

Clinical efficacy of systemic antibiotics as an adjunctive therapy to one stage full mouth disinfection (OSFMD) and full-mouth scaling and root planning in the treatment of chronic periodontitis: a systematic review of randomised clinical trials

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Summary

Periodontitis is a chronic inflammatory disease that results from a complex polymicrobial infection. The purpose of this review was to assess the efficacy of systemic administered antibiotics as an adjuvant to full mouth scaling and root planing with antiseptics (full mouth disinfection) and without the use of antiseptics in conjunction with systemic antibiotics in the treatment of chronic periodontitis. The following systemic review was conducted in agreement with the recommendations of the Cochrane Collaboration and the principles of the PRISMA (Preferred Reporting Items for the Systemic Reviews and Meta Analyses statement). The search resulted in 31 studies. Only 6 studies fulfilled the inclusion criteria and were eligible to be included in this systemic review. Further, long term randomised control trials with careful case selection of specific treatment protocols as well as standardised regimens for antibiotic use is required to obtain sufficient scientific evidence based treatment clinical guidelines for adjuvant use of systemic antibiotics with full mouth scaling and root planing and full mouth

disinfection in treatment of chronic periodontitis.

Key Words: antibiotics, randomised clinical trials, disinfection, periodontitis.

Introduction

Periodontitis is a chronic inflammatory disease that results from a complex polymicrobial infection, leading to tissue destruction as a consequence of the perturbation of the homeostasis between the subgingival microbiota and the host defenses in susceptible individuals (1). Initial phase of treatment should aim to reduce or eliminate the pathogenic microorganisms associated with disease. Treatment strategies involve scaling and root planing. This can be achieved in various visits or as full mouth scaling and root planing within 48 hours. Full mouth scaling and root planing has been associated with additional clinical and microbiological benefits (2, 3). Full mouth disinfection as suggested by Quirynen et al. (4) differs from the full mouth scaling and root planing. It is a protocol that involves full mouth scaling and root planing within 24 hours, subgingival irrigation of all pockets with a 1% chlorhexidine gel in order to kill remaining subgingival bacteria, tongue brushing with the chlorhexidine 1% gel for 1 min, mouth rinsing with a 0.2% chlorhexidine solution for 2 min to reduce the flora in the saliva and on the tonsils before and after scaling and root planing and optimal oral hygiene, supported for the first 2 weeks by mouth rinsing with 0.2% chlorhexidine solution. The conventional form of staged nonsurgical periodontal therapy involves scaling and root planing (SRP) has been shown to result in clinical improvements of periodontal health (5, 6). It has been suggested that it carries the risk for recontamination of already-treated areas from untreated sites still harbouring large amounts of periodontal pathogens (7). Based on this hypothesis, Quirynen introduced the protocol of one-stage full mouth disinfection (OSFMD) in order to reduce the bacterial load in pockets and intraoral niches, prevent the intra-oral transmission of periodontal pathogens from periodontal pockets to recently instrumented and healing periodontal sites and therefore produce a less pathogenic subgingival environment (4).

Systemic antibiotics have been used as an adjuvant to full mouth scaling and root planning to achieve further clinical improvements. Different antibiotic regimens have been indicated in the treatment of moderate to advanced chronic periodontitis including penicillins (amoxicillin), tetracyclines (doxycycline, minocycline, tetracycline), macrolides (azithromycin, clarithromycin, spiramycin, clindamycin), quinolones (moxifloxacin, ciprofloxacin) and nitroimidazole (metronidazole, ornidazole) (8, 9). The rationale for the use of systemic antibiotics in combination with non-surgical periodontal therapy is to suppress pathogenic bacteria to levels that are associated with health (9). The purpose of this review was to assess the efficacy of systemic administered antibiotics as an adjuvant to full mouth scaling and root planing with antiseptics (full mouth disinfection) and without the use of antiseptics in conjunction with systemic antibiotics in the treatment of chronic periodontitis.

One-stage full mouth disinfection (OSFMD)

