ORIGINAL ARTICLE
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UDC: 615.33::616.314-089-06-084
DOI: https://doi.org/10.2298/VSP200909122S

A comparative analysis of the efficacy of moxifloxacin and cefixime in the reduction of postoperative inflammatory sequelae after mandibular third molar surgery

Uporedna analiza efikasnosti moksifloksacina i cefiksima u smanjenju posledica zapaljenja posle hirurškog vađenja impaktiranih donjih trećih molara

Branimir Stošić*, Ivan Šarčev*, Siniša Mirković*, Branislav Bajkin*, Ivan Soldatović†

***University of Novi Sad, Faculty of Medicine, Novi Sad, Serbia; †University of Belgrade, Faculty of Medicine, Belgrade, Serbia**

Abstract

Background/Aim. There is no scientific evidence that the prophylactic use of antibiotics as a part of the mandibular third molar surgery is effective in suppressing postoperative pain, edema, trismus, and dry socket. The aim of the study was to investigate the effects of antibiotics from the fluoroquinolone (moxifloxacin) and cephalosporin (cefixime) groups in reducing postoperative inflammatory sequelae (pain, edema, and trismus), as well as in possibly reducing the incidence of dry socket after mandibular third molar surgery. **Methods**. This double-blind study was completed by 157 subjects, comprising two study groups (who received the aforementioned antibiotics) and a control group, who received placebo tablets. Subjects were assessed on the first, second, and seventh day following surgery. In the postoperative course, patients were monitored for the occurrence, intensity, and duration of postoperative inflammatory sequelae and dry socket. **Results.** Both antibiotics, especially moxifloxacin, had a pronounced effect on reducing all inflammatory sequelae (pain, edema, and trismus) as the most common postoperative complaints following mandibular third molar surgery, and also contributed to reducing the incidence of dry socket. **Conclusion**. Antibiotic prophylaxis with cefixime and, especially moxifloxacin, reduced the occurrence of postoperative inflammatory sequelae and alleviated discomfort. It is interesting, that both antibiotics, especially moxifloxacin, also contributed to reducing the incidence of postoperative dry socket, which is not provoked by inflammation. Therefore, further research into the underlying mechanisms behind such an effect is warranted.

Key words:
anti-bacterial agents; dental prophylaxis; molar, third; postoperative complications.

Apstrakt

Uvod/Cilj. Ne postoje naučni dokazi da je profilaktička primena antibiotika posle hirurškog vađenja donjeg trećeg molara efikasna u suzbijanju postoperativnog bola, edema, trizmusa i alveolitisa. Cilj rada bio je da se istraže efekti antibiotika iz grupe fluorohinolona (moksifloksacin) i cefalosporina (cefiksim), na smanjenje zapaljenjskih postoperativnih sekvela (bol, edem i trizmus), kao i na eventualno smanjenje učestalosti nastanka alveolitisa posle hirurškog vađenja donjih trećih molara. **Metode**. Ovu dvostruko slepu studiju završilo je 157 ispitanika, od kojih su formirane dve studijske grupe (ispitanici koji su koristili navedene antibiotike) i kontrolna grupa, koja je koristila placebo tablete. Ispitanici su kontrolisani prvog, drugog i sedmog dana nakon operacije. U postoperativnom periodu praćeni su učestalost, intenzitet i trajanje postoperativnih zapaljenjskih sekvela, kao i pojava alveolitisa. **Rezultati.** Oba antibiotika, naročito moksifloksacin, imali su izražen efekat na smanjenje svih sekvela (bol, edem i trizmus), kao najčešćih tegoba nakon hirurškog vađenja donjeg trećeg molara i doprinela su smanjenju učestalosti pojave alveolitisa. **Zaključak.** Antibiotska profilaksa cefiksimom i, posebno, moksifloksacinom, smanjila je pojavu postoperativnih sekvela i ublažila tegobe. Interesantno je da su oba antibiotika, pogotovu moksifloksacin, doprineli smanjenju učestalosti alveolitisa, koji nije bio izazvan zapaljenjem. Neophodna su dalja istraživanja mehanizama ovakvog efekta.

Ključne reči:
antibiotici; profilaksa, stomatološka; molar, treći; postoperativne komplikacije.

