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The effect of systemic antibiotics administered during the active phase of non-surgical periodontal therapy or after the healing phase: a systematic review

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ABSTRACT

Objective: The aim of this systematic review was to compare the clinical effectiveness of systemic antibiotics administered in the active stage of periodontal treatment or after the healing phase. Material and Methods: An electronic search was performed in the databases EMBASE, MEDLINE and Cochrane Central Register of Controlled Trials (CENTRAL), in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement. A manual search of the reference list of selected studies and of review articles was also performed up to November 2013. Randomized Clinical Trials (RCT) that evaluated the systemic administration of antibiotics as adjuvants to scaling and root planning (SRP) at different phases of periodontal treatment were included. Systematic reviews and studies that evaluated subjects with systemic diseases and those that used subantimicrobial doses of antibiotics were excluded. Results: The initial search identified 1,039 articles, of which seven were selected, and only one met the inclusion criteria. This study showed that subjects taking metronidazole and amoxicillin at the initial phase of treatment exhibited statistically significantly greater reduction in pocket depth and gain in clinical attachment level in initially deep sites (PD≥7 mm) than subjects taking antibiotics after healing ($p<0.05$). This comparison was conducted 2 months after antibiotic intake, at the healing phase. Conclusion: To date, only one short-term RCT has directly compared different moments of systemic antibiotics administration, as adjuncts to SRP, in the treatment of periodontitis. Although the results of this study suggested some benefits for antibiotics intake during the active phase of therapy, these findings need to be confirmed by larger placebo-controlled randomized clinical trials with longer follow-up periods.

Keywords: Periodontal diseases. Chronic periodontitis. Aggressive periodontitis. Therapy. Antibiotics.

INTRODUCTION

Periodontal diseases are infectious-inflammatory conditions that may lead to the loss of teeth. Scaling and root planing (SRP) is the most commonly therapy used for the treatment of periodontitis. Although SRP promotes an improvement in the clinical periodontal parameters in the majority of cases, it is frequently insufficient to change the bacterial profile associated with periodontitis to a profile compatible with periodontal health, i.e., with lower levels and proportions of periodontal pathogens and higher proportions of beneficial microorganisms, such as the *Actinomyces* species[4]. Therefore, the clinical beneficial results achieved with this procedure in the short-term are frequently not maintained in the long term, particularly in more advanced cases[6,22] or in those associated with risk factors, such as smoking[16] and diabetic patients[19]. These individuals normally respond less favorably to mechanical treatments, either because of the impaired host response as in the case of smokers,

or due to the higher severity of disease observed in patients with diabetes mellitus[3,13]. For this reason, other treatments, such as the administration of systemic antibiotics have been proposed in association with SRP, with the goal of potentiating the effects of this therapy.

In spite of the clinical relevance and effective use of systemic antibiotics in the treatment of various infectious diseases, clinical studies on the effects of these agents in the treatment of periodontal diseases only began in the 1970s[25]. Over the course of the last few decades, antibiotics have been widely studied as adjuvants to mechanical periodontal therapy and several clinical studies have shown additional benefits with the use of these agents[5,10,12]. However, it is important to highlight that antibiotics are biologically active substances that can lead to side effects of various intensities and their indiscriminate use might lead to the increase in the pool of bacterial species tolerant to the antibiotics[4]. In the light of this knowledge, it is important to highlight that the decision of whether or not to use these agents to treat periodontitis should follow the same principle used for the treatment of any other infection in the body, which is: the risks need to be clearly offset by benefits to the patient. The only way to determine this risk/benefit ratio is by evaluating the results of well-conducted randomized clinical trials (RCTs).

Recent RCTs and systematic reviews have suggested that the combination of metronidazole (MTZ) and amoxicillin (AMX) are effective for the treatment of aggressive periodontitis[17,18,24] and chronic periodontitis[2,6,8,23,29]. However, although a notable therapeutic advantage has been shown when MTZ+AMX are used in periodontal therapy, some questions relative to the protocol for the use of these medications remain obscure, such as: "which would be the best phase of the non-surgical periodontal therapy treatment for the administration of antibiotics?".

In clinical practice, the decision to use antibiotics is commonly taken after the healing phase of the mechanical treatment, which may vary from 2 to 5 months[9] post-SRP. However, some biologic concepts suggest that the effects of antibiotics could be potentiated if they were used during the active phase of treatment[5]. Apparently, a rapid and more profound reduction of the subgingival microbial load may lead to a more beneficial recolonization of the recently scaled pockets in the long term. Lighter and sequential disturbances of the biofilm may not be sufficient to change the highly stable climax community of biofilm[26,27]. Therefore, since there is no consensus in the literature about the ideal time for the administration of these agents, a systematic review of the literature could help with taking the correct clinical decision and could guide future studies on this topic.

MATERIAL AND METHODS

This systematic review was conducted in accordance with the recommendations of PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analysis)[20].

Focused question

"At which phase of non-surgical periodontal therapy would systemic antibiotics promote the best clinical results, including reduction in probing depth (PD) and gain in clinical attachment level (CAL): during the active phase or after the healing phase of mechanical therapy?"

