# AMOXICILLIN/METRONIDAZOLE OR SCALING AND ROOT PLANING IN THE TREATMENT OF CHRONIC PERIODONTITIS

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***ABSTRACT***

*The aim of the present study was to evaluate the treatment with amoxicillin or metronidazole in comparison to scaling and root planing in the treatment of chronic periodontitis. Randomised clinical trials were searched in the databases MEDLINE, EMBASE, SciELO, Cochrane and Scopus from 1989 to 2010. The search started with 2895 articles.. From this initial number of articles, 10 publications were selected and included in the study according to fixed criteria. Studies included adult patients of both sexes aged between 21 and 80, diagnosed with chronic periodontitis and treated with amoxicillin and/or metronidazole or scaling and root planning. From each article, details were abstracted relating to sample size, design, sex, age, oral hygiene habits, the exposure to drug (doses, schedule), and results such as clinical effect, analysis methods, stratification variables. Conclusion: this meta-analysis showed absence of statistically significant difference between the effects studied.*

*Key words: chronic periodontitis, antimicrobial agents, Meta-Analysis.*

## AMOXICILINA/METRONIDAZOL O RASPADO Y ALISADO RADICULAR EN EL TRATAMIENTO DE LA PERIODONTITIS CRÓNICA

***RESUMEN***

*El objetivo del presente estudio fue evaluar el tratamiento con amoxicilina o metronidazol en comparación con el raspado y alisado radicular en el tratamiento de la periodontitis crónica. Ensayos clínicos aleatorios se seleccionaron de las bases de datos MEDLINE, EMBASE, Scielo, Cochrane, y Scopus desde el año 1989 a 2010. La búsqueda comenzó con 2895 artículos. A partir de este número inicial de artículos, 10 publicaciones fueron seleccionadas e incluidas en el estudio de acuerdo a los criterios fijados. Los estudios incluyeron pacientes adultos de ambos sexos, con edades entre 21 y 80 años, diagnosticados con enfermedad periodontal crónica y tratados con amoxicilina y/o metronidazol o raspaje y alisado radicular. De cada artículo se extrajo el tamaño muestral, diseño, género y edad, hábitos de higiene oral, medicación (dosis y esquema), resultado clínico, método de análisis y variables de estratificación. Conclusión: este meta-análisis mostró ausencia de significación estadística entre los efectos estudiados.*

*Palabras clave: periodontitis crónica, agentes antimicrobianos, Meta-Análisis.*

## INTRODUCTION

Periodontitis is known to be very common among the most deprived populations, especially among certain ethnic groups. In the latest WHO document, rules were agreed upon regarding equity and determinants of health, among which professional dental care is a major component for achieving and maintaining oral health[1]. Nevertheless, in Latin American countries, the availability of oral health services is poor in many communities that are vulnerable from a socio-economic standpoint[2].

Chronic periodontitis is a multifactorial disease, caused by dental biofilm and other local and systemic factors. Adults generally suffer from chronic periodontitis associated to the presence of calculus, plaque, gingival inflammation, probing depth and clinical attachment level loss. In some cases the disease develops slowly. Factors such as tobacco, stress and systemic diseases have been described in relation to this pathology[3].

In clinical practice, it is well known that periodontal disease is mainly produced by bacteria, which is why the control of pathogenic microorganisms is essential for its therapy[4]. The goal of anti-infection therapy is to reduce the level of pathogenic microorganisms and maintain or strengthen the levels of beneficial species. The traditional therapies used in the clinical practice of periodontics, such as scaling and root planing together with gingival hygiene are not enough to heal periodontitis in a short time in a significant number of patients. One explanation for this is the complexity of the technique and the frequency of its application[5].

Severe periodontitis is usually treated with antimicrobials such as tetracycline, minocycline or metronidazole[6]. However, chronic periodontitis is not usually treated with antimicrobials, although nowadays there are studies that report improvements by combining scaling and root planing with antimicrobial agents[7].

Published papers present conflicting results about antimicrobial therapy in chronic periodontitis, which is why it is necessary to determine the evidence on this issue.