The various steps in the original protocol for OSFMD of the oral cavity propagated by the Leuven group (4) included full-mouth scaling and root planing within 24 hours; in order to reduce the total number of subgingival pathogenic bacteria (10, 11); subgingival irrigation of the pockets with chlorhexidine gel to further eliminate bacteria (12); tongue brushing with chlorhexidine and mouth rinsing & gargling with chlorhexidine mouthwash to reduce the bacterial load in saliva and tonsils. The protocol also included oral rinses twice daily for 1 min with chlorhexidine for 2 weeks, during the initial healing phase to deplete the supragingival plaque deposits and prevent biofilm formation (13). The research group at the Catholic University at Leuven, Belgium conducted a series of clinical trials to explore the effectiveness of one stage full mouth disinfection protocol, (3, 7, 14, 15), and they consistently demonstrated a superior clinical outcome. This was in contrast with other groups findings which didn't report any difference using this protocol (16). In 1995, Quirynen et al. (4) compared full-mouth disinfection with quadrant wise periodontal therapy in 10 patients with advanced periodontal disease. Reduction of plaque and probing depths, as well as pathogenic species, was significantly greater at 1 month for the OSFMD group. The deep pockets (7 - 8 mm) exhibited a better response than the moderate pockets (5 to 6 mm). Culture analyses showed that samples from the test group harboured significantly fewer pathogenic species at 1 month and significantly more beneficial bacteria at 2 months post-treatment. *P. gingivalis* was eliminated from the test group. Long-term results of this pilot study were reported later (17) which demonstrated statistically significant greater reduction of probing depth in full mouth disinfection up to 1 mm. Therefore, they concluded that one-stage full-mouth disinfection demonstrated significant clinical and microbiological advantages over conventional treatment on a short-term basis. Bollen et al. conducted a randomised clinical trial with microbiological

findings in patients with advanced chronic periodontitis. They compared the OSFMD protocol using chlorhexidine for 2 months against conventional SRP. There was a significant reduction in bleeding scores, plaque, a probing depth reduction in probing depths especially in deep pockets (>7 mm) in the test group. Microbiologically, there was reduction in the putative periodontal pathogens in both groups however the full mouth disinfection group was always significantly higher. It was concluded that OSFMD was effective on medium term at improving the clinical outcomes associated with periodontal health (3). Mongardini et al. (15) investigated the clinical results of OSFMD in comparison to scaling and root planning per quadrant at 2-week intervals, in the control of severe periodontitis over an 8-month period in 40 subjects using a randomised control trial. Significant additional improvements were reported in the OSFMD group in terms of plaque, bleeding scores, and probing depth reduction (1.2 mm for single-rooted and 0.9 mm for multi-rooted teeth, with corresponding additional gains in attachment of 1.0 mm and 0.8) in patients with advanced chronic periodontitis. The Authors concluded that OSFMD results in significant clinical improvements over conventional periodontal therapy for an 8-month period in the treatment of severe adult and/or generalized early onset periodontitis, especially when treating deep pockets. Many theories were proposed for the reported success of the OSFMD in these studies through the reduction of the translocation of periodontopathogens. The exact mechanism however was unknown. It was hypothesized that it could be due to the reduction of the bacterial overload in a short period and prevention of re-infection. It could be due to the indirect impact of change in the supra gingival plaque which may extend sub gingivally as suggested by several studies (10, 18). The role of antiseptics in OSFMD was explored in 2006 by Quirynen (19). He compared the effects of full mouth disinfection, with and without concomitant use of different types and durations of antiseptics in comparison with quadrant scaling and root planning in chronic periodontitis, over 8 months. Again, he demonstrated superior clinical outcomes for the OSFMD group. In subsequent study (20), use of a strong antiseptic in the OSFMD was found to play a significant role compared to full mouth scaling and root planning. These results were inconsistent with findings from other research groups which conducted research involving the full mouth disinfection concept (2, 16, 21-23). These researchers were able to observe some statistically significant improvements in some outcome variables; however concluded that these improvements, whilst statistically significant; were not of a significant amount to be of clinical relevance (2). They considered the Leuven studies "proof of principle" experiments which provoked the recolonization in the control group. They argued that they had long time intervals before completion of debridement (6 weeks), no oral hygiene instructions were advised for the untreated quadrants and only 7 patients with ad-

