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Review Article

Dentistry Section

Effectiveness of Tetracycline Drugs in the Non Surgical Treatment of Peri-implantitis: A Systematic Review and Meta-analysis

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ABSTRACT

Introduction: Peri-implantitis is a significant factor affecting the success rate of oral reconstruction. Hence, it is vital to prevent it. To control peri-implant disease, non surgical treatment is the first line of defense. While peri-implant mucositis can be entirely treated, there are unforeseen repercussions for the treatment of peri-implantitis, according to many studies using non invasive approaches.

Aim: To investigate the clinical effects of the tetracycline group of medications in the treatment of non surgical peri-implantitis.

Materials and Methods: Electronic bibliographic databases PubMed (MEDLINE), EBSCO, Cochrane database, Clinical trial registry, DOAJ, Google Scholar, and Manual reference searches were performed for articles published January 2010 to August 2021. Total five Randomised Controlled Trials (RCTs) were selected. Three reviewers independently performed the data extraction using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement for reporting. The risk of bias was assessed with the ROB-2 tool and the quality of evidence was determined with the GRADE (Grading of Recommendations, Assessment, Development and Evaluations) approach. A quantitative meta-analysis was performed to compare the reduction in Bleeding On Probing (BOP), Probing Pocket Depth (PPD) and Clinical Attachment Level (CAL).

Results: In the overall analysis, BOP and PPD, was statistically reduced in the tetracycline drugs compared to the tetracycline groups. When comparing experimental and control groups, the mean reduction in BOP was -9.71 mm, (95% CI: -11.74 to -7.68), The random-effects model showed a statistically significant difference Z=9.40 (p-value <0.00001). The mean PPD was reduced by -1.18 mm in the experimental groups compared to the control groups (95% CI: -2.35 to -0.02). The CAL gain was -0.98 mm from 3.23 to 1.28 mm in the experimental group which was statistically non significant. The minocycline revealed statistically significant mean difference in BOP (mean difference was -0.72 (95% CI: -6.84, -3.24 mm but non significant difference reduction in PPD (p-value >0.05). High heterogenicity was reported in all analyses.

Conclusion: The non surgical treatment with the tetracycline medication group resulted in a significant clinical reduction in BOP and PPD without a significant change in CAL when compared to other non surgical therapies. The minocycline has resulted in clinical decreases in BOP except PPD. Long-term randomised controlled trials are needed to assess the efficacy of treatments that do not prevent further bone loss, implant survival rates and oral health-related quality of life standards.

Keywords: Antimicrobials, Gingival bleeding, Mechanical debridement, Peri-implant inflammation, Probing depth

INTRODUCTION

Peri-implantitis is an inflammatory condition that affects the soft tissues surrounding an osseointegrated implant, resulting in bone loss [1]. Currently, it is widely assumed that the start of peri-implantitis is linked to bacterial microorganisms in the implantation site. Plaques accumulate near the implants as a result of poor oral hygiene, triggering an inflammatory response in the body. Peri-implantitis is a significant factor affecting the success rate of oral reconstruction, hence it is vital to prevent it [2].

Clinical and radiological data are used to diagnose peri-implantitis. Probing depth changes associated with bleeding or suppuration on probing suggests peri-implant inflammation, and radiographs are utilised to demonstrate peri-implant bone loss [3]. The eradication of bacterial biofilm and disinfection of the implant surface are the goals of peri-implant disease treatment. The presence of screw threads and surface roughness, on the other hand, makes implant disinfection problematic [3]. To control peri-implant disease, non surgical treatment is the first line of defense. While peri-implant mucositis can be entirely treated, there are unforeseen repercussions for the treatment of peri-implantitis, according to many studies using non invasive approaches [3].

There are numerous modern biomaterials, each with its unique properties, that can be used to prevent or treat disease. Several alternatives or interventions have been offered over the years to improve the effectiveness of non invasive therapies like air-abrasive systems, dental laser implants, or local antibiotics), but few have proved clinical effectiveness [4]. Antibiotics have been shown to help with clinical treatment, intraoral biofilm control and radiographic bone filling in peri-implantitis [4]. Systemic antibiotics, on the other hand, are frequently linked to adverse consequences such as dysbacteriosis, antibiotic resistance and digestive disturbances. After adjunctive delivery of local resorbable antibiotics and chlorhexidine gel, clinical and microbiological improvements of peri-implantitis lesions were found, although significant allergic reactions such as sensitivity or oral discomfort were noted after chlorhexidine use [5]. Antibiotics and other antimicrobials (metal and hydroxyapatite nanoparticles) can be applied locally and have a short-term effect [5].

To avoid peri-implantitis, minocycline hydrochloride loaded graphene oxide sheets have been placed to implant abutment surfaces; they have shown remarkable antibacterial action, but no results on bone gain. Antibacterial drugs used to inhibit biofilm formation may impair the osteogenic function of osteoblasts in general. Antibiotic prophylaxis given before or after surgery decreases early implant failures in healthy individuals, according to a systematic review and meta-analysis [5].