The *aim* of this work was to evaluate amoxicillin and/or metronidazole versus the application of scaling and root planing (SRP) to improve results in the therapy of chronic periodontitis.

## DATA SOURCES

This study was done according to the reporting items for systematic reviews and meta-analyses PRISMA guidelines[8]. We conducted a meta-analysis of studies of randomized clinical trials (RCT) from the MEDLINE, EMBASE, Scielo, Cochrane and Scopus databases, between January 1989 and January 2010, in order to provide evidence of the application of antimicrobials in chronic periodontitis treatment.

## STUDY SELECTION

The search was started with 2895 articles from PubMed, EMBASE, Cochrane, Scopus and Scielo databases. Those authors that did not clearly establish inclusion criteria for the patients, or in which pharmaceutical forms were different from other studies, were discarded (Fig 1).

When analyzing the main requirements for selecting the papers, we observed differences in answers related to design and form of result presentation. The most important result of the studies included is a great reduction in PD and improved BOP when antimicrobial -amoxicillin and metronidazole- therapy is used in comparison to control groups.

### Data extraction and quality assessment

From each article, details were abstracted relating to sample size, design, sex, age, oral hygiene habits,

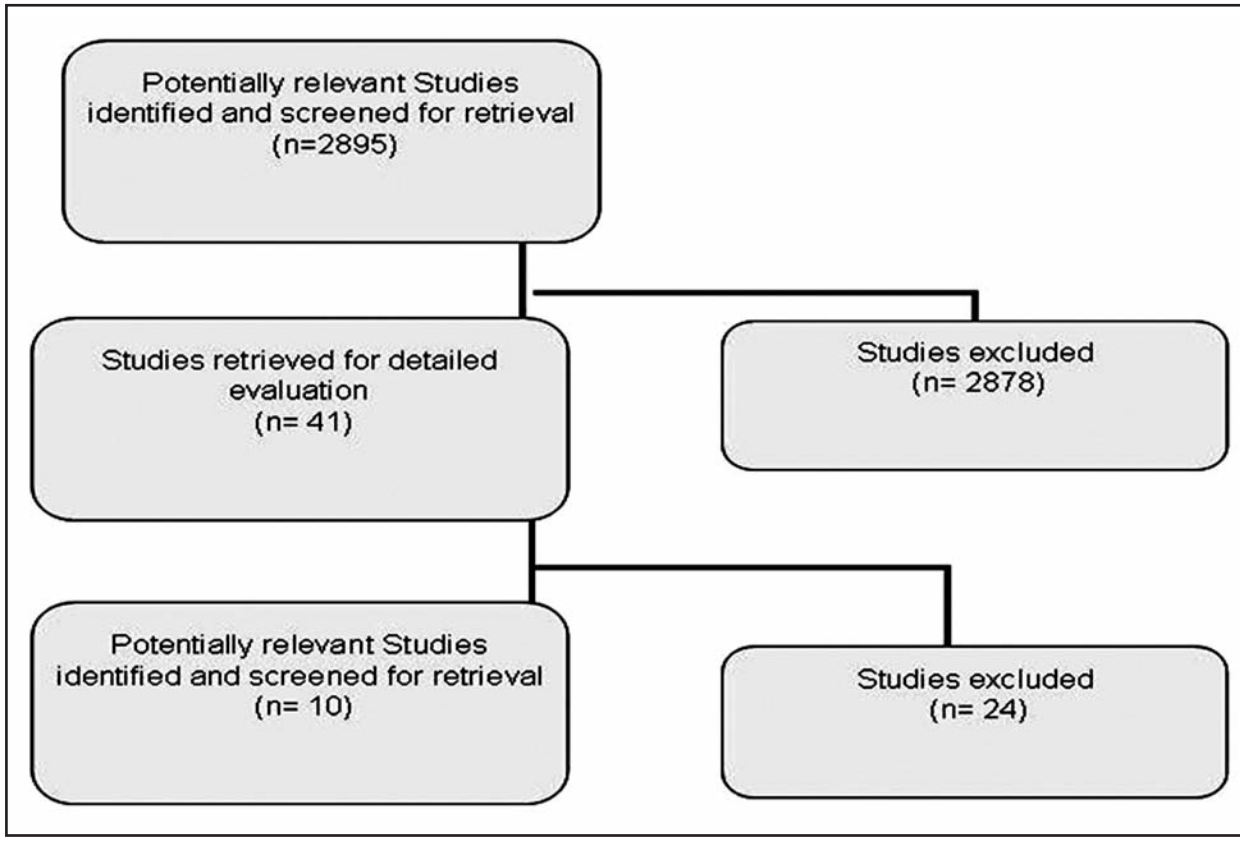


*Fig. 1:Study flowchart to select articles according to fixed criteria.*

**Table 1: Characteristics of studies included in this meta-analysis.**

| Authors/year | Characteristics of studies included | |
|---|---|---|
| Carvalho et al. 2004[25] | Place | Brazil |
| | Time | 90 days |
| | Doses | 400 mg metronidazole, three times daily for 10 days |
| | Design | RCT |
| | Participants | 44 patients |
| | Age range | 45± 6 years |
| Feres et al., 2001[26] | Place | USA |
| | Time | 360 days |
| | Doses | 500 mg amoxicillin in combination with 250 mg metronidazole for 14 days |
| | Design | RCT |
| | Participants | 17 patients |
| | Age range | Adults, 20 years |
| Feres et al., 2002[15] | Place | USA |
| | Time | 90 days |
| | Doses | amoxicillin 500mg, three times daily for 14 days or metronidazole 250mg, three times daily for 14 days |
| | Design | RCT |
| | Participants | 20 patients |
| | Age range | Adults, 20 years |
| López et al. 2000[27] | Place | Chile |
| | Time | 12 months |