vanced periodontal disease and significant calculus deposits were selected for the studies. This generated an ongoing debate as to whether full-mouth disinfection should be the treatment of choice. It must be noted that none of these studies followed the original protocol of full mouth disinfection, originally suggested by Quirynen (4) concerning the use of antiseptics in the Full Mouth Disinfection protocol. Some studies, (21, 22) employed antiseptics, but they used less potent povidone iodine. Systematic reviews published in 2008 (22,23), substantiated that OSFMD with and without antiseptics found only minor differences between the treatment strategies for adults with chronic periodontitis. The studies compared for the OSFMD with antiseptics did not consider the different protocols and different types of antiseptics used in the OSFMD protocols. In 2009, (24) Swierkot reviewed the OSFMD concept by conducting a study to compare clinical and microbiological effects of the original OSFMD protocol, full mouth scaling and root planning as well as conventional quadrant scaling and root planning in 28 patients with chronic periodontitis at 1, 2, 4 and 8 months. It concluded that all the different modalities resulted in significant clinical effects at any time. OSFMD displayed higher reduction in probing depths and bleeding on probing sites after 1 and 2 months. However, a major limitation in the study was the reduced number of probing depths >7 mm in this study which could lead to incomparable results to the Leuven group studies that noticed statistical differences mainly in moderate to deep probing depths. Considering the advantages of OSFMD technique, patient and operator comfort, systemic effects and its cost-effectiveness, the use of this technique in periodontitis patients is recommended. The most recent meta-analysis by Fang (25) showed that even though OSFMD had modest statistically insignificant additional clinical benefits over quadrant scaling and root planing in pocket depth reduction and clinical attachment level gain, they recommend OSFMD as the first choice for the treatment of adult chronic periodontitis. A recent comprehensive study published in by Fonseca (26), which also compared different treatment modalities for chronic periodontitis, compared OSFMD, Quadrant conventional therapy, and Full mouth scaling and root planning with and without use of systemic azithromycin. It reported a significant reduction in all clinical parameters in all treatment modalities however the OSFMD group with chlorhexidine showed higher reductions in probing depths, percentage of diseased sites as well as lower bacterial counts than all the other groups at a 180 days which again reinforces the superiority of the OSFMD protocol with concomitant use of chlorhexidine. The OSFMD protocol results in significant additional clinical and microbiological improvements with nonsurgical periodontal therapy. The scientific basis of the improved results with this protocol are yet to be completely understood. Reduction in the probability of bacterial cross contamination, combination of antiseptics (chlorhexidine) and or Schwartzman reaction

are all possible hypothesizes. OSFMD requires less time to complete the treatment than multiple visits without any disadvantages to the patient which is also an important factor. More research is needed to further explore the scientific concepts related to it as well as the use of other adjuvants such as antibiotics with the full mouth disinfection protocol in treatment of chronic periodontitis.

Materials and methods

The following systemic review was conducted in agreement with the recommendations of the Cochrane Collaboration (27) and the principles of the PRISMA (Preferred Reporting Items for the Systemic Reviews and Meta Analyses statement) (28).

Focused question (PICO)

The focused question that has been used was: "Do systemic antibiotics combined with full mouth scaling and root planing vs full mouth scaling and root planing alone in treatment of chronic periodontitis have an additional effect on the clinical outcomes"?

PICO Criteria

Participants: participants of any age with chronic periodontitis receiving full mouth scaling and root planing or full mouth disinfection protocol (within 48 hours).

Intervention: the intervention evaluated the use of systemic antibiotics with or without chlorhexidine (antiseptics).

Comparison: comparison of results with or without use of systemic antibiotics.

Outcomes: primary outcomes is PD (probing depth) reduction, CAL (clinical attachment level) gain. Secondary outcomes included reduction in full mouth bleeding scores, plaque scores and microbiological changes.

Search strategy

The PubMed database was searched from their earliest records until January 2019. The following search terms were used: Periodontal diseases [MESH]/(TEXT)OR chronic Periodontitis AND Full mouth scaling and root planing [MESH]/(TEXT) OR Full mouth disinfection [MESH] /(TEXT) AND Antibiotics [MESH](TEXT) AND Prospective Clinical trial. In addition, a manual search was performed on issues from the past 10 years of the Journal of Clinical Periodontology and Journal of Periodontology and bibliographies of all the retrieved papers.

Study inclusion and exclusion criteria

The following eligibility criteria were imposed for inclusion in the systemic review: 1. Studies were limited to randomised controlled clinical trials, sample size of at least 20 patients, with follow-up of at least more than three months duration; 2. The population was limited to subjects in good general health with chronic periodontitis; 3. The interventions of interest

were full mouth disinfection (SRP within 24 hours, FMSRP with use of chlorohexidine) or full mouth scaling and root planning (SRP within 48 hours) with or without the use of systemic antibiotics; 4. No specific systemic antibiotics were excluded; 5. Clinical parameters of interest of PD and CAL as primary outcome parameters, with BOP and FMPS as secondary outcome parameters, data presented by means of pre- and post-treatment data, incremental data or both; 6. Only papers in the English language were included. Only studies that met all the inclusion criteria were analysed.

Exclusion criteria:

- 1) History of refractory periodontitis
- 2) Combination of local and systemic antibiotics
- 3) Primary outcome of interest was not analysed
- 4) Duplicated studies.

Outcome variables

The primary outcome variables in the studies were reduction in probing depth, changes in clinical attachment level. Secondary outcomes included differences in bleeding on probing (BOP). Other outcome variables included were microbiological changes due to treatment.