Because it reduces the number of pathogenic bacteria in peri-implantitis, the tetracycline group of medications is one of the non surgical treatment options for peri-implantitis [6]. They are predominantly bacteriostatic antimicrobials, meaning they work by suppressing microbial protein production. It also possesses

anti-collagenolytic properties [6]. Mechanical submucosal debridement alone has a very limited effect on the clinical indications of peri-implantitis [7,8]. In comparison to submucosal debridement alone, adjunctive locally delivered or systemically administered antibiotics have been reported to improve clinical outcomes, however this did not resolve all lesions [7-9]. The results of laser treatment or ultrasonic scaling were not found to be statistically different from the results of submucosal debridement [9]. Earlier systematic reviews assessed the efficacy of local antimicrobial medicines to other therapies or placebo in the treatment of non surgical and surgical peri-implantitis [10]. Antimicrobial medications have been shown to be effective in the treatment of peri-implantitis [5]. But the lack of clear evidence prohibits their usage in clinical practice. It is unknown whether these antibacterial medicines are beneficial during non surgical treatment.

Similarly, the significance of certain antimicrobial medicines, such as tetracycline medications, in non surgical peri-implantitis therapy is unknown. As a result, this systematic review was carried out to determine the efficacy of antimicrobial drugs, specifically the tetracycline group, in the non surgical management of peri-implantitis as compared to alternative topical antimicrobial therapies. It clarifies the clinical effects of the tetracycline group of medications in the non surgical treatment of peri-implantitis.

MATERIALS AND METHODS

The current systematic review was designed and carried out by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement between between 31st March 2020 to 31st October 2021, and it was registered into PROSPERO prospectively (CRD no: 42021247569, dt: May 14, 2021) (https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=247569). The focus research question was "Is the tetracycline family of medications (minocycline, tetracycline, doxycycline, etc.) beneficial in the non surgical treatment of peri-implantitis in resolving peri-implant inflammation?" It was presented in the PICO (Patient, Intervention, Comparison, Outcomes) format.

Population (P): Patients above the age of 18 years who have been diagnosed with peri-implantitis (peri-implant bone loss 0.5-2 mm, probing pocket depth 4-6 mm, concurrent haemorrhage on probing) [11].

Interventions (I): Patients with peri-implantitis treated with a tetracycline group of drugs such as minocycline, tetracycline, doxycycline, etc. in the form of local delivery, gingival irrigation, or systemic therapy in hospitals or private clinics.

Comparator (C): In hospitals or private clinics, the administration of antibiotics or any other therapy in the form of local delivery, gingival irrigation, or systemic therapy.

Outcome (O): Clinical peri-implant bone loss, clinical attachment loss and probing haemorrhage were measured and compared to baseline data.

Inclusion criteria: Only randomised clinical trials which included with patients above the age of 18 who have been diagnosed with peri-implantitis (peri-implant bone loss of 0.5-2 mm, probing pocket depth of 4-6 mm, and concomitant bleeding on probing [11].

Exclusion criteria: Non randomised clinical trials, case reports, case series, letters to editors, and languages other than English were all eliminated from the study, as were relevant medical conditions affecting peri-implant inflammation and therapy approaches.

Search Methods for Identification of Studies

The electronic bibliographic databases viz. PubMed (MEDLINE), EBSCO, Cochrane database, Clinical trial registry, DOAJ, Google Scholar, and Manual references were searched from January to August 2021. MeSH terms related to or describing the intervention and peri-implantitis "peri-implantitis" OR "peri-implant inflammation" OR "peri-implant abscess" OR "peri-implant infection" AND "Tetracycline", "minocycline", "doxycycline", "atridox" were included in the search strategy. Wherever possible, the Boolean operators "OR" and "AND" are utilised.

Minimum two independent reviewers conducted a computerised search of databases of publications and reports after resolving discrepancies by discussion or a fourth reviewer. The data was first reviewed based on the title and abstract. Following the screening, full-text articles were evaluated for quality and validity using data extraction forms that included the following information: study setting; study population and baseline characteristics, details of the intervention and control conditions, time of intervention, study methodology, recruitment and study completion rates, measurement times and outcomes.

Method of Analysis

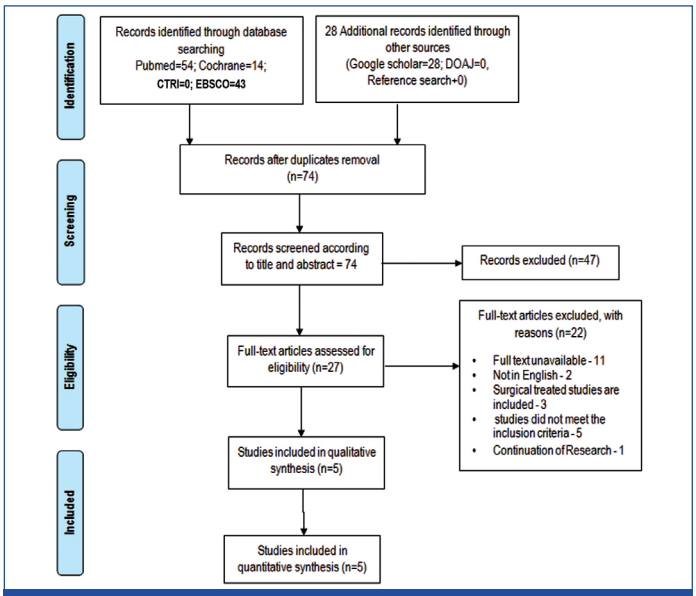
The relevant data of included publications were collected in data extraction files. Prior to actual scoring, the rating forms were tested by all reviewers. Each reviewer first decided on each study's eligibility for inclusion in the systematic reviews, based on the reported parameters. The data reported from the included studies were summarised based upon clinical and radiographic outcomes in the follow-up period. Both qualitative and quantitative analyses were used to synthesis the data by two reviewers. For the critical appraisal of the body of evidence for each outcome, qualitative synthesis was considered, putting the results of quantitative synthesis, if any, into perspective. Revman software (Review Manager 5.3) was used to undertake the quantitative analysis of the data. A funnel plot and I^2 values were used to examine statistical heterogeneity. When there was considerable heterogeneity (I^2 >30%), we adopted random model analysis; otherwise, we used fixed model analysis [12].