| | Doses | 400 mg of metronidazole three times a day for 10 days. |
| | Design | RCT |
| | Participants | 46 patients |
| | Age range | 36 to 68 years |
| Knöfler et al., 2007[18] | Place | Germany |
| | Time | 12 months |
| | Doses | Not mentioned |
| | Design | RCT |
| | Participants | 37 patients |
| | Age range | 37 to 65 years |
| Vergani et al., 2004[16] | Place | Brazil |
| | Time | 90 days |
| | Doses | 250 mg metronidazole three times a day for 10 days |
| | Design | RCT |
| | Participants | 20 patients |
| | Age range | 29 to 63 years |
| Carvalho et al. 2005[28] | Place | Brazil |
| | Time | 90 days |
| | Doses | 400 mg metronidazole, three times a day for 10 days |
| | Design | RCT |
| | Participants | 44 patients |
| | Age range | 45 ± 6 years |
| Cionca et al. 2009[7] | Place | Switzerland |
| | Time | 6 months |
| | Doses | Metronidazole 500 mg, amoxicilin 375 mg three times a day for 7 days |
| | Design | RCT |
| | Participants | 51 patients |
| | Age range | Not mentioned |

**Table 1: Cont.**

| Authors/year | Characteristics of studies included | |
|---|---|---|
| Haffajee et al., 2008[17] | Place | USA |
| | Time | 12 months |
| | Doses | Metronidazole 250 mg three times daily for 14 days |
| | Design | RCT |
| | Participants | 92 patients |
| | Age range | Adults 20 years |
| Moeintaghavi et al., 2007[10] | Place | Iran |
| | Time | Six to eight weeks |
| | Doses | 500 mg amoxicillin in combination with 250 mg, metronidazole every eight hours for the following seven days |
| | Design | RCT |
| | Participants | 50 patients |
| | Age range | 34.42 ± 8.23 years |

RCT: randomized controlled trial; *All adjusted for oral hygiene.

the drug treatment (doses, schedule), and results such as clinical effect, analysis methods, stratification variables.

All studies included adult patients of both sexes aged between 21 and 80 years, diagnosed with chronic disease according to the international classification criteria of periodontal disease[9] and treated with amoxicillin and/or metronidazole or scaling and root planing. They are designed as RCT studies with suitably matched controls, and sample sizes from 10 to 90 subjects. Furthermore, the studies measured common clinical parameters such as bleeding on probing (BOP), plaque, probing depth (PD), and periodontal attachment level (AL). The selected studies excluded patients with systemic diseases or with syndromes, pregnant women and with indication of other medicine.