Selection strategy

Eligibility assessment was performed through titles and analysis of the abstracts and full text. If the search key words and the relevant information to the eligibility criteria were present in the title, the abstract, or both, the study was selected for full-text reading. Titles and abstracts of the search results 10 were screened independently by two reviewers (AQ, EE, IV), for possible inclusion in the literature review. Studies without abstracts but with titles suggesting they were related to the objectives of this review were also selected for full-text screening to avoid excluding potentially relevant articles. A hand search of the reference lists of all selected studies for additional relevant articles was completed. The full text articles of all the selected studies were included in the full text analysis. The full text of all the studies with possible relevance was assessed by two reviewers (EE, AQ). After selection, full-text studies were read in detail by reviewer. Those studies that fulfilled all the selection criteria were processed for data extraction. Data of the included articles were extrapolated. The full texts of all studies of possible relevance were obtained for independent assessment by the reviewers. Any disagreement was resolved by discussion. Data were extracted independently by the reviewers using a data extraction form. Disagreement regarding data extraction was resolved by consensus.

Quality assessment

Assessment of methodological study quality was performed combining the proposed criteria by the Cochrane hand book for systemic reviews for interventions (27). It comprises evaluating quality through four methodological RCT aspects: I. Se-

quence generation; II. Allocation concealment; III. Blinding of personnel and outcome assessors; IV. Handling of incomplete outcome data. Assessment of methodological study quality was performed by the reviewer using the criteria proposed by the Cochrane Reviewer's Handbook (Higgins and Green 2009) (27). Included articles were evaluated through methodological RCT aspects into "Low risk", "High risk", or "Unclear" (27). These included a. Selection bias (Random sequence generation, Allocation concealment); b. Performance bias (Blinding of the participants and personnel); c. Detection bias (Blinding of the outcome assessment); d. Attrition bias (Incomplete outcome data); e. Reporting bias (Selective reporting); f. Other bias (Other sources of bias). To be included articles had to be considered adequate in all six aspects.

Characteristics of the study design

All selected studies were randomised controlled clinical trials. The evaluation period varied between the studies from 6 months to 5 years. A considerable heterogeneity in the design, duration (evaluation period), and regimen of SRP was present in the studies. The number, sex, and age of the participants and the periodontal diagnosis also varied among the studies.

Risk of bias: Risk of bias was evaluated through quality analysis performed by the reviewers. Quality analysis of the RCT was done according to the Cochrane Handbook risk assessment. Four included studies estimated risk of bias is "Low Risk" according to the Cochrane Handbook criteria for judging risk of bias assessment tool. This includes assessment if six RCT issues: randomisation, concealment, incomplete outcome data, selective reporting, other bias. All the size criteria were assessed as adequate, inadequate or unclear.

Results

Search and selection

The search resulted in 31 studies. Only 6 studies fulfilled the inclusion criteria and were eligible to be included in this systemic review. Most of the studies were excluded because the completion of SRP occurred in a period greater than 48 hours or because many studies reported on cases of aggressive periodontitis (Fig. 1). All five studies included in the systematic review were randomised clinical control trials that assessed clinical parameters before and after intervention at different time points after treatment. All the studies assessed the clinical parameters for 6 months, except one study that extended the results to 1-year post treatment. The length of follow-up ranged from 6 months to 5 years in the studies included. Detailed information regarding the selected study characteristics and the Authors' conclusions are presented in Table 1. Two studies had a high risk of bias due to the inclusion of patients in the analysis despite the discontinuation of the intervention. Detailed analysis is presented in Table 2.

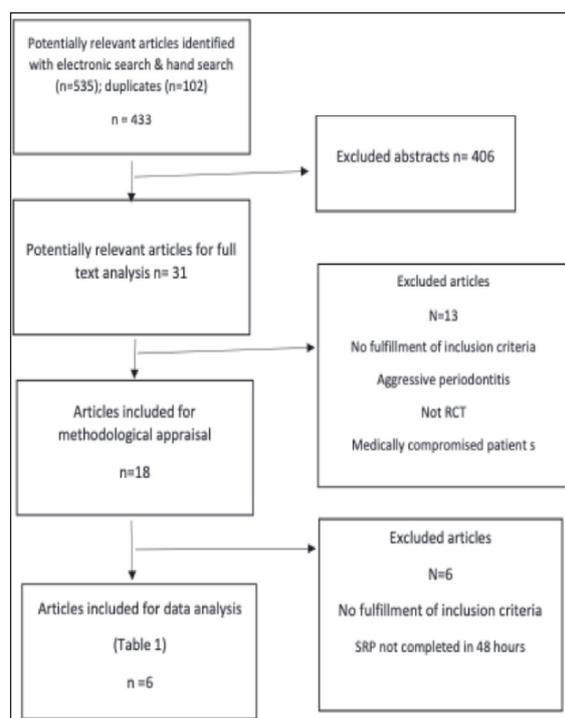


Figure 1. Flowchart of literature search and inclusion.

