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Could Ofloxacin Be an Alternative to Amoxicillin–Metronidazole as an Adjunct to Non-surgical Periodontal Therapy?

Ofloksasin, Cerrahi Olmayan Periodontal Tedaviyle Beraber Kullanılan Amoksisilin Metronidazolün Alternatifi Olabilir mi?

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ABSTRACT

Objective: The best antibiotic approach for generalized periodontitis remains under debate. Therefore, in this study, the systemic administration of ofloxacin was compared against amoxi cillin–metronidazole in terms of clinical periodontal parameters.

Materials and Methods: A prospective, experimental, double-blind, active-controlled, randomized, parallel-grouped, and single-centered clinical trial was carried out at a university hospital in Istanbul, Turkey, between April 2017 and August 2019. Seventy-four patients with generalized periodontitis were randomized into 2 study groups (ofloxacin and amoxicillin–metronidazole groups). Clinical periodontal parameters were recorded at baseline and at 1-, 3-, and 6-month follow-ups following phase 1 periodontal therapy. Changes in clinical periodontal parameters from baseline to 6 months were evaluated and compared between groups.

Results: Thirty-eight patients were lost to follow-up and excluded from the analysis. Thirty-six patients completed the study (ofloxacin group, n = 18; amoxicillin–metronidazole group, n = 18). The clinical periodontal parameters were significantly reduced in both groups at all time points compared to baseline ($P < .05$). No significant differences in plaque or gingival indices were observed between the groups at any time point ($P > .05$). Bleeding on probing at 1 month as well as probing depth and clinical attachment loss at 6 months were significantly lower in the amoxicillin–met ronidazole group compared to the ofloxacin group ($P < .05$). No adverse effects were reported.

Conclusion: Systemic ofloxacin administration as an adjunct to non-surgical periodontal therapy showed significant clinical improvement during the first 3 months but was not as effective as amoxicillin–metronidazole at 6 months.

Keywords: Amoxicillin, metronidazole, ofloxacin, periodontitis, root planning

ÖZ

Amaç: Generalize periodontitis için en iyi antibiyotik yaklaşımının hangisi olduğu tartışma konusudur. Bu nedenle, bu çalışmada, klinik periodontal parametreler açısından, ofloksasinin sistemik uygulaması amoksisilin-metronidazolünkiyle karşılaştırıldı.

Metodlar: Prospektif, deneysel, çift körlü, aktif kontrollü, randomize, paralel gruplu ve tek merkezli klinik çalışma, Nisan 2017 ile Ağustos 2019 tarihleri arasında İstanbul, Türkiye'deki bir üniversite hastanesinde gerçekleştirildi. Generalize periodontitisli 74 hasta, iki çalışma grubuna (ofloksasin ve amoksisilin-metronidazol grupları) randomize edildi. Klinik periodontal parametreler başlangıçta ve faz 1 periodontal tedaviyi takiben birinvi, üçüncü ve altıncı ay takiplerinde kaydedildi. Klinik periodontal parametrelerdeki değişiklikler, başlangıçtan altıncı aya kadar değerlendirildi ve gruplar arasında karşılaştırıldı.

Bulgular: Otuz sekiz hasta takip edilemedi ve analizden çıkarıldı. Otuz altı hasta çalışmayı tamamladı (ofloksasin grubu, n = 18; amoksisilin-metronidazol grubu, n = 18). Klinik periodontal parametreler, başlangıca kıyasla tüm zaman noktalarında her iki grupta da önemli ölçüde azaldı ($p < 0.05$).

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Herhangi bir zaman noktasında, gruplar arasında, plak veya gingival indeksinde anlamlı fark gözlenmedi ($p > 0.05$). Ofloksasin grubuyla karşılaştırıldığında amoksisilin-metronidazol grubunda birinci ayda sondalamada kanama, altıncı ayda sondalama derinliği ve klinik ataşman kaybı anlamlı olarak daha düşüktü ($p < 0.05$). Herhangi bir yan etki bildirilmemiştir.

Sonuç: Cerrahi olmayan periodontal tedaviye ek olarak kullanılan sistemik ofloksasin uygulaması, ilk üç ayda önemli klinik iyileşme gösterirken, altıncı ayda amoksisilin-metronidazol kadar etkili değildi.

