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Original Article

Comparison the Effect of Ciprofloxacin Versus Amoxicillin and Metronidazole as an Adjunctive Therapy to Full Mouth Scaling and Root Planing of Chronic Periodontitis

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Abstract

Background: So many people worldwide have chronic periodontitis. Chemotherapeutic agents can reduce host responses to bacterial pathogens and as a result reduce bone loss.

Objectives: The aim of this study was to compare the effect of antibiotics such as amoxicillin and metronidazole (AMX+MTZ) with ciprofloxacin (CPF) as an adjunct to scaling and root planing (SRP) in pocket depth (PD) and clinical attachment loss (CAL) in patients with moderate to severe chronic periodontitis.

Methods: In this randomized double-blinded placebo-controlled clinical trials, 45 patients with chronic moderate to severe periodontitis were randomly divided into 3 groups: the control group which received SRP plus placebo, the test 1 group which received SRP plus AMX+MTZ, and the test 2 group which received SRP plus CPF. PD and CAL were measured in each group at 3 time points (baseline, 1 month and 3 months after SRP). Statistical analysis was done using a paired t test and ANOVA.

Results: Mean PD and CAL in the test groups were compared to the control group and no significant changes were found ($P<0.05$). Most changes in PD and CAL were seen at one month after intervention. Better outcomes were seen in the test groups (test 2 better than test 1).

Conclusions: AMX+MTZ or CPF as an adjunct to SRP had better outcomes but did not have any significant impact on reducing PD and CAL over one 1 and 3 months after treatment in patients with chronic periodontitis.

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Background

So many people worldwide have chronic periodontitis which can cause tooth loss. Chronic periodontitis is an inflammatory disease of supportive dental tissues whose progress rate is slow to moderate. Specific microorganisms cause chronic periodontitis which results in advanced periodontal ligament destruction and bone loss with pocket formation or gingival recession or both of them. Chemotherapeutic agents can reduce host responses to bacterial pathogens and as a result reduce bone loss (1,2).

Bacteria cause an increase in pocket depth (PD) and attachment loss (3-5). They invade periodontal tissues, so mechanical therapies are not sufficient and systemic antibiotic therapies are used (6-8). Amoxicillin (AMX) is effective on gram positive and negative bacteria, while metronidazole (MTZ) is effective only on gram negative bacteria. The use of systemic antibiotics as a necessary adjunct in controlling bacterial infection was reported in previous studies (5,9-13).

Nowadays, it is proved that different kinds of periodontal diseases are associated with bacterial infection. Bacteria construct a complex and organized biofilm in periodontal pocket. As this biofilm spreads to deeper parts of gingiva, the ordinary oral hygiene becomes more difficult (3,14).

Thus, it is reasonable to omit local factors by mechanical therapy and subgingival biofilm. Mechanical therapy includes scaling and root planing (SRP). Anti-infective therapy of antibiotics can be systemic or local (3).

MTZ is not the drug of choice for the treatment of infections caused by *Actinobacillus actinomycetemcomitans* (Aa), but it is effective because of its hydroxy metabolite. But MTZ in combination with other antibiotics can be

Highlights

- Use of AMX+MTZ or CPF as an adjunct to SRP has better outcomes but no significant impact on reducing PD and CAL was observed over 1 and 3 months after treatment in patients with chronic periodontitis.
- Better treatment outcomes were achieved in the CPF group.
- CPF therapy is better than the combination therapy for patients' compliance.

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effective against Aa (1,2).

MTZ is also effective against anaerobic bacteria such as *Porphyromonas gingivalis* (PG) and *Prevotella intermedia* (15).

AMX is a semi-synthetic penicillin with a wide range of actions against gram positive and negative bacteria. It is not resistant against β-lactamase (16).

Ciprofloxacin (CPF) is a second-generation fluoroquinolone antibiotic. Its spectrum of activity includes most strains of bacteria such as gram negative rods in periodontal disease. Polymorphonuclears leukocytes (PMN) act as the reservoir of CPF, so they cause an increase in the delivery of CPF to inflamed sites (1).

The combination of AMX+MTZ has been used as an adjunctive therapy for periodontal disease treatment and according to some studies it has benefits in treatment (17-20). Considering side effects these drugs especially MTZ and patient compliance, we suggest CPF as an adjunct therapy. CPF is usually used in combination with MTZ, but considering its range of action and drug-resistant bacteria against commonly used AMX+MTZ, we used it as a monotherapy.