Intervention

All six studies compared full mouth scaling and root planning and/or full mouth disinfection with or without the use of systemic antibiotics. Different regimes of antibiotics were used in each study (Tab. 1). Data from each article were collected, and a descriptive report was generated about the type of study, number of patients, mean follow-up period (Tab. 1), and clinical parameters: bleeding on probing, pocketing depth, clinical attachment level and microbiological assessment. Data from each study was analysed and information about the type of study, number of participants, Mean PD (pocket depth) reduction, Mean CAL (clinical attachment level) gain, changes in BOP in each group after intervention, and length of follow-up, is recorded in Table 1.

Characteristics of included studies

Participants

The included studies involved a total of 440 participants (Tab. 1).

Quality analysis: Quality analysis was completed utilising the GRADE approach outlined in the Cochrane hand book, which specifies four levels of quality. All studies included in the review were randomised trials with a high-quality rating. Limitations in the implementation of the study design in two studies which have the same design as one reported 12 months while the other reported 5 years had a high risk of bias, this eventually reduced the quality of the body of evidence from high to moderate quality evidence.

Outcomes: In the present review, the reduction in mean pocket depth after intervention ranged from 2-3 mm in all the studies. The length of follow-up was 6 months in all studies except one study that reported up to 5 years post intervention.

Results of individual studies: The comparison of the findings in the selected studies is difficult due to the heterogeneity of the data, different protocols followed in each study therefore it was decided to report the type of intervention of each study and specific methodology used. The articles are reported in chronological order.

Primary outcomes

Ribeiro (29). Reported results at 6 months showed an additional reduction in PD depth was noted in the test group (0.83 mm) in PD [P2 mm at 43.52% of sites (control) compared to 53.03% (test)]. However, both groups had similar RAL gain [1.68 (control) and 1.88 mm (test) group]. It was therefore concluded by the group that both treatments resulted in significant clinical improvements.

Cionca (30). Clinical results obtained at 3 months were maintained at 6 months, the mean PD reduction in test group was 3.0 mm in test group, and 3.1 in placebo group. Sites presenting with pockets initially >6 mm showed a mean decrease in mean PD from 7.3 \pm 0.3 mm at baseline to 3.6 \pm 0.8 mm at 3 months and 3.7 \pm 0.6 mm at 6 months in the test group unlike the placebo group that showed a decrease from 7.2 \pm 0.7 mm to 5.2 \pm 1.1 mm at 3 months and 4.9 mm \pm 1.4 mm at 6 months, which shows a clear 16 advantage of use of systemic antibiotics in these sites. The results of the study show a significant improvement in the clinical outcomes of full mouth nonsurgical periodontal debridement with antibiotics and significantly reduced need for additional therapy.

Preus (31). No statistically significant differences were noted between the different groups at baseline, 3 and 12 months. All the groups displayed significant improvements in all the analysed parameters. Mean Clinical attachment level (CAL) ranged 1.06 to 1.29 mm at 3 and 12 months, mean PD was around 2.20 to 2.28 mm at 3 and 12 months in all four groups. The mean gain in CAL from baseline to 1 year was slightly more in groups with antibiotics {0.72, (0.60 to 0.85) and 0.81 (0.67 to 0.96) compared to 0.61 (0.51 to 0.72) and 0.64 (0.52 to 0.76) in groups with no antibiotics. Metronidazole treatment was significantly influential of the mean probing depth (PD) reduction which ranged from 0.81 to 1.03 mm. Metronidazole was found to exert an adjunctive effect on the mechanical periodontal therapy for \leq 12 months after treatment. It resulted in additional gain of CAL, reduction in PDs and more frequent eradication of the pockets \geq 5 mm, [Absence of pockets \geq 5 mm at 1 year was found to be 72.7% (FDis group +met) and 62.2% (SRP + met) compared to 42.2% (Displace) and 39.1% (SRP+ placebo) in groups without metronidazole].

Table 1. Characteristics of included studies in literature review.