Anahtar kelimeler: Amoksisilin, kök yüzeyi düzleştirme, metronidazol, ofloksasin, periodontitis

INTRODUCTION

Periodontitis is an inflammatory disease associated with microbial dental plaque and characterized by loss of tooth-supporting tissues. Treatments include mechanical non-surgical interventions, such as intensive oral hygiene instructions and the mechanical removal of supra- and sub-gingival plaque accumulations (scaling and root planing (SRP)) and surgical interventions on inflamed periodontal tissues. However, non-surgical periodontal therapy alone does not always produce the anticipated tissue-healing results in severe cases of periodontitis.[1] Therefore, adjuvant treatments such as systemic antibiotics are used to improve clinical periodontal parameters (CPPs).

Amoxicillin (AMX), one of the most commonly used antibiotics globally,[2] is a beta-lactam antibiotic, and metronidazole (MET), one of the most frequently prescribed antimicrobials in periodontal recipes,[3] is a nitroimidazole-derivative medical agent. In addition to non-surgical periodontal therapy, the adjunctive use of AMX+MET has been shown to produce significant benefits in the improvement of CPPs compared with control groups.[4] However, the development of antibiotic resistance in periodontopathogens[5] and various side effects such as allergic reactions and gastrointestinal problems have been reported.[2] Therefore, the effectiveness of new medical agents to support periodontal therapy should be assessed.

Ofloxacin (OFX) is a fluoroquinolone antibiotic used against periodontal disease-associated pathogens.[6-11] It is used for treating oral infections including periodontal infections, pericoronitis, and osteitis; moreover, it shows minimal toxic effects on periodontal ligament fibroblasts and gingival epithelial cells,[12,13] and the reported adverse drug reactions are mild.[14,15] It has been suggested that the pharmacokinetics of OFX, which include the maintenance of high serum and tissue concentrations because of the prolonged half-life, allow once-daily dosing on an empty or full stomach, which may improve cost-effectiveness and facilitate patient compliance with drug therapy.[16]

As far as we know, no randomized controlled clinical trials have evaluated the effects of OFX as an adjunct to SRP in the treatment of generalized periodontitis at stages III-IV/grade C. Therefore, this work aimed to compare the clinical outcomes of OFX versus AMX+MET as an adjunctive therapy to full-mouth SRP in patients with generalized periodontitis. We hypothesized that SRP treatment in combination with systemic OFX therapy would result in equivalent clinical periodontal outcomes to the combination treatment in patients with generalized periodontitis.

MATERIALS AND METHODS

Trial Design

This was a prospective, experimental, double-blinded, active-controlled, randomized, parallel-grouped, and single-centered clinical trial with a 6-month follow-up period. The study procedure was reviewed by the İstanbul Medipol University Ethics Committee (Date/Number: 22.12.2016/10840098-604.0 1.01-E.27503) and adhered to the 1964 Declaration of Helsinki and its latest amendments. The ClinicalTrials.gov registration number for the study is NCT04353362. All patients were briefed on the study procedure and gave written informed consent for participation.

Participants

This study was conducted on a voluntary basis with patients who visited the university hospital in İstanbul, Turkey, between April 2017 and August 2019. Each participant completed a questionnaire asking about their general background and medical and dental history. An obesity assessment was based on body mass index, which was calculated according to the criteria recommended by the World Health Organization.[17]

Inclusion criteria were as follows: systemically healthy; 18-40 years of age (35 years or younger at the time of diagnosis); clinically diagnosed with generalized aggressive periodontitis[18] (e.g., rapid attachment loss, rapid bone destruction, systemically healthy except for periodontal inflammation, plaque deposition disproportionate to the severity of bone destruction, and generalized interproximal attachment loss affecting at least 3 permanent teeth other than first molars and incisors); the presence of at least 20 teeth (at least 1 molar tooth in each quadrant); and no antibiotic therapy within the previous 6 months. All cases were then re-evaluated according to the new classification of periodontal diseases and conditions[19] based on secondary evidence. Cases were found to be in the "generalized stages III-IV/grade C periodontitis" group.