To evaluate the quality of the papers, data collection was performed by two reviewers independently (Dr. G. Bono, Pernambuco University, Brazil and Mauricio Kremer, Córdoba National University, Argentina), assessing studies for inclusion in duplicate. The papers were encoded and delivered independently to each reviewer. To accept/reject articles selected by the reviewers, the Kappa coefficient estimated by the Monte Carlo method was applied, setting a value > 0.8.

A search was made of combined electronic databases, and manual searches were performed of journals and published doctoral theses. Furthermore, the bibliography of all selected papers was searched to identify grey literature. Results were expressed as average ± standard deviation.

## RESULTS

All studies correspond to Randomized Clinical Trial design (RCT) and their characteristics are shown in Table 1. A few limitations of this study are evident, such as the sample size and the protocol scheme. The studies do not have identical indications regarding doses or time of intake of metronidazole and amoxicillin for treating periodontitis. The time varies between 7 and 14 days with the drug taken three times daily. The main doses are: metronidazole 250 mg and amoxicillin 500 mg.

The meta-analysis was performed by standardised means differences and the total effect was estimated by random effect model using the software R version 2.9.0 (www.r-project.org), package *meta,* using the function *metacont.*

PB showed a value $I^2 = 95\%$, the greatest effect is obtained with the study Mointaghavi[10], SMD -4.2160 [-4.9295, -3.5025] IC 95% (Fig 2). For AL there was high heterogeneity, $I^2 = 81.6\%$, with a total effect value of 0.45 (Fig 3), and BOP showed $I^2 = 97\%$, with a total SMD -1.053 (Fig 2). In relation to plaque index, the value for $I^2$ was 0%, showing a null effect of treatment, the greatest effect was obtained in the test Feres, 2001 with an SMD of 0.5 (Fig 3).