Study	Design and Evaluation period	Diagnosis, No of Subjects (end), Age	Regimen as Adjunct to SRP	Regimen for Antiseptics use	Follow-up	Conclusion of the Authors	Bias Assessment Bias (Cochrane "Risk of bias" assessment tool) (29)
Ribeiro, et al.	RCT Parallel Double masked	Ch P 25 patients, 12 =c, 13 = T Mean age= 46	Amoxicillin 375 mg, metronidazole 250 mg 3 times daily for 7 days	Nil	6 months	Both groups showed a reduction in PD, and gain in RAL. Mean Decrease in PD 2.45 mm± 0.5 mm in control group and 3.28±0.41 mm in test group At 6 m, lower Bo P and additional reduction (0.83 mm) in PD Similar RAL Gain in Antibiotics group	Low risk
Cionca, et al.	RCT Single centre Double masked, Placebo controlled RCT	Ch P 47 patients 24=C, 23=T Mean Age 50.5	Metronidazole 500 mg, amoxicillin 375 mg 3 times daily for 7 days	Subgingival irrigation with 0.1% chlorhexidine solution rinse with 0.25 CHX twice daily (10 days)	6 months	Systemic metronidazole + amoxicillin improved 6 month clinical outcomes of full mouth non-surgical periodontal debridement .0.4 ± 0.8 persisting pockets were still present in test group compared to 3.0 +-4.3 in control	
Preus, et al.	RCT Four arm parallel group, double masked clinical trial	Ch P 180 patients G1=44 (FDIS+ Met) G2= 45 (FDIS +placebo) G3=45 (SRP +Met) G4=46 (SRP + placebo)	Metronidazole 400 mg, 3 times daily for 10 days	Subgingival irrigation with 1% CHX gel tongue brushing with CHX gel 1 minute every night (9 days) -0.2% CHX mouthwash every morning (9 days)	12 months	Metronidazole has a significant adjunctive effect on clinical parameters of CAL, PD and absence of pockets >=5 mm	High risk (Patients discontinued intervention in all groups were still included in the analysis)

To be continued

continue from Table 1

Fonseca, et al.	RCT Four arm parallel group, double masked clinical trial	Ch P 186 participants (6 groups) G1=15 (FAZ) G2=15 (FC) G3=15 (FNC) G4=14 (QSAZ) G5=13 (QSC) G6= 13 (QSNc)	FAZ + QSAZ (Azithromycin 500 mg once daily for 3 days)	FC=Subgingival irrigation with 0.12% CHX gel for 1 minute Mouthwash 0.12% CHX for 30 secs at beginning and end of each session + CHX 0.12% mouthwash twice daily for 2 weeks QSC=daily used of CHX 0.12% for 60 days	6 months	Adjuvant use of azithromycin did not provide any significant improvement on clinical and microbiological parameters. The adjuvant use of CHX especially in FMD protocol (FC) followed by QS showed more significant improvement	Low risk
Preus, et al.	RCT Four arm parallel group, double masked clinical trial	Ch P 161 (7 lost at initial treatment, 16 at 5-year follow-up. Patient G1 (FDIS+ Met) G2 (FDIS + placebo) G3 (SRP + Met) G4 (SRP + placebo)	Metronidazole 400 mg, 3 times daily for 10 days	Subgingival irrigation with 1% CHX gel Tongue brushing with CHX gel 1 minute every night (9 days) 0.2% CHX mouthwash every morning (9 days)	5 years	Metronidazole increased the highest CAL recording statistically insignificantly by 0.17 mm while FDIS decreased it by 0.12 mm small statistically significant differences, too small to recommend metronidazole treatment as an adjuvant treatment	High risk (Patients discontinued intervention in all groups were still included in the analysis)
Cosgarea, et al.	RCT Three arm parallel group, double masked clinical trial	Ch P 102 patients (33 groups), 91 patients only completed. G1=30 (SRP + placebo) G2=30 (SRP + AMX + MET 3 days) G3=31 (SRP + AMX + MET 7 days)	Amoxicillin + metronidazole 500 mg TID for 3 days amoxicillin + metronidazole 500 mg TID for 7 day	All groups: PPDs>4 mm rinsed with Chlorhexidine digluconate solution. Chlorhexidine digluconate solution 0.2% rinse twice daily for 14 days	6 months	Patients with severe chronic periodontitis SRP in conjunction with amoxicillin and metronidazole 500 mg lead to greater clinical improvements. No statistical difference between 3 and 5-day regimen	Low risk

Legend of abbreviations: RCT, Randomised control trials; AZ, Azithromycin; FAZ, Full mouth SRP within 24 hrs with AZ; FC, FMD with CHX (FMD protocol + CHX 0.12% twice daily for 2 weeks); BOP, Bleeding on Probing; CHX, chlorhexidine; QSC, SRP per quadrant with CHX (daily 0.12% for 60 days); FNC, Full mouth SRP without CHX; PD, Pocket depth; SRP, Scaling and root planning; QSNc, SRP per quadrant without CHX; QSAZ, SRP per quadrant with AZ; CAL, Clinical attachment level; Ch P, Chronic periodontitis; FMD, Full mouth Disinfection (FMD protocol + CHX 0.12% twice daily for 2 weeks); RAL, Relative attachment level, measured from fixed point occlusal splint to base of pocket.

Table 2. Risk of bias assessment according to Cochrane Handbook Risk of Bias Assessment (27) (H= HIGH, L=LOW).