Exclusion criteria were as follows: systemic disease such as diabetes mellitus or taking medication such as cortisone that has a possible influence on the periodontium; current smokers who smoked more than 20 cigarettes per day;[20] lactation; current or suspected pregnancy; systemic antibiotics taken within the previous 6 months; medication that could interact with OFX, AMX, or MET; history of previous periodontal surgery; and history of SRP within the last year.

Interventions

During the first appointment, full-mouth CPPs were recorded by a blinded investigator (B.A.) at 6 sites per tooth using a periodontal probe (Williams Probe; Hu-Friedy, Chicago, Ill, USA) including plaque and gingival indices (PI, GI),[21] probing depth (PD), bleeding on probing (BOP), and clinical attachment loss (CAL). Following the measurements, supra-gingival debridement using an ultrasonic instrument and polishing using a rubber cup with a polishing paste were performed. All patients were instructed to brush their teeth twice daily with a toothbrush (Oral B Vitality, Braun, Hesse, Germany) followed by an interdental brush (Oral-B

Pro-Expert Clinic Line Interdental Kit, USA). A follow-up appointment was made 1 week later, and all patients who adhered to the twice-daily cleansing regimen were selected for study inclusion and randomized in 1 of the 2 study groups in order of arrival. The OFX group (experimental group) received 400 mg of OFX once a day for 5 days, and the AMX+MET group (gold standard group) received 500 mg AMX and 500 mg MET 3 times a day for 7 days. The use of chlorhexidine digluconate mouthwash was prohibited during the study. All participants were called the day before their visits to remind them to attend their appointment, and the first dose of medication was taken on the morning of the treatment day under the supervision of an investigator. At the next appointment, an experienced periodontist (N.A.) completed the full-mouth SRP procedure using local anesthesia, Gracey curettes (Hu Friedy, Chicago, Ill, USA), and ultrasonic instruments. Patients were screened at 1, 3, and 6 months after completion of the SRP. During these appointments, all CPPs were recorded. In addition, supra-gingival professional dental cleaning and polishing procedures were re-performed, but sub-gingival areas were not re-instrumented with curettes. The endpoint for the first SRP appointment was the smoothness of the scaled roots, and the endpoint for each control appointment was the complete absence of calculus in the dentition.

Outcomes

The primary outcome measure selected for this study was PD reduction between baseline and follow-up visits. The changes in PI, GI, BOP, and CAL were assessed as secondary outcome measures of efficacy.

Sample Size

A power calculation (G-Power software, Dusseldorf, Germany) based on the data suggested that a sample size of 30 participants per group would have 85% power at an effect size of 1.0 and an α level = 0.05.[22] Considering a loss of approximately 15%,[23] it was foreseen that at least 35 subjects should be included in each group.

Randomization

After obtaining informed consent from the patients and recording their CPPs, participants were randomized into 1 of 2 treatment groups by drawing lots, with the constraint that there should be an equal number of participants in each group. The allocation was implemented by a person who was blinded to patient data. The identity of the patients participating in the study was kept confidential.

Blinding

Although the patients knew which drug they were using as their names were on the medication packaging, they were not aware of which group (experimental or gold standard) they belonged to. Furthermore, the investigators performing the treatment (N.A.) and collecting the data (B.A.) were blinded to the allocation.

Statistical Methods

The Statistical Package for Social Sciences version 24.0 software (IBM Corp.; Armonk, NY, USA) was used for the analyses. Pearson's chi-squared and Mann–Whitney *U* tests were used to compare categorical variables and determine differences between groups at given times, respectively. Differences within the groups over time were evaluated using Friedman's and Wilcoxon signed-rank tests. A post hoc analysis was carried out to test for specific differences between groups. Statistical significance was defined as $P < .05$.