Quality Assessment of the Articles

Three reviewers separately assessed the risk of bias in RCTs using Risk Of Bias (ROB-2) tool and the Grading of Recommendation Assessment Development Evalaution (GRADE) approach was used to grade overall quality [13,14]. Disagreements among the review authors on the risk of bias in specific studies were resolved through discussion with the participation of a fourth reviewer.

RESULTS

The electronic database search and manual references search yielded a total of 139 papers published between January 2010 to August 2021. On Mendeley software, 65 of the study papers were found to be duplicates. Following title and abstract screening, 47 records were eliminated as they were reviews, case reports/series, non randomised studies. Total 27 full-text papers were evaluated for inclusion in the study. Finally, this systematic review included five papers for qualitative and quantitative synthesis [2,15-18] after excluding 22 articles due to full-text unavailable, published in other than English language, surgical treated studies are included, studies did not meet the inclusion criteria and continuation of research [Table/Fig-1].



[Table/Fig-1]: Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) (2020) flow diagram of the search.

This study included five RCTs that satisfied the inclusion criteria and had the desired characteristics [2,15-18]. Increased probing depths and evidence of peri-implant mucosal inflammation, such as Bleeding On Probing (BOP), and/or suppuration, were utilised as inclusion criteria in all investigations and clinical attachment loss was employed in two of them. In total, 392 people were treated in the five Randomised Control Trial (RCT) [Table/Fig-2].

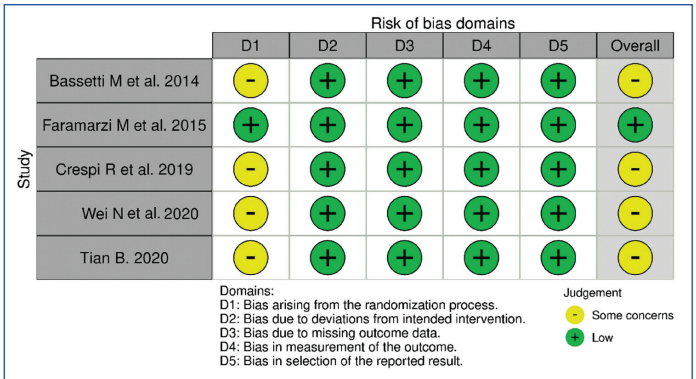
Overall one study was found to be high quality due to reporting of low risk of bias in all domains [18], whereas, remaining four studies raise some concerns about the randomisation method [Table/Fig-3] [2,15-17]. According to the GRADE system, the pooling of studies for a reduction in peri-implant bleeding, Probing Pocket Depth (PPD) and Clinical Attachment Level (CAL) provided high-quality evidence [Table/Fig-4,5]. Wide confidence intervals and some risk of bias in studies should also be considered while interpreting the results with caution.

Overall meta-analysis: When comparing experimental and control groups, the mean reduction in BOP was -9.71 mm, (95% CI: -11.74 to -7.68), The random effects model showed a statistically significant difference Z=9.40 (p-value <0.00001). Heterogeneity was substantial (I^2=100%). The experimental group was favoured in the forest plot graph. The Funnel plot graph shows significant heterogeneity [Table/Fig-6,7].

The mean PPD was reduced by -1.18 mm in the experimental groups compared to the control groups (95% CI: -2.35 to -0.02). High heterogeneity of 99% was found, and the mean value of the random model outcomes revealed a statistically significant difference (Z=1.99, p-value=0.05). In favour of the experimental group, the