	Ribeiro, et al. (29)	Cionca, et al. (30)	Preus, et al. (31)	Fonseca, (26)et al.	Preus, et al. (32-34)	Cosagrea, et al. (33)
Random sequence generation (selection bias)	L	L	L	L	L	L
Allocation concealment (selection bias)	L	L	L	L	L	L
Blinding of participants and personnel (performance bias)	L	L	L	L	L	L
Blinding of outcome assessment (detection bias)	L	L	L	L	L	L
Incomplete outcome data (attrition bias)	L	L	L	L	L	L
Selective reporting (reporting bias)	L	L	L	L	L	L
Other bias	L	L	H	L	H	L

Preus (32). This study is the follow treatment of the previous study for 5 years, 161 patients only were available for the 5-year review. Statistically significant additional changes in CAL with adjuvant metronidazole were found at 5 years of 0.40 mm in the SRP group and 0.06 mm in full mouth disinfection group. However additional benefit with use of systemic metronidazole was small and doesn't justify use of antibiotics. No mention of.

Fonseca (26). All groups in this study presented significant reduction in the percentage of periodontal diseases sites, gingival index, plaque score, and CAL gain at 90 days, demonstrating all treatment modalities were effective. However, the FC group [Full mouth disinfection (FMD) with chlorhexidine (CHX) for 2 weeks] showed a higher reduction in probing depth reduction (from 2.10 +- 0.50 to 1.53 +- 0.41 mm) and percentage of periodontal disease sites (from 6.58+- 7.95 to 2.13+- 3.90) as well as lower total bacterial counts at 90 and 180 days. The full mouth scaling and root planing group plus azithromycin in this study unlike other studies in the literature demonstrated less reduction in probing depth compared to the full mouth disinfection group. Therefore, it was concluded that adjuvant used of azithromycin did not provide any significant benefit.

Cosgarea (33). All groups presented significant clinical improvement. Average pocket reduction at 6 months in the placebo group (1.90 +-0.69 mm) was significantly smaller compared to 3-day antibiotic (AB) (2.5+-0.62) and (2.76+-0.62) for the 7-day AB

regimen. CAL gain was statistically significantly increased in the antibiotic groups (1.63+-0.5 mm) and (1.7+-0.53 mm) in the 3 and 7-day AB regimen compared to 1.13+-0.74 mm in the placebo group.

Secondary outcomes

Ribeiro (29). 6 months resulted in lower bleeding on probing (BOP) (7,755 at test sites, compared to 21.11% at control sites). Real time PCR and Elisa failed to identify any significant differences between the groups. However only the test treatments group reduced the numbers of all microorganisms below the levels of detection. Both groups presented statistically significant reduction of PG and Tf only.

Cionca (30). The number of persisting bleeding pockets was 7.5 times greater if the subjects had not received the antibiotics after full mouth scaling and root planing. The mean PS, GI, REC, were not significantly different.

Preus (31). The distribution of sites with plaque at 12 months was like baseline, however the percentage of sites with BOP reduced in all groups.

Preus (32). The 5-year results reported reduced plaque score and BOP in all groups that was maintained at 5 years.

Fonseca (26). All groups in this study presented significant reduction in the percentage of periodontal diseases sites, gingival index, and plaque score at 90 days, demonstrating all treatment modalities were effective.

Cosgarea (33). All groups presented similar decrease in BOP at 6 months, there was more reduction of BOP in AB groups (9.47+-5.34 and 7.75 +- 6.64) compared to placebo group (13.07+-9.02). FMPS was similar in all treatment groups.

Discussion

There is a lot of evidence in the literature which suggests that systemic antibiotics in combination with scaling and root planing result in additional clinical benefits compared to scaling and root planing alone, (29, 30) most of the studies compare the effect of conventional scaling and root planing carried out in staged visits that could be weeks apart. Since the proposal of the full mouth disinfection protocol, by Quirynen et al. (4) which suggest that additional clinical benefits were compared to conventional scaling and root planing, many studies have revealed better clinical and microbiological outcomes with this new protocol (3, 4, 15, 34). Other studies have failed to demonstrate such results (21-23). A review by Lang et al. (22) on the effects of full mouth scaling and root planing with or without chlorohexidine and conventional scaling and root planing has shown statistically significant differences between the full mouth debridement with and without antiseptics and conventional scaling and root planing however, they were inconsistent and small and therefore concluded both treatment modalities were effective, it also delineated that full mouth scaling and root planing provided additional benefits in terms of time as treatment is carried out in less time. The aim of this review is to analyse the additional effects provided by systemic use of antibiotics in the non-surgical treatment of chronic periodontitis using full mouth scaling and root planing with or without use of antiseptics. Only 6 studies fulfilled the criteria to be included in this review, which is a very limited number, most of these studies were randomised controlled trials with a low risk of bias. Different systemic antibiotics 18 and regimens were used in each of the studies, which ranged, from combination (amoxicillin and metronidazole, metronidazole alone and azithromycin). It must be noted that in the literature there is no recommendations for a specific antibiotic regimen to be used in the treatment of chronic periodontitis. Probing reduction, CAL changes were the primary outcome of all the studies, 2 studies analysed the microbiological outcomes after treatment as well and one study analysed the levels of inflammatory mediators (PGE2, IL and interferon) after treatment. 3 of the studies demonstrated significant probing depth reduction with relation of systemic antibiotics when compared to full mouth scaling and root planing without antibiotics. One study reported no significant changes with the use of systemic antibiotics compared to full mouth scaling and root planing and reported more significant changes with the full mouth disinfection protocol instead in terms of PD reduction, CAL gain