RESULTS

Figure 1 depicts the flow chart of the study. A total of 95 patients with generalized periodontitis were included in the study; 21 patients, who were unable to maintain oral hygiene, were excluded at the first appointment. Thus, a total of 74 patients were randomized into 2 groups, OFX (n = 39) and AMX+MET (n = 35), with 36 patients completing the study. In the OFX group, 14, 6, and 1 participants were withdrawn from the study at 1, 3, and 6 months, respectively. In the AMX+MET group, 15 participants were withdrawn at the 1-month follow-up, and 1 participant each was withdrawn from the group at the 3- and 6-month follow-ups. The baseline characteristics and CPPs for the 36 patients that completed the study are presented in Table 1. There were no differences between the groups in terms of gender, smoking status, age, body mass index, and baseline CPPs ($P > .05$) (Table 1). The number of smokers was the same in both groups and 1 female participant from each group was in the obesity class I category without any other systemic symptoms. Each patient in the OFX group received 400 mg OFX (1 × 1 for 5 days), and each patient in the AMX+MET group received 500 mg of AMX and 500 mg of MET (3 × 1 for 7 days). There were no patients to receive antibiotics repeatedly during the whole study. No drug-related adverse events were reported by any of the patients, including those who dropped out. Both groups exhibited significant decreases in all CPPs at the end of all the follow-up times compared to baseline (PI, GI, PD, BOP, CAL, $P < .05$, Table 2). No significant differences were observed for the PI and GI parameters between the groups at any time points ($P > .05$) (Table 2). The BOP (after 1 month) and the PD and CAL (after 6 months) were significantly lower in the AMX+MET group than in the OFX group ($P < .05$) (Table 2).

DISCUSSION

As far as we know, this is the first study to assess the clinical effectiveness of systemic OFX compared to AMX+MET as an adjunct to non-surgical periodontal therapy for the treatment of generalized periodontitis stages III-IV/grade C. Based on the current findings, systemic OFX was not superior to the combination therapy in the treatment of generalized periodontitis. The results indicate that our hypothesis should be partially accepted, as CPPs were significantly decreased in both groups at the end of months 1, 3, and 6 compared to baseline; however, PD was significantly lower in the AMX+MET group than in the OFX group by month 6.

Similar to our results, some studies have indicated that OFX treatment results in considerable CPPs recovery.[6,7,14,15,24] Most of the reported clinical studies investigating the effects of local and systemic OFX administration on periodontal therapy have found that it has positive effects on periodontal healing.[14,15,24-26] Kleinfelder et al[6] concluded that systemic OFX therapy as an adjunct to surgical periodontal therapy resulted in a significant reduction of PD and a significant increase in clinical attachment compared to a control group that did not receive antibiotic treatment. One study investigated the clinical effects of OFX+MET topical gel as an adjunct to periodontal therapy and reported that the GI, PD, and BOP results from the OFX+MET topical gel group were similar to those in a MET gel group but better than those taking a placebo gel.[27] In an observational study on the effectiveness of systemic OFX+MET treatment in periodontal patients, the bleeding index, PD, and height of the alveolar bone in an OFX+MET group were better than those in a MET group alone.[24] In a published case series, 2 Papillon–Lefèvre syndrome children with severe periodontal destruction were treated with systemic OFX