Author	Sample size	Study groups	Time of intervention	Baseline characteristics	Follow-up characteristics	Conclusions
Tian B 2020 [2]	Test-90 Control-90	Minocycline HCL ointment versus 10% iodine	Peri-implantitis detected following Implant restoration for ≥6 months.	**Bleeding on probing:** • Test group- minocycline hydrochloride ointment- 4.39±0.46 • Control group- 10% of iodine was placed around the teeth in patients of the control group 4.28±0.22 **Probing pocket depth:** • Test group- 4.10±0.52 • Control group- 4.16±0.40	**Bleeding on probing:** 4 weeks after treatment • Test group- 1.95±0.22 • Control group- 3.72±0.50 **Probing pocket depth:** • Test group- 1.95±0.22 • Control group- 3.72±0.50	The minocycline hydrochloride ointment could be used to improve the treatment outcome and promote the good recovery of patients.
Bassetti M et al., 2014 [15]	20 subjects per group	PDT versus minocycline	Implant in function for ≥1 year	**Bleeding on probing:** At baseline, the mean number of BOP-positive sites per implant • Test group- 4.03±1.66 • Control group- 4.41±1.47 **Probing pocket depth:** At baseline, the mean PPD 4.39±0.77 mm at implants in the LDD and 4.19±0.55 mm at implants in the PDT group, respectively. **Clinical attachment level**: Mean CAL in LDD: 2.72±0.72 PDT: 2.66_0.73	**Bleeding on probing:** At 12 months • Test group- 1.55±1.26 • Control group- 1.74±1.37 **Probing pocket depth:** At 12 months • Test group- 4.08±0.81 • Control group- 3.83±0.85	The mechanical disruption of the submucosal biofilm with the adjunctive delivery of PDT or LDD in conjunction with optimal self performed plaque control yielded improvements in clinical, microbiological, and host derived parameters. Both treatment modalities yielded comparable reductions in mucosal inflammation and pocket probing depths up to 12 months.
Wei N et al., 2020 [16]	Test-43 Control-43	Mechanical debridement+minocycline hydrochloride versus mechanical debridement+iodine glycerine.	Not reported	**mSBI:** • Study group- 1.93±0.25 • Control group- 1.94±0.23 **Probing pocket depth:** • Study group- 4.32±0.34 mm • Control group- 4.33±0.37 mm	**mSBI:** At four weeks • Test group- 0.79±0.27 • Control group: 1.23±0.34 **Probing pocket depth:** • Study group- 3.31±0.42 mm • Control group- 3.97±0.48 mm	The mechanical debridement combined with minocycline hydrochloride has a good curative effect on peri-implantitis. It can effectively improve dental plaque, haemorrhaging, and inflammatory factors in the gingival cervicular fluid.
Crespi R et al., 2019 [17]	Test-24 Control-20	Mechanical debridement+0.2% chlorhexidine chemical detoxification+ chlortetracycline hydrochloride versus mechanical debridement alone	Implant in function for ≥1 year	**Bleeding on probing:** • Test group- 94.8±10.4% • Control group- 92.5±11.8% **Probing pocket depth:** • Test group- 7.47±1.11 mm • Control group- 7.24±0.99 mm **Clinical attachment level**: • Test- 8.18±1.29 mm • Control- 7.55±1.18 mm	**Bleeding on probing:** At 36 months • Test group- 20±16.0% • Control group- 88.5±10% **Probing pocket depth:** At 36 months • Test group- 3.15±0.32 mm • Control group- 5.97±0.90 mm **Clinical attachment level**: • Test- 4.26±0.80 mm • Control- 6.39±1.01 mm	The mechanical removal of bacterial biofilm, chemical detoxification of implant surfaces, and maintenance of granulation tissues in the pockets provided better clinical outcomes than mechanical debridement alone.
Faramarzi M, et al., 2015 [18]	Test-23 Control-21	Minocycline hydrochloride microspheres versus mechanical debridement	Implant in function for ≥1 year	**Bleeding on probing:** • Test group- 75±13.23 mm • Control group- 75±13.23 mm **Probing pocket depth:** • Test group- 4.75±0.26 mm • Control group- 4.75±0.26 mm	**Bleeding on probing:** • Test group- 6.25±6.48 mm • Control group- 75±13.23 mm **Probing pocket depth:** • Test group- 2.25±0.25 mm • Control group- 4.75±0.26 mm	The use of MSM and EMD can be an adjunctive treatment for the management of Peri-implant mucosal inflammation and improves clinical parameters and reduces *P. gingivalis* burden three months after treatment.

[Table/Fig-2]: Characteristics of all included studies [2,15-18].
BOP: Bleeding on probing; PPD: Probing pocket depth; CAL: Clinical attachment level; MSM: Microspherical minocycline; EMD: Enamel matrix derivative; mSBI: modified sulcus bleeding index



[Table/Fig-3]: Risk of bias of included studies [2,15-18].

PPD forest structure diagrams are presented in [Table/Fig-8]. The Funnel plot graph depicts systematic heterogeneity [Table/Fig-9].

Only two studies reported CAL gain in this systematic review [15,17]. The mean CAL reduction was 0.98 mm from 3.23 to 1.28 mm when compared to the test and control groups (95% CI: 3.23 to 1.28). The effect size was statistically non significant (p=0.39). Heterogeneity was significantly high (I^2=97%) [Table/Fig-10,11].

Subgroup analysis of minocycline: Subgroup analysis of the four studies that used minocycline microspheres as an adjuvant to submucosal debridement was performed taking bleeding on probing and pocket depth into account (Review Manager 5.3) [2,15,16,18]. Due to the heterogeneity of the included study, random effect models were used in the meta-analysis, and statistical heterogeneity was investigated using I^2 statistics. One study was eliminated from the meta-analysis because it used mechanical debridement in combination with chemical detoxification using 0.2 % chlorhexidine and chlortetracycline hydrochloride, which was used for qualitative analysis [17].