Objectives

The aim of this study was to compare the effect of antibiotics; AMX+MTZ with CPF as an adjunct to SRP in PD and clinical attachment loss (CAL) in patients with moderate to severe chronic periodontitis.

Methods

In this randomized double-blinded placebo-controlled clinical trial, 45 patients were enrolled (27 female and 18 male). All of them referred to the Department of Periodontics, Faculty of Dentistry in Hamadan during 2013-2014.

Moderate to severe chronic periodontitis was diagnosed in the selected patients, their disease was diagnosed by a periodontist after clinical examinations. The patients' age was ranged from 25 to 70.

The study procedure was explained to all of them and the informed consent was signed. Patients who had the following conditions participated in the study:

Being systemically healthy; having at least 12 teeth (without orthodontic appliances, implant, fixed partial dentures, crown, third molar); moderate to severe chronic periodontitis with mean clinical attachment level greater than 3 (CAL > 3); having at least 4 teeth with probing depth greater than four (PD > 4) and positive bleeding on probing (BOP); having radiographic view of bone loss.

The patients who did not meet the following criteria were excluded from the study:

Systemic antibiotic and nonsteroidal anti-inflammatory drugs (NSAIDs) usage in the last 2 months; SRP or periodontal surgery in the last year; pregnancy, lactating, smoking, allergy to AMX, MTZ or CPF.

PD and CAL were measured (Williams periodontal probe) at the baseline in all the patients (all by one clinician). PD and CAL were measured at six sites per tooth (mesiobuccal, buccal, distobuccal, distolingual, lingual and mesiolingual) in all teeth, excluding third molars. PD and CAL measurements were recorded to the nearest millimeter.

Then SRP was performed by one clinician using ultrasonic scalers. All subjects received oral hygiene instructions (OHI).

Patients were randomly divided into 3 groups, 15 patients were included in each group (one control and two test groups).

The control group only received OHI and SRP+ placebo, while test groups received antibiotic in addition to those. In test 1 group, patients were given 500 mg AMX+ 250 mg MTZ tid (3 times a day) for 1 week as an adjunctive therapy to SRP. Test 2 group received 500 mg CPF bid (twice a day) for 1 week after SRP.

PD and CAL were measured in each group at baseline, 1 month and 3 months. We considered PD as the primary outcome variable and CAL as secondary.

We asked all the patients to inform us of any unusual condition or adverse events. PD and CAL changes were compared between 3 groups at baseline.

Statistical analysis was done using a paired *t* test and ANOVA. SPSS version 20.0 was used for analysis.

Results

Forty-five patients participated in this study. All of them completed the study protocol (one month and three months after SRP). Thus, a total of 45 subjects completed the study, 15 in the control group (SRP+ placebo), 15 in the test 1 group (SRP+AMX+MTZ), and 15 in the test 2 group (SRP + CPF). The flow chart of the study is shown in Figure 1.

Overall, adverse events were reported by three subjects in the study, two in the test 1 and one in test 2 group. The adverse effects were diarrhea in test 2 because of CPF and metallic taste in test 1 because of MTZ. No statistically significant differences were observed among the three groups in terms of the number of subjects reporting adverse events, or between the two antibiotic groups regarding the individual adverse effects reported ($P > 0.05$).

Comparing each study variable (PD and CAL) in three groups at each single time point, we found no significant reduction between 1 and 3 months in the test groups compared to the control group.

PD decreased in both groups over time. As shown in Table 1, it changed from 1.03 to 0.3 mm (changes at 3 time points: baseline, 1 month and 3 months) in control group, it changed from 1.37 to 0.6 mm in test 1 group and, it changed from 1.66 to 0.69 mm in test 2 group. PD was always lower in the test groups and showed further reduction compared to the control group over

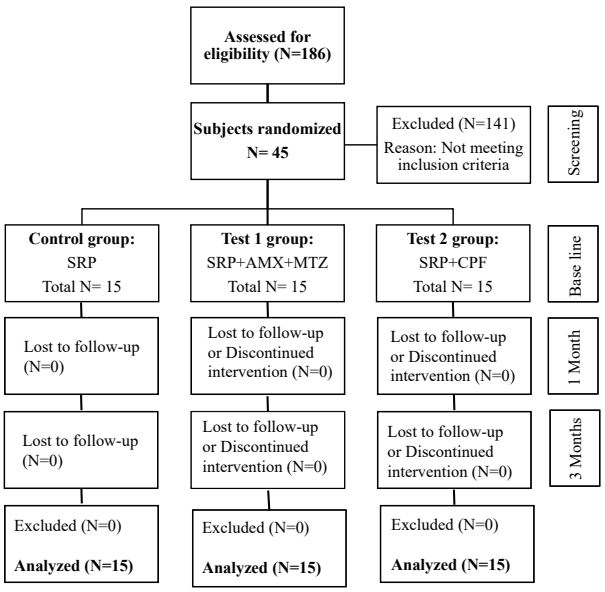

Figure 1. Flow Chart of the Study.