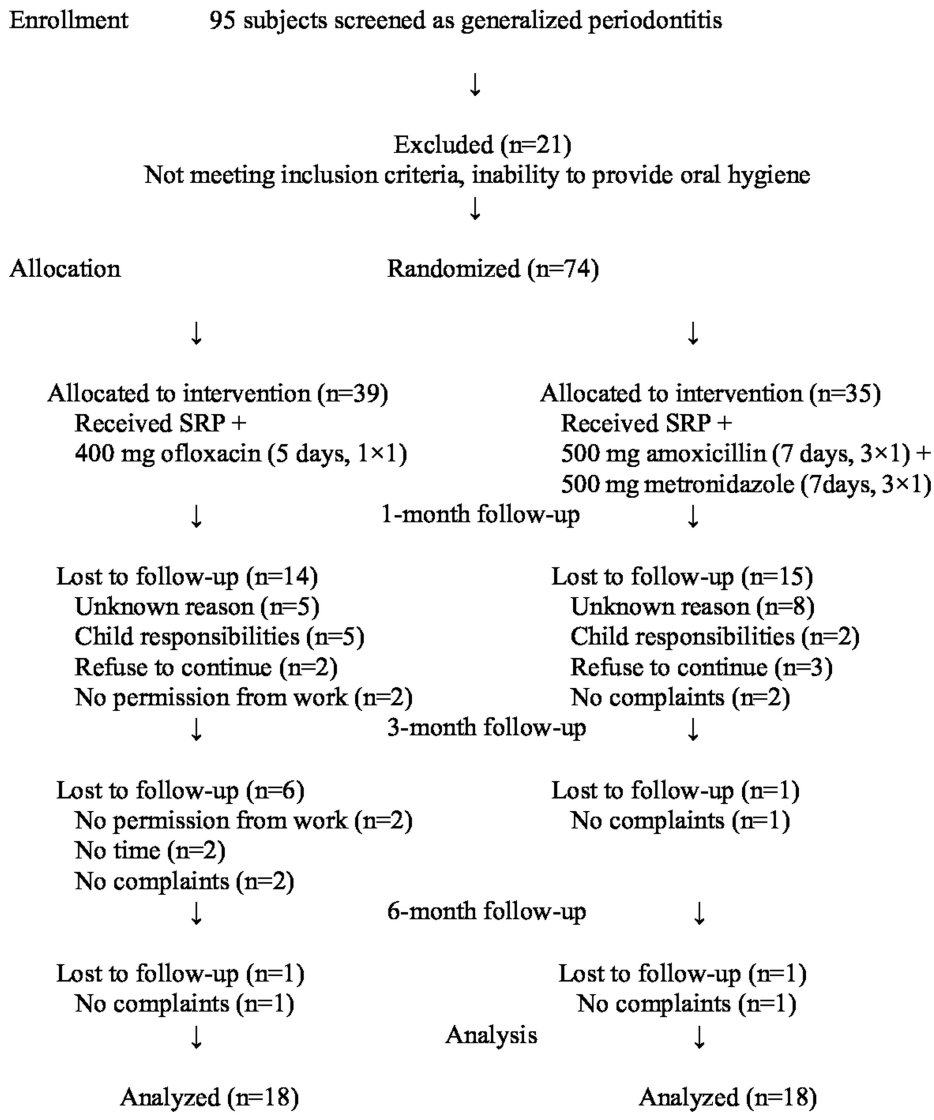

Figure 1. CONSORT flow diagram outlining the current study.

administration as an adjunct to non-surgical periodontal therapy, and gingival inflammation and PD were eliminated.[7] Another study that evaluated a systemic OFX regime as an adjunct to surgical periodontal therapy declared that PD and CAL were significantly decreased in patients who received systemic OFX.[6] However, it is not appropriate to make direct comparisons between our findings and previous studies owing to differences in the methodology and research strategies. Some studies used OFX alone, while others included OFX in combination with different antibiotics, and the inclusion criteria and subsequent periodontal treatment planning were also different. In addition, there is no consensus in the literature as to the best antibiotic regimen for the treatment of generalized periodontitis.[28] Therefore, it is challenging to compare the outcomes of studies owing to differences in the evaluated CPPs, the characteristics of the study populations, and the research methodologies used.

Table 1. Gender, Smoking Status, Age, Body Mass Index, and Baseline Clinical Periodontal Parameters of Participants Who Completed the Study

	OFX Group (n = 18)	AMX+MET Group (n = 18)	*P*
Female/male (n)*	10/8	9/9	.74
Smokers (n, %)*	8, 44.44	8, 44.44	1
Age (year)†,‡	32.72 ± 6.13 (20-40)	34.17±4.43 (26-40)	.66
Body mass index†,‡	24.27±3.49 (19.72-30.80)	26.22 ± 4.13 (19.88-31.64)	.17
Plaque index†,‡	1.58 ± 0.44 (0.87-2.54)	1.44 ± 0.50 (0.25-2.25)	.46
Gingival index†,‡	1.07 ± 0.34 (0.4-1.77)	1.06 ± 0.21 (0.78-1.51)	.82
Probing depth (mm)†,‡	4.44 ± 0.77 (3.51-5.68)	4.67 ± 0.76 (3.3-5.81)	.32
Bleeding on probing (%)†,‡	83.71 ± 11.19 (61.54-100)	79.49 ± 13.98 (43.21-100)	.28
Clinical attachment loss (mm)†,‡	4.79 ± 1.02 (3.53-6.76)	4.84 ± 0.84 (3.3-5.96)	.86

*Pearson chi-square test; †Mean ± SD (minimum–maximum); ‡Mann–Whitney *U* test.
AMX, amoxicillin; MET, metronidazole; OFX, ofloxacin.
P > .05: the difference between the 2 groups is not statistically significant.