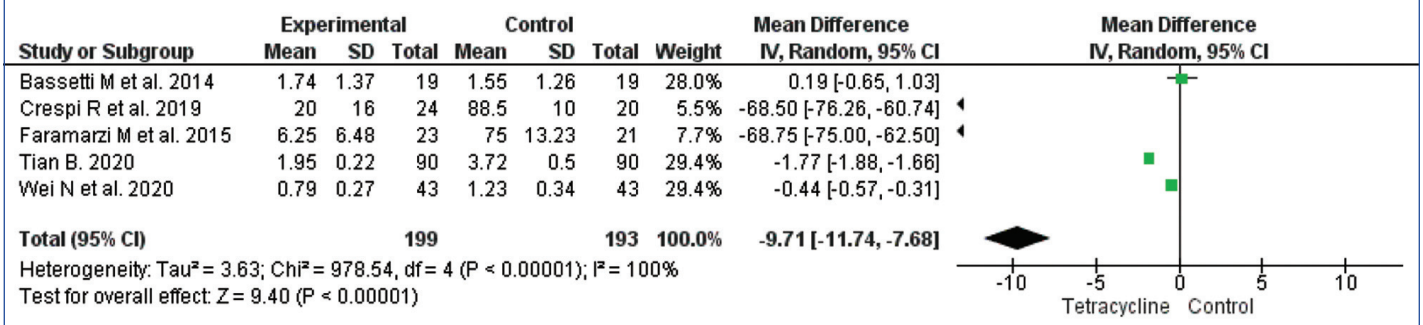
The mean difference in BOP between the minocycline and control groups was -5.07 (95% CI: -6.84 to -3.29). The random effects model analysis resulted in statistically significant (p-value <0.00001) with high heterogeneity (I^2=100%). [Table/Fig-12,13]. The mean PPD reduction in minocycline group was -0.78 mm (95% CI: -2.05 -0.49) when comparing the experimental and control groups. There was statistically non significant difference in PPD (p-value=0.23).

Certainty assessment							Summary of findings			
							Study event rates (%)		Anticipated absolute effects	
Participants (studies) follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of the evidence	Non-tetracycline	Tetracycline	Risk with non-tetracycline	Risk difference with tetracycline
The overall tetracycline group of drugs in lowering BOP										
392 (5 RCTs)	Not serious	Serious	Not serious	Not serious	Publication bias strongly suspected strong associationa	⊕⊕⊕ Moderate	193	199	Mean BOP was 0	MD 9.71 lower (11.74 lower to 7.68 lower)
The overall tetracycline group of drugs in lowering PPD										
392 (5 RCTs)	Not serious	Serious	Not serious	Not serious	None	⊕⊕⊕ Moderate	193	199	Mean PPD was 0	MD 1.18 lower (2.35 lower to 0.02 lower)
The overall tetracycline group of drugs in lowering CAL										
82 (2 RCTs)	Not serious	Serious	Not serious	Not serious	None	⊕⊕⊕ Moderate	39	43	Mean CAL was 0	MD 0.98 lower (3.23 lower to 1.28 higher)

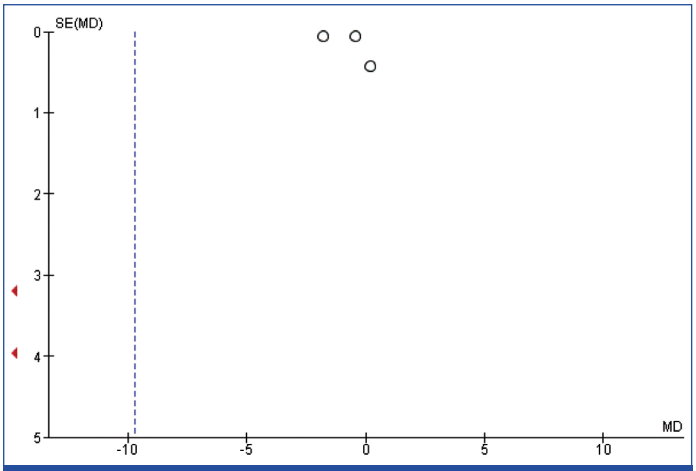
[Table/Fig-4]: Tetracycline group of drugs compared to other non surgical therapy for peri-implantitis adult population.
CI: Confidence interval; MD: Mean difference; a. High heterogeneity found; RCT: Randomised control trial; ⊕⊕⊕: Grade analysis

Certainty assessment							Summary of findings			
							Study event rates (%)		Anticipated absolute effects	
Participants (studies) follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of the evidence	Non-tetracycline	Minocycline	Risk with Non-tetracycline	Risk difference with Minocycline
Minocycline drug in lowering BOP										
348 (4 RCTs)	Not serious	Serious	Not serious	Not serious	Publication bias strongly suspectedb	⊕⊕ Low	173	175	Mean BOP was 0	MD 5.07 lower (6.84 lower to 3.29 lower)
Minocycline drug in lowering PPD										
348 (4 RCTs)	Not serious	Not serious	Not serious	Not serious	None	⊕⊕⊕ Moderate	173	175	Mean PD was 0	MD 0.78 lower (2.05 lower to 0.49 higher)

[Table/Fig-5]: Minocycline drugs compared to other non surgical therapy for the peri-implantitis adult population.
CI: Confidence interval; MD: Mean difference; a. High heterogeneity found; RCT: Randomised control trial; ⊕⊕⊕: Grade analysis



[Table/Fig-6]: Forest plot of overall bleeding on probing in tetracycline drugs [2,15-18].