Inclusion criteria

In order to be included in the sample, the papers had to be: RCTs with at least two groups, one test (systemic antibiotic used in the active phase of mechanical treatment) and one control (systemic antibiotic used after the healing phase of the mechanical therapy) group; studies that included individuals with chronic or aggressive periodontitis; and studies that evaluated PD and CAL.

	Terms used	Number of studies
	periodontitis OR periodontal infection OR chronic periodontitis OR aggressive periodontitis OR periodontal disease	79,029
And	"periodontal disease" OR "periodontitis" OR "alveolar bone loss" OR "oral conditions" OR "tooth diseases" OR "anti-bacterial agents" OR "anti-bacterial" OR "anti-bacterial agents" OR "antibiotics" OR "anti-bacterial agents" AND "OR "anti-infective agents" OR"anti-infective" AND "agents" OR "anti-infective agents" OR "antimicrobials" OR "anti-infective agents" AND "OR "systemic AND "anti-infective agents" OR "anti-infective" AND "agents" OR "anti-infective agents" OR "antimicrobials" OR "anti-infective agents" AND "OR "AND systemic AND "anti-infective agents" OR "anti-infective" AND "agents" OR "anti-infective agents" OR "antimicrobial"	1,039

Figure 1- Descriptors, free terms and key words used in the search strategy

Exclusion criteria

Studies published in languages other than Portuguese, English and Spanish, reviews of the literature, and studies that used antibiotics in subantimicrobial doses were excluded from the sample.

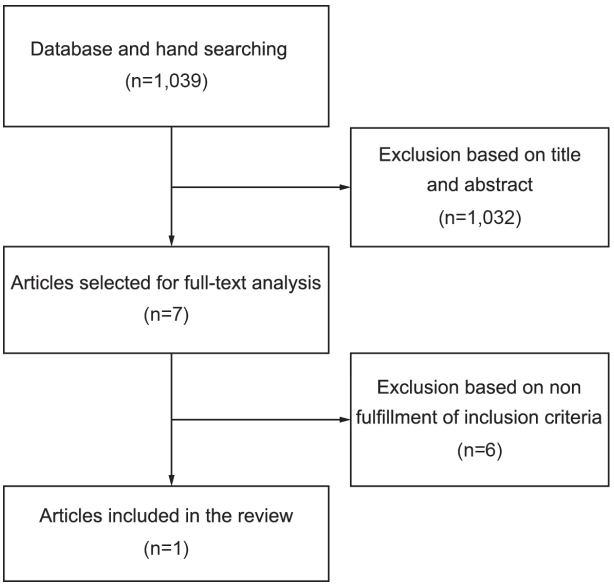

Figure 2- Flow chart of the search strategy

Evaluation variables

Changes in full-mouth mean PD and CAL, as well as changes in mean PD and CAL in different categories of pockets.

Search strategy

The EMBASE, MEDLINE and Cochrane Central Register of Controlled Trials (CENTRAL) were searched up to November 2013 by two researchers (ARFS e CG), using the search strategy described in Figure 1. A manual search of the reference list of selected studies and of review articles about the topic was also performed. Studies were selected by the two researchers in an independent manner, and any disagreement was resolved by a third researcher (MFe).

Data extraction

Studies that fulfilled the inclusion and exclusion criteria were submitted to data extraction by one of the researchers (ARFS). The following items of

Study	Study Design	Sample	Intervention	Follow-up	Results	Conclusion
Griffiths, et al.[9] (2011)	RCT	Group A n=20 5 smokers 16 females GAgP	Group A FMRSD+AMX 500 mg+MTZ 500 mg (TID for 7 days) starting right after the completion of SRP+CHX 0.2% for two weeks	8 months after SRP (2 months post-antibiotic intake in Group B)	Group A: showed greater reduction in mean PD and gain in CAL in initially deep sites (with PD≥7 mm) than Group B. Difference between groups of 0.9 mm (PD reduction) and 0.7 mm (CAL gain) (p<0.05).	Subjects who received MTZ+AMX at the initial therapy showed statistically significant additional benefits compared with those who received the same antibiotic regimen after the healing phase.
		Group B n=21 4 smokers 12 females GAgP	Group B FMRSD+AMX 500 mg+MTZ 500 mg (TID for 7 days) starting 6 months after the completion of SRP+CHX 0.2% for two weeks		The percentage of sites converting from PD≥5 mm to ≤4 mm was 83% in Group A and 67% in Group B (p=0.041)	

RCT: randomized clinical trial; GAgP: generalized aggressive periodontitis; FMRSD: full mouth root surface debridement; AMX: amoxicillin; MTZ: metronidazole; TID: three times a day; SRP: scaling and root planning; PD: probing depth; CAL: clinical attachment level; CHX: chlorhexidine

Figure 3- Description of the analyzed study

information were collected and recorded on a piloted form: 1) place where the research was conducted – country and environment in which the patients were treated (private clinic or hospital/university clinics); 2) randomization method; 3) sample characteristics – sample size, age, gender, local and systemic health conditions, characteristics of the interventions performed, statistical significance; 4) clinical results; 5) conflict of interest; 6) funding.