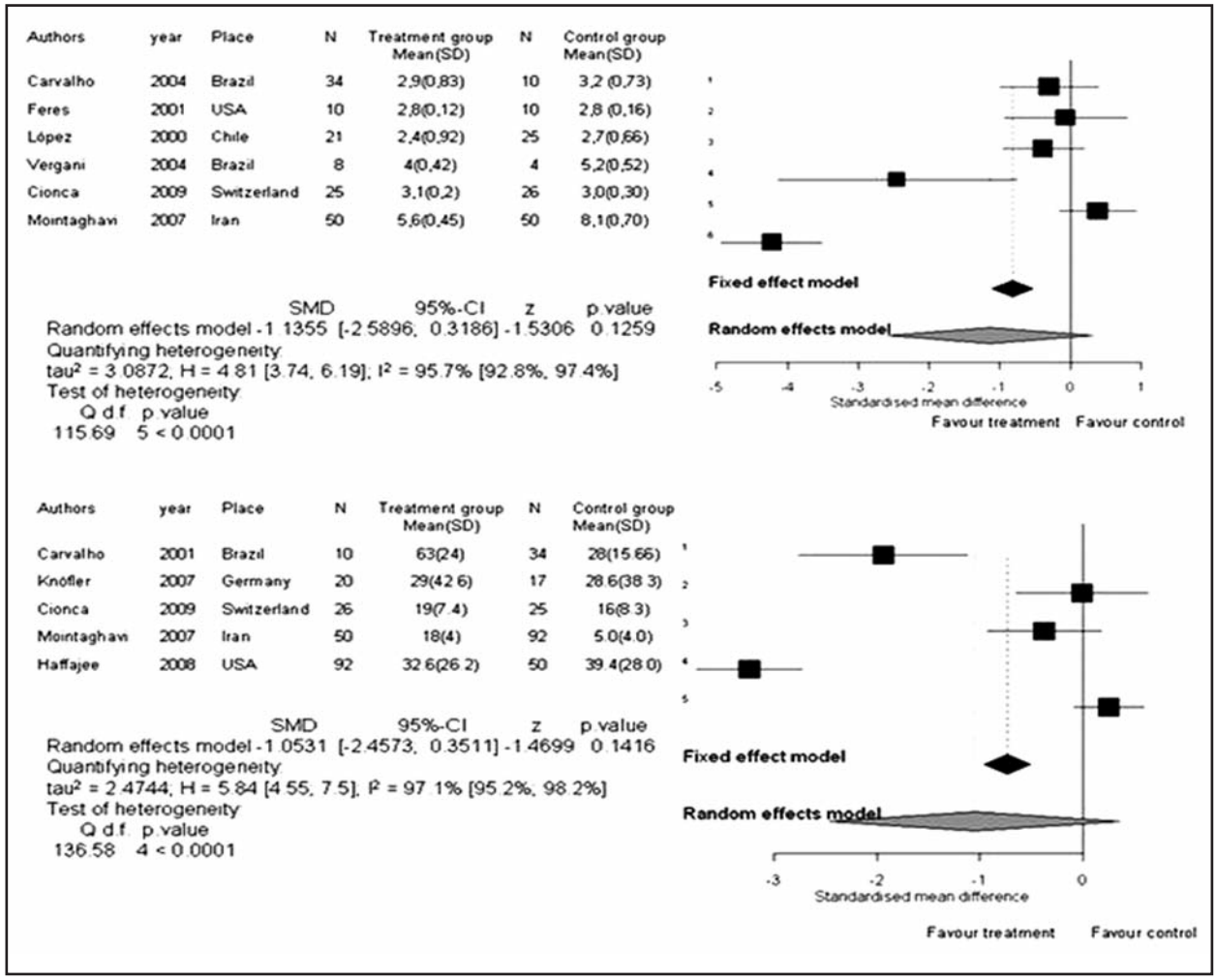


*Fig. 2: Effect of antimicrobial treatment vs SRP therapy, probing depth outcomes (top). Effect of antimicrobial treatment vs SRP therapy, bleeding on probing outcomes (bottom).*

## DISCUSSION

Periodontal disease is one of main oral health issues, because it is the most prevalent oral pathology in several countries[1]. It is therefore important to evaluate alternative ways of attaining therapeutic options that will allow faster and more effective resolution than conventional therapies.

The treatment of periodontal disease includes SRP therapy to reduce dental biofilm. However, studies on lipopolysaccharide (endotoxin) report that it can induce activation of macrophages to secrete lysosomal enzymes, oxygen radicals, chemokines, cytokines and prostaglandin E-2 (PGE-2), which contribute to inflammation and bone resorption[11-12]. The host response may be normal or pathological. In the latter case it may be due to a hyper-specific response involving T- and B- lymphocytes and production of neutralizing antibodies or not. Both the effect of bacteria and pathological host response determine destructive phenomena in periodontal tissues and the formation of pockets. This might promote a low redox potential and allow the growth of anaerobic microorganisms[13]. The results of this meta-analysis showed that the application of antimicrobials produces a remission of some of the clinical parameters in less time, without costly and aggressive interventions.

Cionca et al. 2009[7] suggested that scaling and root planing and full-mouth disinfection may reduce the need for supplementary therapies. They observed no difference in clinical parameters before treatment, but a significantly lower mean PD and BOP, which suggested the need for additional treatment. On the other hand, 6 months after treatment plus antibiotics, the average probing depth was significantly lower

