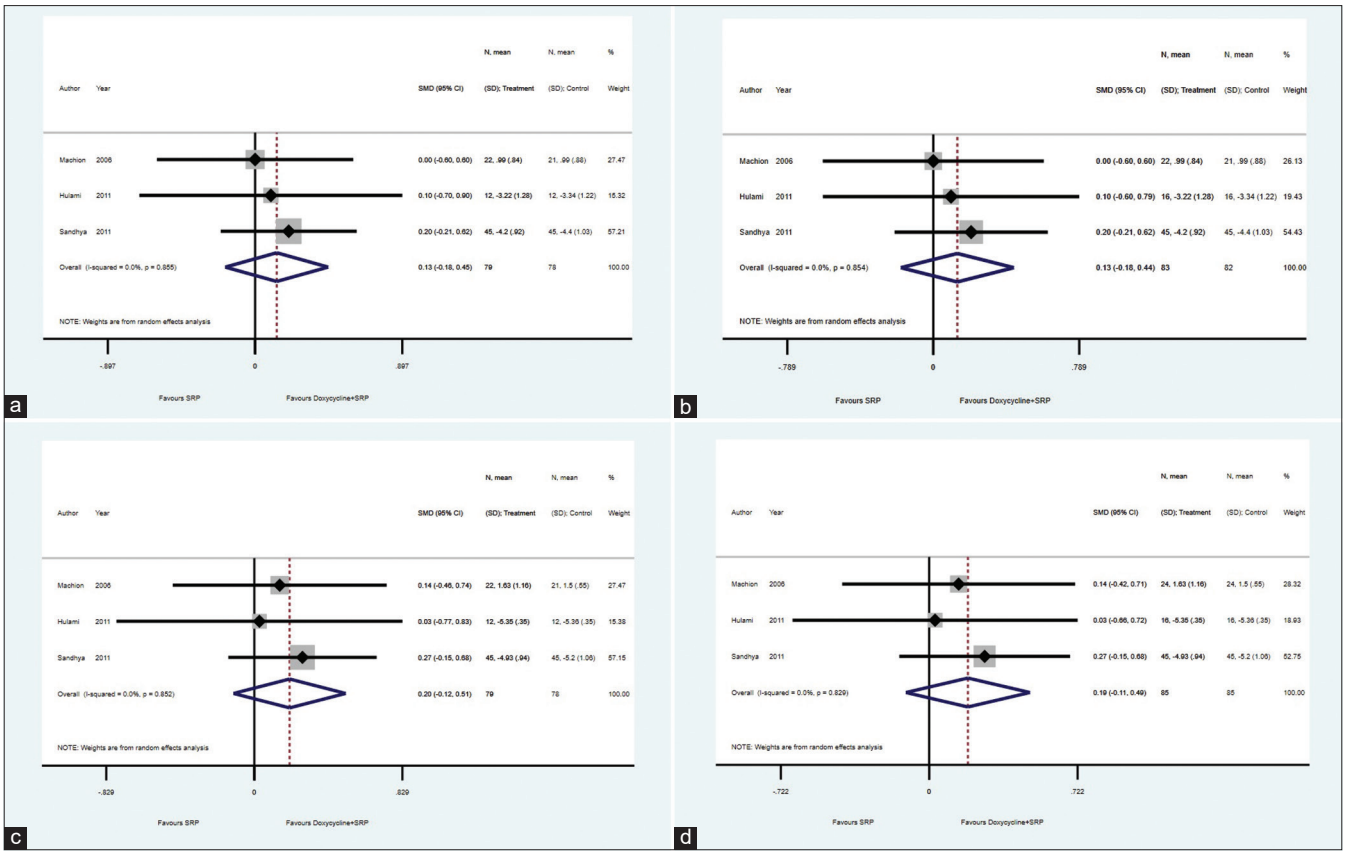
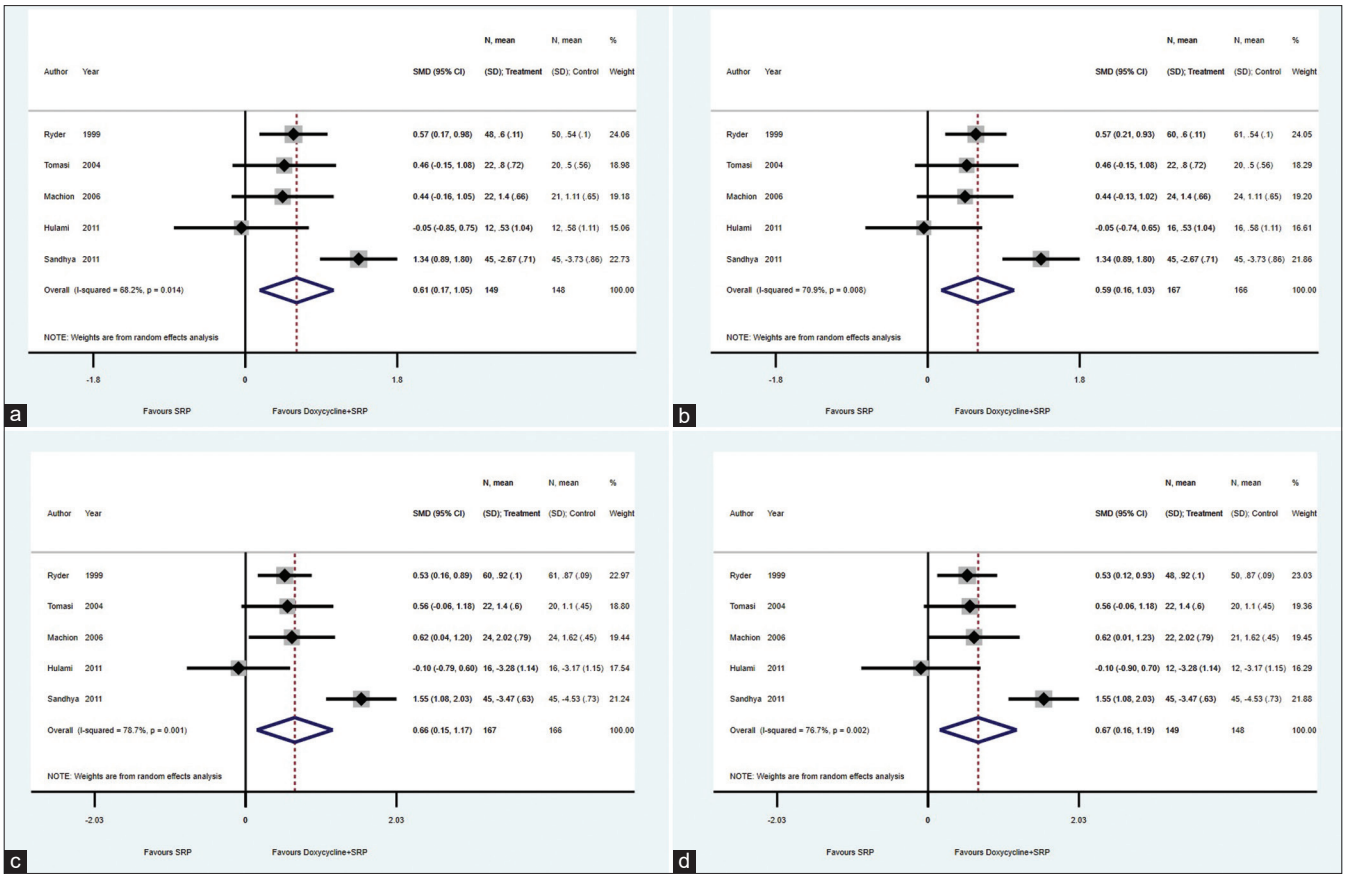
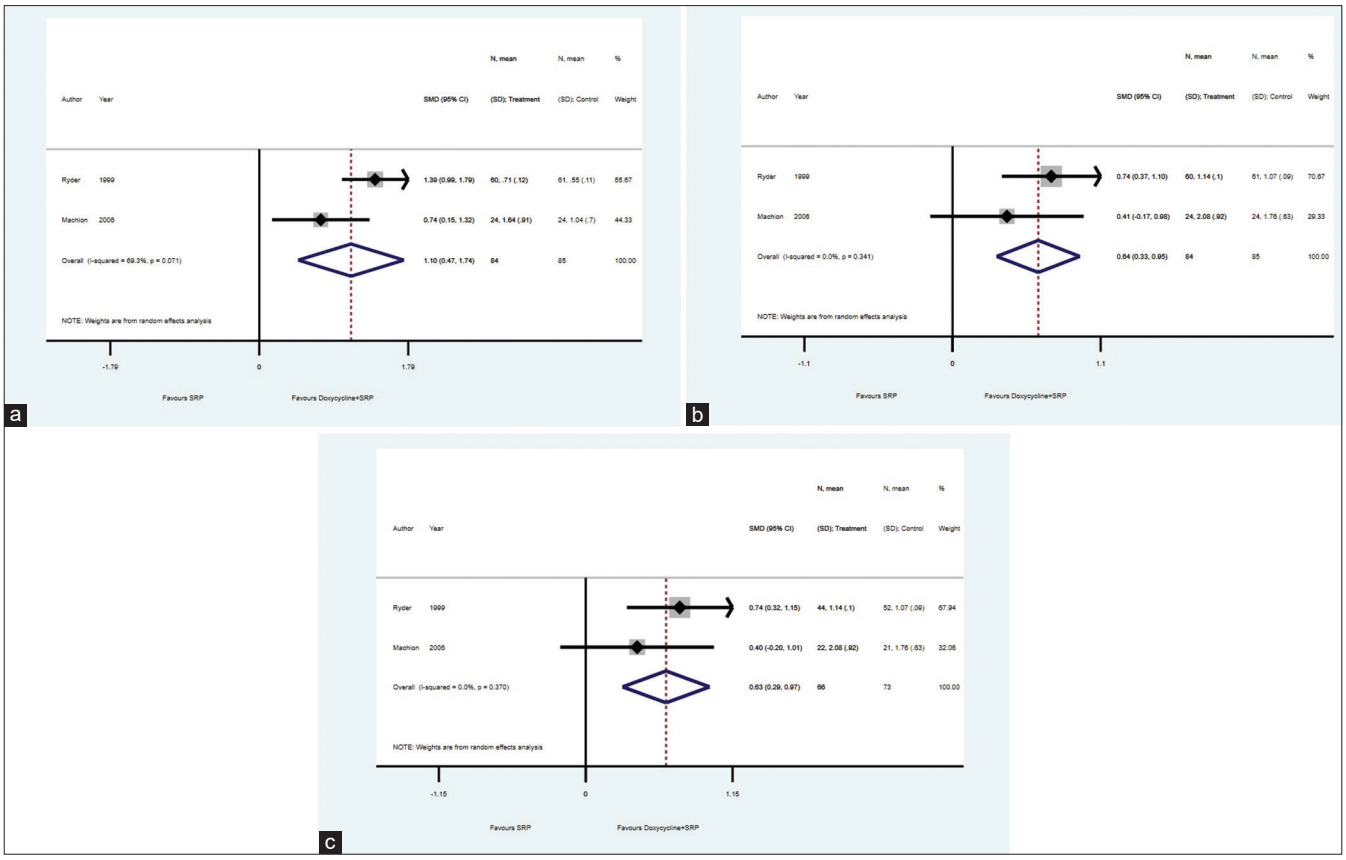


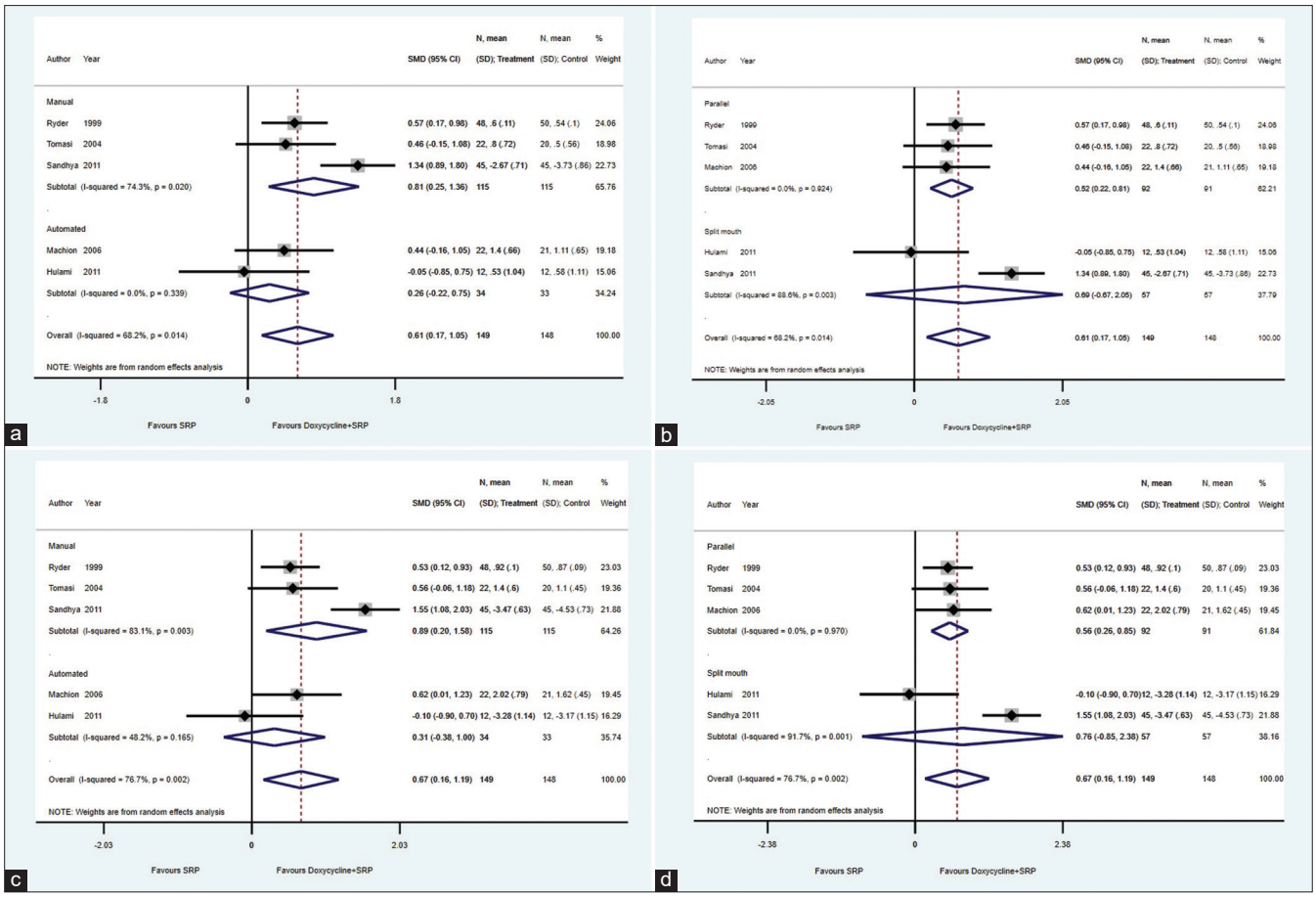
Supplementary Figure 1: (a) Forest plot of clinical attachment gain at 1-month, actually randomized groups. (b) Forest plot of clinical attachment gain at 1-month, initially randomized groups. (c) Forest plot of pocket probing reduction at 1-month, actually randomized groups. (d) Forest plot of pocket probing reduction at 1-month, initially randomized groups.



Supplementary Figure 2: (a) Forest plot of clinical attachment gain at 3 months, actually randomized groups. (b) Forest plot of clinical attachment gain at 3 months, initially randomized groups. (c) Forest plot of pocket probing reduction at 3 months, actually randomized groups. (d) Forest plot of pocket probing reduction at 3 months, initially randomized groups.



Supplementary Figure 3: (a) Forest plot of clinical attachment gain at 6 months, initially randomized groups. (b) Forest plot of pocket probing reduction at 6 months, actually randomized groups. (c) Forest plot of pocket probing reduction at 6 months, initially randomized groups.



Supplementary Figure 4: (a) Forest plot of clinical attachment gain at 3 months, subgroup analysis by probing method. (b) Forest plot of clinical attachment gain at 3 months, subgroup analysis by study type. (c) Forest plot of pocket probing reduction at 3 months, subgroup analysis by probing method. (d) Forest plot of pocket probing reduction at 3 months, subgroup analysis by study type.