RESULTS

The flow diagram of this study is represented in Figure 2. In the electronic search, 1039 studies were identified. After reading the titles and abstracts, 1032 studies were excluded, and 7 were selected. No article was identified in the manual search. After reading the full text of the 7 selected studies, 6 were excluded[1,2,11,15,21,28] because they did not directly compare the moment of administration of the systemic antibiotics in the treatment of periodontitis. Therefore, only 1 study[9] was included in this review. In this study, the authors compared the clinical efficacy of MTZ+AMX administered in the active phase of periodontal treatment, i.e., together with the SRP procedure (initial antibiotic therapy – Group A, n=20) or after the healing phase, i.e., 6 months after the completion of the SRP (antibiotic after healing – Group B, n=21). All subjects received periodontal maintenance scaling at 6 months. Clinical parameters were registered at 2 months after the treatment of Group B with antibiotics (i.e., 8 months after treatment of group A/Baseline). The data showed that subjects taking antibiotics at the initial phase of treatment exhibited statistically significant greater reduction in pocket depth and gain in clinical attachment level in initially deep sites (PD≥7 mm) than subjects taking antibiotics at re-assessment (difference between groups of 0.9 mm and 0.7 mm, respectively). In addition, the percentage of sites converting from PD≥5 mm to ≤4 mm was 83% in Group A and 67% in Group B (p=0.041) (Figure 3).

DISCUSSION

The results of this systematic review demonstrated that up until today, only one study in the literature compared the effects of systemic antibiotics administered in different phases of mechanical therapy. This study, published by Griffiths, et al.[9] (2011), suggested there were greater clinical benefits when MTZ+AMX were prescribed during the active phase of periodontal therapy than after the healing phase. Individuals treated with antibiotics together with SRP in the initial phase of treatment, showed greater reduction in PD and greater gain in CAL in deep pockets than individuals treated with antibiotics 6 months after SRP. It is worth pointing out that this study presents some limitations, for example, the fact of not having used placebo and having had a short longitudinal evaluation time (the comparison between the two groups was conducted at 2 months post-antibiotic intake at the healing phase). The use of placebo allows blinding of the study, which is one of the criteria that define the high quality of a RCT[20]. In addition, a longer follow-up period would be important in order to establish whether or not these results would be maintained over the course of time.

Apart from the study included in this review, Kaner, et al.[14] (2007) conducted a retrospective evaluation of individuals with generalized aggressive periodontitis treated with SRP+MTZ+AMX administered immediately or 3 months after mechanical treatment, and observed that the time of administration of the antibiotics influenced the clinical response. Three months after the second group had taken the antibiotics, the group treated in the active phase of therapy obtained statistically significantly higher reductions in the mean PD (4.09 mm) and relative gain in CAL (2.50 mm) in deep sites (with PD>6 mm) in comparison with the group that took MTZ+AMX at the time of re-evaluation (2.80 mm and 1.41 mm, respectively) (p<0.05).

The results of the studies of Griffiths, et al.[9] (2011) and Kaner, et al.[14] (2007) suggest a benefit for the administration of MTZ+AMX in the active phase of mechanical treatment. These results suggest that the systemic antibiotics administered together with the mechanical treatment in the initial phase of therapy has a greater potential to change the pathogenic bacterial community to a community compatible with periodontal health in the short term. This statement is in agreement with the concept that a rapid and striking reduction in the subgingival microbiota would be necessary in order to obtain more beneficial and stable recolonization over time in the recently scaled pockets[26,27]. The biofilm structure, especially the mature biofilm found in the subgingival pockets of individuals with periodontitis, presents resilience, meaning that they tend to go back to their original structure (i.e., a composition observed in disease, with high proportions of pathogens and low proportions of beneficial species). Therefore, intense treatments applied at once, such as the association of SRP and antibiotics during the initial therapy, might have greater potential to create an entirely new and stable biofilm community, similar to that observed in healthy individuals[5]. In addition, a hypothesis related to the high degree of inflammation observed in non-treated periodontal patients may also help to explain the greater clinical benefit observed in the individuals who took antibiotics in the initial phase of treatment[7,14]. In the presence of an

intense inflammatory process, there are higher levels of gingival fluid; therefore, higher levels of antibiotic are also released into the subgingival environment[7,14]. In addition, inflammation is also associated with great capillary permeability, which may contribute to better absorption of these agents[7,14].

Implications for research and clinical practice

In daily clinical practice, periodontists tend to postpone the administration of antibiotics to the re-assessment phase, rather than as part of the initial treatment. An evidence-based appraisal of current literature presented in this manuscript showed that, to date, only one short-term RCT has directly compared different moments of systemic antibiotics administration as adjuncts to SRP in the treatment of periodontitis. Although the results of this study suggested some benefits for antibiotics intake during the active phase of therapy, these findings need to be confirmed by larger placebo-controlled randomized clinical trials with longer follow-up periods. This information could help clinicians with their decision-making in the daily practice.

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