time. More reduction in PD was seen between baseline and one month after SRP in all 3 study groups. Some differences were detected among groups at the follow-up appointments, such as a greater reduction in overall mean PD in the two antibiotic groups in comparison with the control group at two follow-up time points ($P > 0.05$). PD showed significant changes between PD 0 and PD 1 in evaluating test groups ($P = 0.009$) and control group ($P < 0.001$) according to Figure 2. Repeated measures ANOVA showed no significant differences between groups ($P = 0.082$).

CAL decreased in all groups over time, especially between CAL 0 and CAL 1. Mean CAL in control group changed from 0.96 to 0.3 mm (CAL 0-CAL 1 to CAL 1-CAL 2), it changed from 1.06 to 0.5 mm in test 1 group, and it changed from 1.2 to 0.6 mm in test 2 group (Table 1). CAL showed lower values in the test groups and showed further reduction compared to the control group over time. More reduction in CAL was seen between CAL 0 and CAL 1 in all three study groups. Some differences were detected among groups at the follow-up appointments, such as a greater reduction in overall mean CAL in the two test groups in comparison with the control group at two follow-up time points ($P < 0.05$). CAL showed significant changes between CAL 0 and CAL 1 in evaluating groups ($P < 0.001$) (Figure 3). Repeated measures ANOVA showed no significant differences between groups ($P = 0.540$).

Overall, the reduction in mean PD was greater in test 2 group (not significant compared to test 1 ($P < 0.05$). Despite the effectiveness of all medications on the reduction of PD and CAL, these changes are not significant in comparison with the control group.

Discussion

Periodontitis is an inflammatory disease of supportive tissues of the tooth and CAL is the important clinical appearance of it. Periodontitis usually causes pocket and bone loss. Chronic periodontitis is the most prevalent type of it (2).

Gram positive cocci and negative filaments cause an increase in PD and CAL, they invade supportive periodontal tissue; so mechanical therapy is not sufficient for the cure (6-8).

Antibiotics (systemically or local) are used in the treatment of periodontitis because of bacteria invasion to periodontium (2).

Some studies have investigated the effect of antibiotics (monotherapy or combined) as an adjunctive therapy to periodontal treatments such as SRP. Overall, in all of these studies, AMX+MTZ is known as the most effective combination as adjunct. Although AMX is a commonly prescribed drug, bacterial resistance is a great concern. Many patients do not show compliance because of the side effects of MTZs. We suggest CPF as an adjunctive antibiotic to SRP. Our study revealed that patients who had received CPF showed significant reductions in mean CAL and PD after 25 weeks in comparison to the subjects who had only received SRP. Some studies revealed the advantages of systemic antibiotics as adjunctive therapy to non-surgical treatments (10,21). SRP is not

Table 1. Comparison of PD and CA at Baseline, 1 and 3 Months

Variable	Time point	Control	Test 1	Test 2
PD (mm)				
PD 0	Baseline	5.81± 0.79[a]	5.65 ± 0.55	5.76 ± 0.73
PD 1	1 month	4.78 ± 0.71	4.28 ± 0.78	4.1 ± 0.68
PD 2	3 months	4.48 ± 0.66	3.68 ± 0.69	3.41 ± 0.65
CAL (mm)				
CAL 0	Baseline	5.65 ± 1.28	4.96 ± 0.49	5.48 ± 0.64
CAL 1	1 month	4.69 ± 1.19	3.9 ± 0.62	4.28 ± 0.56
CAL 2	3 months	4.39 ± 0.89	3.4 ± 0.36	3.68 ± 0.48

[a] Data are shown as mean ± SD.
Control= SRP; Test 1= SRP+AMX+MTZ; Test 2= SRP+ CPF.