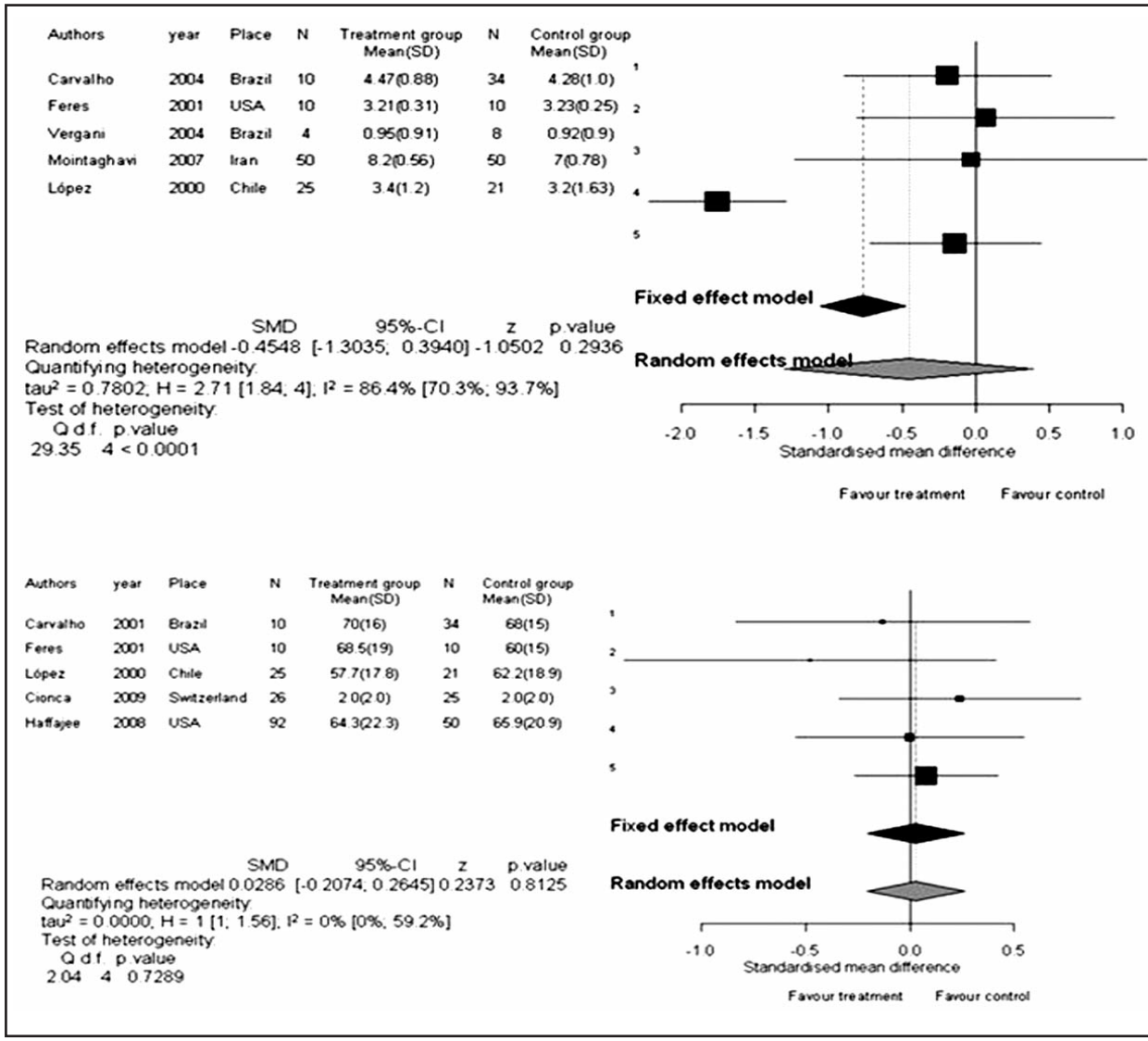


*Fig. 3: Effect of antimicrobial treatment vs SRP therapy, periodontal attachment level outcomes (top). Effect of antimicrobial treatment vs SRP therapy, plaque outcomes (bottom)*

in the problem group than in the control group. The conclusion of this research is that treatment with systemic metronidazole and amoxicillin significantly improved the 6-month clinical outcomes.

In addition, Matarazzo et al. 2008[14] showed the greatest improvements in probing depth and clinical attachment level in subjects receiving the two antibiotics together in comparison to the subjects treated with SRP alone. The investigation further showed significant reductions in the average counts and proportions of periodontal pathogens. Feres et al, 2002[15], concluded that metronidazole and amoxicillin are useful antibiotics because they rapidly diminish counts of putative periodontal pathogens, but must be accompanied by other procedures to bring about periodontal stability. On the other hand, authors such as Vergani Alonso et al. 2004[16] believe that it is not necessary to prescribe metronidazole in chronic periodontitis therapy. Haffajee et al. 2008[17] conclude that the therapy did not appear to create lasting changes in the percentage of resistant isolates or sites harboring resistant species. The SRP protocol is variable in the different times of the studies that enable chronic periodontitis to be resolved.