According to the findings of our study, the PD parameter was significantly lower in the AMX+MET group compared to the OFX group at the end of month 6, indicating that OFX was not superior to AMX+MET. In a study[29] examining the concentrations of 500 mg AMX and clavulanic acid in gingival crevicular fluid (GCF) after the first and tenth oral dose, the mean AMX concentration was measured as 14.05 mg/mL approximately 1 hour after administration on day 0 and 13.93 mg/mL approximately 1 hour after

Table 2. Mean ± Standard Deviation (Minimum–Maximum) Values for Clinical Periodontal Parameters of the 2 Groups for Each Follow-Up Period

	OFX Group (n = 18)	AMX+MET Group (n = 18)	*P* (Between the Groups)
Plaque Index			
Baseline	1.58 ± 0.44 (0.87-2.54)	1.44 ± 0.50 (0.25-2.25)	.46
1 month	0.47 ± 0.19 (0.21-0.87)*	0.38 ± 0.21 (0.14-0.79)*	.64
3 months	0.45 ± 0.25 (0.20-1.21)†	0.33 ± 0.21 (0.14-0.91)†	.78
6 months	0.41 ± 0.24 (0.09-0.87)‡	0.19 ± 0.13 (0.03-0.58)‡	.17
Gingival index			
Baseline	1.07 ± 0.34 (0.40-1.77)	1.06 ± 0.21 (0.78-1.51)	.82
1 month	0.27 ± 0.16 (0.10-0.67)*	0.24 ± 0.17 (0.06-0.61)*	.66
3 months	0.24 ± 0.13 (0.06-0.51)†	0.16 ± 0.14 (0.04-0.54)†	.53
6 months	0.22 ± 0.15 (0.03-0.65)‡	0.10 ± 0.10 (0.03-0.44)‡	.52
Probing depth (mm)			
Baseline	4.44 ± 0.77 (3.51-5.68)	4.67 ± 0.76 (3.3-5.81)	.32
1 month	3.32 ± 0.62 (2.68-4.53)*	3.46 ± 0.67 (2.66-4.82)*	.38
3 months	3.18 ± 0.62 (2.15-4.30)†	3.23 ± 0.55 (2.53-4.04)†	.12
6 months	3.14 ± 0.65 (2.12-4.48)‡	2.91 ± 0.40 (2.38-4.02)‡	.02
Bleeding on probing (%)			
Baseline	83.71 ± 11.19 (61.54-100)	79.49 ± 13.98 (43.21-100)	.28
1 month	49.62 ± 13.44 (27.98-71.43)*	26.01 ± 15.77 (3.57-52.56)*	.00
3 months	46.14 ± 13.80 (28.47-70.83)†	19.84 ± 11.80 (2.38-42.95)†	.82
6 months	42.59 ± 19.82 (13.70-77.78)‡	–	.49
Clinical attachment loss (mm)			
Baseline	4.79 ± 1.02 (3.53-6.76)	4.84 ± 0.84 (3.3-5.96)	.86
1 month	3.82 ± 0.98 (2.70-5.87)*	3.79 ± 0.76 (2.86-4.88)*	.18
3 months	3.73 ± 1.03 (2.67-6.10)†	3.62 ± 0.58 (2.68-5)†	.87
6 months	3.77 ± 1.10 (2.57-6.42)‡	3.49 ± 0.54 (2.51-4.27)‡	.03

Friedman test, Wilcoxon signed-ranks test.
*Significant difference between baseline and 1-month follow-up within the group ($P < .05$).
†Significant difference between baseline and 3-month follow-up within the group ($P < .05$).
‡Significant difference between baseline and 6-month follow-up within the group ($P < .05$).
P-value < .05, the difference between the 2 groups is statistically significant.