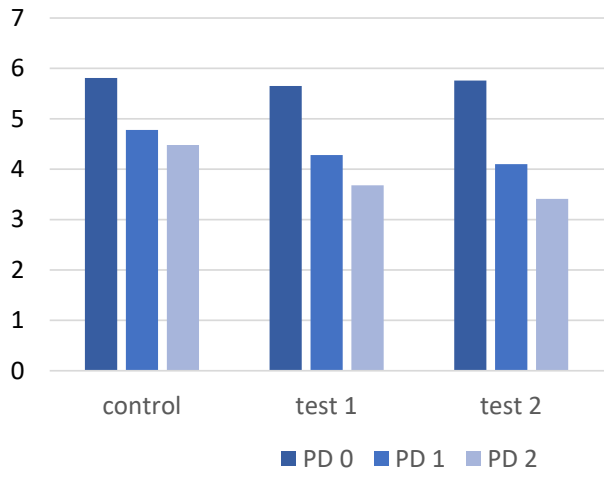

Figure 2. PD Changes in Study Groups During the Time. Control= SRP; Test 1= SRP+AMX+MTZ; Test 2= SRP+ CPF.

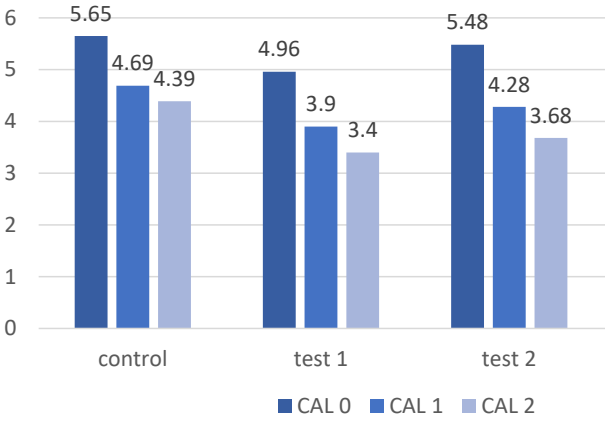

Figure 3. CAL Changes in Study Groups During the Time. Control= SRP; Test 1= SRP+AMX+MTZ; Test 2= SRP+ CPF.

an adequate monotherapy according to the results of this study. It means that a combination therapy protocol should be used in the treatment of patients with chronic periodontitis.

The findings of this study are in agreement with the study of Ribiero et al and Goodson et al. They evaluated the effect of AMX+MTZ as adjunctive therapy in chronic periodontitis. They found reductions in BOP and PD after 6 months (18,19).

Some studies reported significant changes after using adjunctive systemic antibiotics. Moreno found significant changes in CAL and PD after using AMX+MTZ or doxycycline in aggressive or chronic periodontitis (17). Cionca et al (22) and Zandbergen et al (23) and Feres-Filho et al (12) found the same results as Moreno. These results can be attributed to the longer time of study and use of chlorhexidine mouthwash usage.

A systematic review reported improvement in CAL and PD after using AMX+MTZ adjunctive to SRP; however, the changes in BOP and suppuration were not significant. This article supported adjunctive therapy and recommended further researches in the future (24).

As discussed before, we mentioned CPF as a new systemic antibiotic adjunctive to SRP. CPF is the lone antibiotic which is effective against all spices of Aa.

Erdemir et al showed that the use of CPF in addition to SRP decreased the amount of IL-8. No significant relationship between present therapeutic modalities and sICAM-1 levels in GCF was observed (25).

The widespread use of antibiotics is reflected in the level of resistance of Aa and PG in patients with periodontal infections. High resistance against CPF, MTZ and AMX in PG and Aa is seen in isolated samples of periodontal disease. Clinical studies with antibiotics should take these differences into account (26).

It can be concluded that use of AMX+MTZ or CPF as an adjunct to SRP has better outcomes but no significant impact on reducing PD and CAL was observed over 1 and 3 months after treatment in patients with chronic periodontitis. Better treatment outcomes were achieved in the CPF group. It is obvious that CPF therapy is better than the combination therapy for patients' compliance. The other benefits include less prescription and bacterial resistance compared to the other routine adjunctive therapies.

Authors' Contribution

Study concept, design and acquisition of data: JMH, PR; analysis, interpretation of data and drafting of the manuscript: NR; critical revision of the manuscript for important intellectual content: JMH, PR; statistical analysis: NR; administrative, technical, and material support: NR; study supervision: JMH, PR.

Ethical Statement

This trial was approved by the Ethics Committee of Hamadan University of Medical Sciences, Hamadan, Iran (registry code 2931/9/35/16). This study was also approved by Iranian Registry of Clinical Trials (identifier: IRCT2014010816141N1)

Conflict of Interest Disclosures

The authors declare that they have no conflict of interests.

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