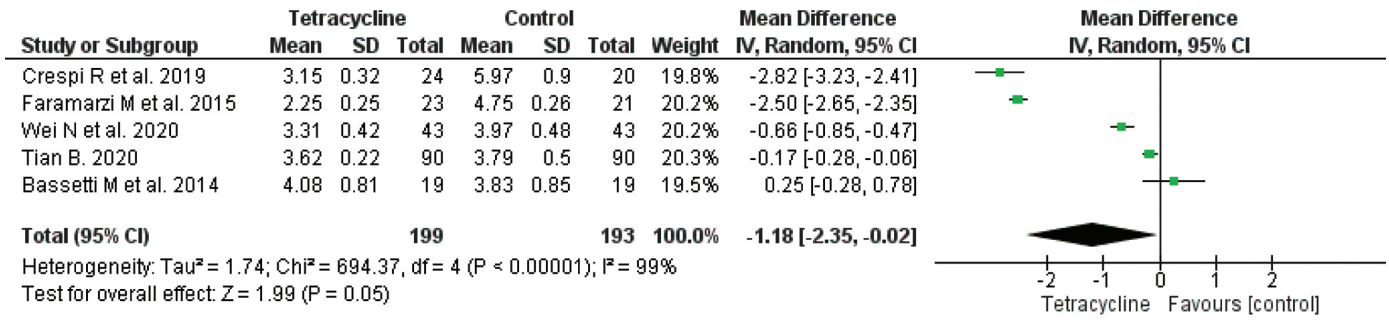


[Table/Fig-7]: Funnel plot of overall BOP in tetracycline drugs.
Standard error (SE) and mean differences (MD)

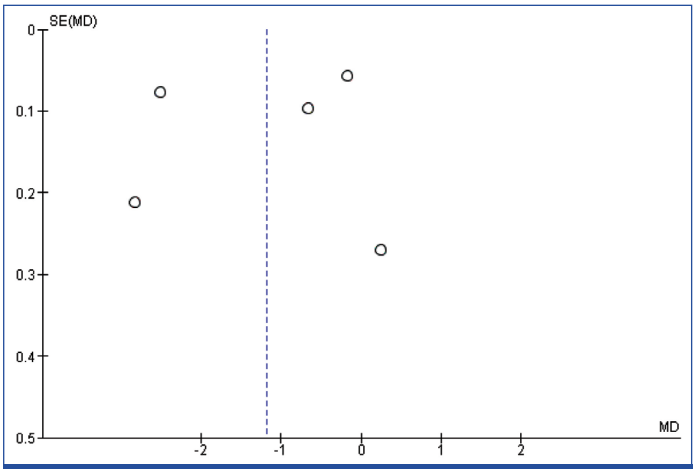
around the implant, which is caused by infection induced failure of bone implant contact [2]. Inflammation around the implant can lead to bone loss, which can lead to implant failure [2]. Treatment of peri-implantitis in a timely and effective manner is critical to enhancing the quality of life for patients [2].

The goal of this systematic review and meta-analysis was to gather the most reliable scientific evidence on the efficacy of the tetracycline group of antibiotics as an antibiotic in terms of probing pocket depth and bleeding reduction during probing. There were five RCTs in total [2,15-18]. According to this study findings the tetracycline group of drugs reduced BOP and PPD statistically significantly, but there were no significant variations in CAL. On the other hand, the subgroup analysis of minocycline, shows that it has benefits in terms of clinical BOP reduction but no benefits in terms of PPD decrease.

The quantitative analysis of minocycline in non surgical peri-implantitis therapy revealed a statistically significant reduction in BOP [2,15,16,18].



[Table/Fig-8]: Forest plot of overall Probing Pocket Depth (PPD) in tetracycline drugs [2,15-18].

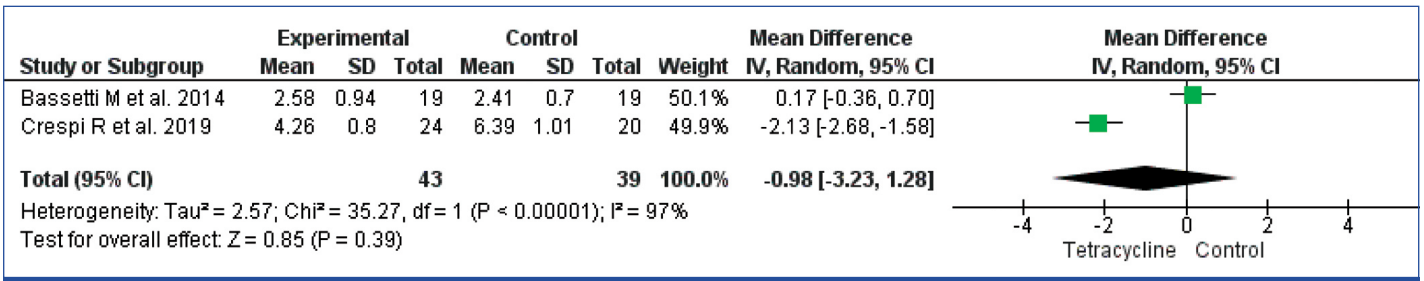


[Table/Fig-9]: Funnel plot of overall Probing Pocket Depth (PPD) in tetracycline drugs.