administration on day 3. In a clinical study[30] examining the mean MET concentration in GCF after a single 250 mg oral dose, the concentration peaked at the second and seventh hours following application (~4 µg/mL) and was still at a detectable concentration after 18 hours (~1 µg/mL). In a clinical study[26] examining OFX concentrations in GCF after a single 200 mg oral dose, the concentration was reported to have peaked at 7 µg/mL approximately 2 hours after administration and gradually decreased to 2 µg/mL after 10 hours. We did not test the concentrations of antibiotics in GCF; however, the reason for this difference between the groups in the sixth month may be related to their concentration capability in GCF.

It has been reported that the adjunctive use of AMX+MET in non-surgical periodontal treatment results in statistically significant improvements in CPPs and reduces the need for periodontal surgery compared with non-surgical treatment alone.[4] We did not include a group without antibiotics in our study. In clinical trials designed to test the effectiveness of new antimicrobial regimens as an adjunct to SRP, establishing a group without medication would be unethical. Therefore, the AMX+MET group served as both the gold standard group and the control group in the present study. Patients were prescribed 500 mg of AMX and 500 mg of MET 3 times a day for 7 days to ensure that an adequate concentration of antibiotics was reached in the GCF and the blood.

The starting point and duration of systemic antibiotic regimens for periodontal therapy vary between studies. However, by focusing on randomized clinical trials and systematic reviews, a consensus report on systemic antibiotic administration concluded that antibiotic tolerance in biofilms increases within the first 24 hours after non-surgical periodontal therapy.[31] Therefore, in our study, antibiotic treatment was initiated on the morning of the day that the SRP was due to be carried out, and the full-mouth SRP treatment was completed on the same day as the first dose of antibiotics.

The principal limitation of this trial is that, although it is related to the use of antimicrobials, no microbiological analysis was performed. According to van Winkelhoff,[32] assuming all patients with periodontitis are infected with the same microorganisms sub-gingivally is controversial. However, a study comparing the sub-gingival microbial flora of periodontitis patients and healthy controls found little difference between the groups.[33] In in vitro[11,34-36] and in vivo[6,7,37] studies, resistance and susceptibility to tested antibiotics have been found to vary among periodontal pathogens. Therefore, antibiotic treatment as an adjunct for controlling periodontal disease should be selected based on the results of a microbial analysis of subgingival plaque samples. However, given the difficulties in identifying complex subgingival microflora, the time needed to conduct laboratory procedures, and the high cost of the analysis limit the routine use of microbiological laboratory tests in dental clinics.

The second weakness of this study was the very high dropout rate during the follow-up period. The number of patients who completed the study was below the target sample size (36 participants finished the study as opposed to the planned 60). One possible explanation for this high dropout rate may be the absence of personal contact participants had with the researchers. The administrative staff was responsible for calling patients and arranging appointments. Patients who consistently missed their appointments were called by a researcher to try to understand the reasons for their non-attendance. Noncompliance with medical treatment involving check-up appointments is a chronic issue and can result in unexpected patient losses. This may have been exacerbated by the researchers' lack of telephone contact with patients. In addition, we did not insist that patients stay in the study, but, rather, informed them that it was inappropriate to use antibiotics without medical supervision.

A third weakness of this study concerns intra-examiner reliability and reproducibility, which was not evaluated. Therefore, the possibility of underestimation or overestimation in the measurement interpretation of the clinical parameters should be considered.

Despite these limitations, the clinical trial reported here has several strengths, including the study design, a selection of an appropriate group of periodontitis patients for treatment with antibiotics, and the use of an entry phase to enroll patients with oral hygiene motivation. In conclusion, systemic OFX administration, together with non-surgical treatment, is not as effective as AMX+MET combination treatment for periodontitis based on clinical improvements at 6 months follow-up. Further studies should be undertaken to identify suitable systemic antibiotic regimens as alternatives to the AMX+MET combination as an adjunct to non-surgical periodontal treatment.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of İstanbul Medipol University (Date: December 22, 2016, Decision Number: 10840098-604.01.01-E.27503).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

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