and microbiological changes. It must be noted that the participants in this trial had moderately deep periodontal probing depths, and results were diluted by the mean value of the healthy sites. It was noted in 5 studies that the probing depth reduction was more noticeable in deep (PD >6 mm) and percentage of diseased sites which were sites with 4 mm and BOP decreased significantly in all patients receiving systemic antibiotics, which decreased the need of further periodontal therapy, assumed to be surgery in these patients. Microbiological results were recorded in 2 studies only with conflicting results, as one study demonstrated significant reductions with the use of systemic antibiotics while the other showed no changes with the use of antibiotics but significant reduction with use of the full mouth disinfection protocol. No changes were found with regards to the inflammatory markers in the one study that analysed them in GCF before and after intervention. All the studies reported on the 6 months, except two studies by Preus et al. which reported results up to 12 months (31) and 5 years (32). They reported positive outcomes with the use of systemic antibiotics which was maintained up to 5 years in those studies, however it noted that the difference was minimal despite being statistically significant.

Limitations

Outcome level

This present review only reported on the data presented by 6 studies (RCT Studies) to estimate the treatment effects of the use of systemic antibiotics with full mouth scaling and root planing with or without antibiotics. The excluded publications are listed in Table 3 (35-46). The studies included used different regimens of antibiotics for different duration. The outcome of the review depending on the studies included was influenced by the patient population, the data collection, the type and regimen of the systemic antibiotic used and the analyses that differed between studies.

Study and review level

The main limitation of the present systematic review was the heterogeneity in the design, intervention, data collection, and analyses. The limited number of studies that fulfilled the criteria also limited the amount of data to be analysed as well as the different regimens of systemic antibiotics used and short follow-up duration of only 6 months in most studies. Therefore, more well designed, multicentre studies with long follow-up are required to obtain evidence based guidelines.

Conclusions

Implications for practice

In the present systematic review, despite the limited

Table 3. List of publications excluded in methodological assessment.

Publication	Ref no	Reason for exclusion
Gomi, et al. 2007	(35)	SRP was completed within 7 days
Pradeep, et al. 2012	(36)	SRP was not completed within 24 hours
Matarazzo, et al. 2008	(37)	Patient selection was smokers only (10 cigarettes per day for 5 years)
Smith, et al. 2012	(38)	SRP was carried out within 3 weeks
Jentsch, et al. 2016	(39)	No control group. Both groups received different types of antibiotics (azithromycin or amoxicillin + metronidazole)
Haffajee, et al. 2004	(40)	Patients had previous periodontal therapy and only local antibiotics was used as
Winkel, et al. 2001	(41)	SRP was carried out in 3 to 6 sessions
Silva, et al. 2011	(42)	Treatment was carried out in 4- 6 visits not within 24 hours
Harks, et al. 2015	(43)	Aggressive periodontitis patients were included in the study
Lopez, et al. 2006	(44)	SRP was completed in 2 sessions 3 days apart
Faveri, et al. 2014	(45)	All patients received SRP+ systemic metronidazole and groups were categorised according to smoking status
Haffajee, et al. 2007	(46)	SRP was completed quadrant wise in weeks

number of studies reviewed, it was nevertheless possible to conclude that the use of adjuvant antibiotics with full mouth scaling and root planing and full mouth disinfection provided additional clinical benefits in terms of PD reduction, CAL gain especially in PDs >6 mm. Even though one study did not demonstrate its superiority compared to other treatment protocols, it was an effective clinical modality of treatment (26). Use of antibiotics should be approached with caution as to prevent bacterial resistance to systemic antibiotics. More research is required to further verify these results.

Implications for research

Further, long term randomised control trials with careful case selection of specific treatment protocols as well as standardised regimens for antibiotic use is required to obtain sufficient scientific evidence based on treatment clinical guidelines for adjuvant use of systemic antibiotics with full mouth scaling and root planing and full mouth disinfection in treatment of chronic periodontitis.

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