Mechanical debridement was combined with chemical detoxification using 0.2% chlorhexidine and chlortetracycline hydrochloride [17]. However, because CAL was not reported in the other three trials, it was not possible to incorporate it in the overall meta-analysis [2,16,18].

There is a possibility of bias in all of the research except one study [18]. In terms of methodological flaws, each of the four trials presented a biased randomisation detail [2,15-17]. Overall there was moderate evidence due to serious inconsistencies and suspected publication bias on included studies. Similarly, the evidence for subgroup analysis of minocycline in reducing BOP is low and that of PD reduction was moderate. As a result of this, the evidence should be interpreted cautiously.

The local application of 1 mg of minocycline hydrochloride as an adjuvant to mechanical debridement of implant sites was observed to minimise inflammation shown that using doxycycline as an adjuvant in the treatment of PI is effective [19-21]. When

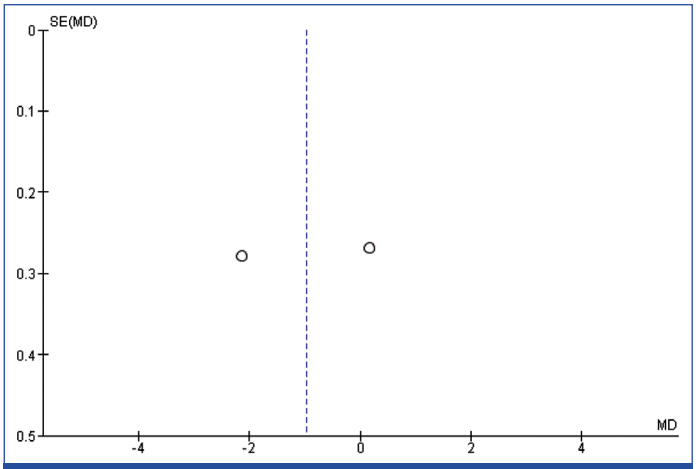


[Table/Fig-10]: Forest plot of overall Clinical Attachment Level (CAL) in tetracycline drugs [15,17].

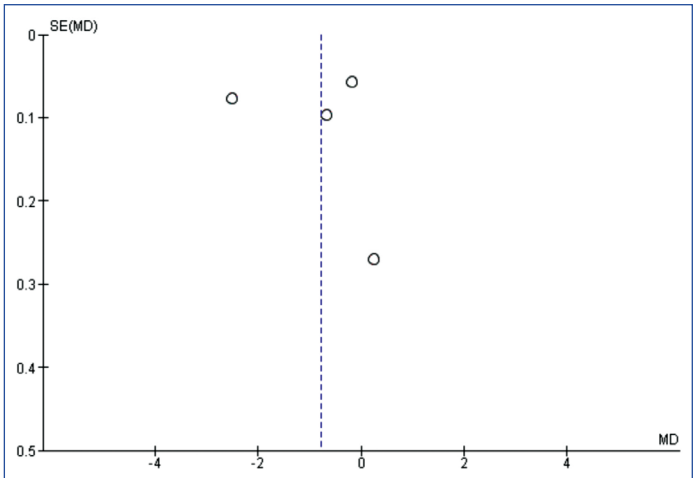
High heterogeneity was found (I^2=100%) (%) [Table/Fig-14,15]. The qualitative analysis could not be determined as there was no study available to determine the effectiveness of CAL.

DISCUSSION

Peri-implantitis is a severe problem that is intimately linked to poor oral hygiene and oral habits after implant therapy. Peri-implantitis is defined by mucosal inflammatory hyperplasia, abscess, and fistula compared to submucosal debridement with concomitant submucosal irrigation and chlorhexidine digluconate, local antibiotics (minocycline microspheres or doxycycline hyclate) may result in a considerable reduction in BOP scores and PPDs [10]. Following the administration of doxycycline, lincomycin, and erythromycin in three consecutive patients in a series of case studies, one study recorded the highest BOP reductions after 6 months trial; bleeding in the trial was reduced by 100% [22]. Even though, present results have shown a complete



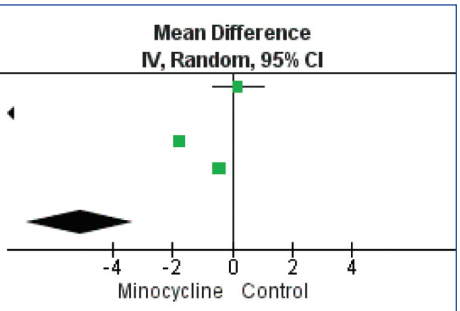
[Table/Fig-11]: Funnel plot of overall Clinical Attachment Level (CAL) in tetracycline drugs.



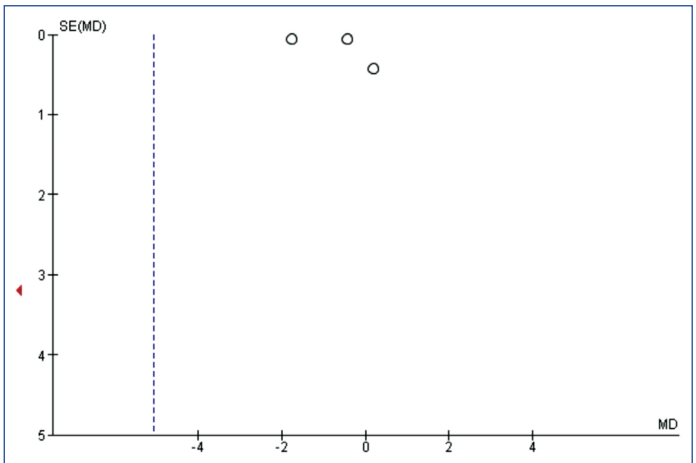
[Table/Fig-15]: Funnel plot of Probing Pocket Depth (PPD) in minocycline drug.