There is clear evidence in these studies that antibiotics significantly reduced clinical attachment level and probing depth in patients; however, there are not many studies available for comparison, thus limiting

general conclusions on the clinical benefit of the application of antibiotics. The treatment time was between 1 and 12 months. Systemic administration of metronidazole and amoxicillin, usually in conjunction with SRP allows beneficial changes in the composition of the subgingival microbiota by reducing pathogens and enables the growth of species compatible with the host. Furthermore, the combination of these drugs with a strict control of supragingival plaque during treatment of chronic periodontitis shows very promising results for treating it[7].

The PD observed in other studies showed a decrease in the group of patients treated with antimicrobials, which would indicate a reduction of inflammation[18-19]. In regard to AL, this meta-analysis showed high heterogeneity among the studies. Evaluation of the formation of a new insertion requires a histological analysis, and thus an increase in probing attachment level after therapy does not necessarily mean that there has been a real increase in the insertion of connective tissue. It is probably due to improved health of the surrounding soft tissues that provide greater resistance to penetration of the probe[20]. The BOP decreased slightly in patients treated with antimicrobials which would indicate that sites with active disease decreased more than in controls (SRP). Recent studies on oral biofilm have shown that there are bacterial associations that have an impact on clinical parameters such as BOP[21]. The IP decreased in both treatments, leading to the disappearance of clinical signs of inflammation. Authors such as Van Dyke et al. 2008[22], remarked that the inflammatory response in periodontitis without a proper resolution is the cause of greater tissue destruction.

In contrast Cobb, 2008[19] believes that the nature and magnitude of the host response that occurs in periodontal disease has an impact on the severity and rate of progression of disease and that the traditional treatment of SRP remains the "gold standard" technique for therapy of this disease, but this treatment has a high probability of relapse in the periodontal pocket. The new PD infection is due to a dental biofilm composition by tolerant microorganism residues, for which the maximum effect is achieved with the combination of SRP and locally applied antimicrobial.

In relation to geographical particularities of chronic periodontitis, this meta-analysis was conducted using data from different parts of the world such as Chile, Brazil, United States, Switzerland and Iran. In general there were no differences between the geographic data. However, it is not feasible to compare the prevalence of periodontal disease around the world, and it varies with the genetics of each person. The quality of available data from developing and developed countries is not comparable, it is expected that future epidemiological investigations will elucidate this issue by appropriate and accurate methodology. Conditions of poor oral health may be due to a number of factors such as socioeconomic status and educational level, which differ between countries and within countries. These different social positions, medical conditions, jobs and economic situations and other personal situations have an impact on general and oral health, being stronger in disadvantaged communities in under-industrialized countries, who have limited resources to protect themselves[23]. Hence it is important to evaluate alternative ways of achieving therapeutic options that allow faster and more effective resolution than conventional ones.

When the main requirements for the selection of items were analyzed, differences were found in items related to study design and presentation of results. Most of the studies included in this meta-analysis reported results of PB and BOP reduction when antimicrobials were used for the treatment of chronic periodontitis.

One limitation of this study is the sample size of the studies included, and patterns of antimicrobial management protocol. The heterogeneity of the meta-analysis is attributed to variability in participants, interventions and presentation of the outcomes (clinical heterogeneity), as well to the variability in study design and bias risk, which can be described as methodological heterogeneity[24]. Some of these components were observed in our study. The limitations of this study corresponded to the size of the sample and outline protocol. The studies do not contain identical information on the dose or time of intake of metronidazole and amoxicillin for the treatment of periodontitis.

Nevertheless, oral health depends on many determinants, including socioeconomic status, educational level, health systems, among others, to improve clinical outcomes reach of traditional treatment, especially considering the use of medication and/or with SRP therapy as a therapeutic strategy for the resolution of chronic periodontitis.

## CONCLUSION

In conclusion, the result of this meta-analysis showed absence of statistically significant difference between the effects studied.

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