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Bassetti M et al. 2014	1.74	1.37	19	1.55	1.26	19	29.8%	0.19 [-0.65, 1.03]
Faramarzi M et al. 2015	6.25	6.48	23	75	13.23	21	6.4%	-68.75 [-75.00, -62.50]
Tian B. 2020	1.95	0.22	90	3.72	0.5	90	31.9%	-1.77 [-1.88, -1.66]
Wei N et al. 2020	0.79	0.27	43	1.23	0.34	43	31.9%	-0.44 [-0.57, -0.31]
Total (95% CI)			**175**			**173**	**100.0%**	**-5.07 [-6.84, -3.29]**

Heterogeneity: Tau² = 2.56; Chi² = 689.43, df = 3 (P < 0.00001); I² = 100%
Test for overall effect: Z = 5.60 (P < 0.00001)



[Table/Fig-12]: Forest plot of bleeding on probing in minocycline drug [2,16-18].



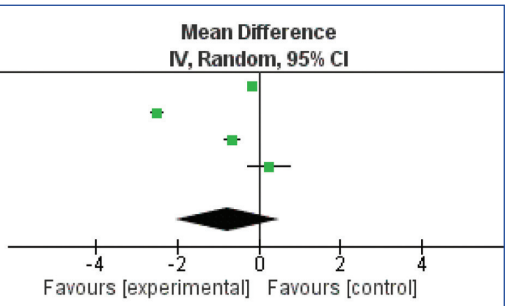
[Table/Fig-13]: Funnel plot of bleeding on probing in minocycline drug.

Limitation(s)

This meta-analysis has few limitations. All studies reported variations in intervention and control groups. In the treatment of peri-implantitis, four studies [2,15,16,18] utilised minocycline microspheres while one study used chlortetracycline [17]. There were no studies that examined radiographic bone loss. Only two studies have investigated clinical attachment loss [15,17]. The follow-up period in the other two trials was one month [2,16]. Few studies compared tetracycline group of drugs to 10% Iodine and PDT [2,15]. In the included trials, a variety of non surgical therapies or combination combinations were evaluated, making direct comparisons of outcomes impossible. The other two studies compared mechanical debridement without iodine glycerine to mechanical debridement with iodine glycerine [16,17]. The trials did not take into account radiographic bone levels. The second limitation is the duration of the study ranged from a month [2] to a 36 months follow-up [16].

Study or Subgroup	Minocycline Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Bassetti M et al. 2014	3.62	0.22	90	3.79	0.5	90	25.3%	-0.17 [-0.28, -0.06]
Faramarzi M et al. 2015	2.25	0.25	23	4.75	0.26	21	25.2%	-2.50 [-2.65, -2.35]
Tian B. 2020	3.31	0.42	43	3.97	0.48	43	25.2%	-0.66 [-0.85, -0.47]
Wei N et al. 2020	4.08	0.81	19	3.83	0.85	19	24.3%	0.25 [-0.28, 0.78]
Total (95% CI)			**175**			**173**	**100.0%**	**-0.78 [-2.05, 0.49]**

Heterogeneity: Tau² = 1.67; Chi² = 616.17, df = 3 (P < 0.00001); I² = 100%
Test for overall effect: Z = 1.20 (P = 0.23)



[Table/Fig-14]: Forest plot of Probing Pocket Depth (PPD) in minocycline drug [2,16-18].

reduction in BOP and PPD with no influence on CAL. Radiographic bone levels have been included in previous systematic review [10]. The current systematic review did not include a radiographic evaluation since none of the included studies revealed peri-implant bone levels. In contrary to the previous systematic review, this study found minocycline in terms of reducing peri-implant bleeding without much change in peri-implant probing depth. in the treatment of peri-implantitis from 2010 to date [10].

Only a few trials are available, and all published studies have a significantly diverse research design [2,15-18]. As a result, clinical data for the therapy of peri-implantitis is difficult to obtain. Other limitations may be related to the utilisation of language constraints in evidence-based clinical outcomes is still unknown. Inclusion of languages other than English, on the other hand, is a massive job. It's crucial to appropriately translate the results without distorting their meaning. It also requires the availability of knowledgeable,

time-consuming, and expensive resources. In traditional medicine, there has recently been no indication of systematic bias resulting from the use of language limits in systematic reviews [23]. Until then, researchers had a preference on whether or not to apply language restriction.

CONCLUSION(S)

Based on the findings of this systematic review and meta-analysis, we found that non surgical treatment with the tetracycline medication group resulted in a substantial clinical reduction in BOP and PPD without a significant change in CAL when compared to other antimicrobial therapies. The non surgical therapy of peri-implantitis with minocycline had resulted in clinical decreases in BOP but not PPD. Long-term randomised controlled trials are needed to assess the efficacy of treatments that do not prevent further bone loss, implant survival rates, and oral health-related quality of life standards.

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