Correspondence to: Branimir Stošić, University of Novi Sad, Faculty of Medicine, Hajduk Veljkova 3, 21 000 Novi Sad, Serbia.
E-mail: brankoddm@gmail.com

Introduction

The extraction of impacted mandibular third molars is among the most common oral surgeries [1] and is typically associated with postoperative clinical sequelae, such as pain, swelling, compromised mouth opening (trismus), and, occasionally, dry socket (in 1–12.6% of cases) [2] and wound infection. Consequently, many surgeons prescribe antibiotics following this intervention aiming to improve patient comfort during the postoperative period [3–6]. Antibiotic treatment is indeed indicated when the operative site is infected (in the presence of acute pericoronitis) [7], as well as when there is a need to protect the patient with endocardial lesions from transient bacteremia. However, the consensus is still lacking on the real benefits of antibiotic prophylaxis use in patients who are in good general health, in whom partially or completely impacted mandibular third molars were surgically removed in the absence of acute pericoronitis.

Antibiotic prophylaxis in healthy patients (without pericoronitis) is usually justified by the fact that surgical extraction of completely or partially impacted mandibular third molars induces surgical trauma to an already contaminated area, such as the oral cavity, thus providing conditions for subsequent infection. Given that postoperative problems and complications after this surgical intervention are common, antibiotics are often routinely prescribed for the immediate postoperative period [8, 9]. However, the unnecessary use of antibiotics is not without negative consequences as it promotes the development of resistant microorganisms and may lead to hypersensitivity to the applied antibiotic, which emphasizes the importance of correctly assessing indications for antibiotic prophylaxis. Moreover, there is no scientific evidence that the prophylactic use of antibiotics as a part of the mandibular third molar surgery is effective in suppressing postoperative inflammatory sequelae.

Authors of numerous articles published in professional and scientific literature advocate for the prophylactic use of antibiotics as a part of the surgical extraction of mandibular third molars and provide the reasons for this recommendation [10–13], while others offer equally compelling reasons for their disagreement with this approach [14–18]. However, neither of these opposing views is founded on scientific evidence. Moreover, even when evidence of antibiotic prophylaxis efficacy is statistically established using scientific methods before any recommendation is made, the clinical significance of such findings should be determined by assessing the relationship between the desired and adverse effects, as suggested by other authors [19, 20]. It is also noteworthy that the extant studies and the resulting recommendations are primarily based on evaluations of several antibiotics that have been in use for many years, most commonly amoxicillin with clavulanic acid, clindamycin, and metronidazole. There is an evident paucity of research involving other antibiotics, and the scant evidence indicates that there is no specific advantage of their prophylactic use following mandibular third molar surgery. A possible advantage of newer antibiotics stems from the fact that, in addition to their fundamental antimicrobial function, they can also exhibit immunomodulatory effects, which have a favorable contribution to the suppression of postoperative inflammatory sequelae in mandibular third molar surgery [21, 22].

Therefore, the aim of the study was to investigate the effects of antibiotics from the fluoroquinolone (moxifloxacin) and cephalosporin (cefixime) groups, which have potential immunomodulatory effects on inflammatory sequelae (postoperative pain, edema, and trismus), while possibly reducing the incidence of dry socket, too.

Methods

This clinical research was conducted for 8 months (from June 2019 to February 2020) at the Dentistry Clinic of Vojvodina, Serbia, adopting the double-blind prospective clinical study design. The study sample included 165 subjects with the same number of impacted mandibular third molars. All participants signed the informed consent. Only adult subjects over 18 years without a confirmed allergy to the drugs used in the study, in whom mandibular third molar surgery was indicated were included, while the exclusion criteria were pregnancy, breastfeeding, antibiotic allergy, and poor general health. Data pertaining to 8 subjects were subsequently excluded from the analyses, as these individuals either failed to adhere to the given instructions during the postoperative period or did not attend all the scheduled follow-up appointments.

The clinical research was approved by the Ethics Committee of the Dentistry Clinic of Vojvodina by decision number 01-33/8-2019.

Prior to data analyses, the participants were distributed into three groups. Those with prescribed antibiotics, moxifloxacin, from the group of fluoroquinolones (Elfonis®, Hemofarm, Serbia, 400 mg film-coated tablets) and cefixime, from the group of cephalosporins (Pancef®, Alkaloid, Northern Macedonia, 400 mg film-coated tablets), were assigned to the two study groups (groups M and C, respectively), while those that received placebo formed the control group (P). The medications, as well as the placebo, were in the form of film-coated tablets that were almost identical in shape and size, which is in line with the double-blind study design principles. Placebo tablets contained neutral substances that do not have any anti-inflammatory effect (99% microcrystalline cellulose, 0.5% silicon dioxide, and 0.5% magnesium stearate) and were made by Phytonet, Serbia. All treatments were administered once a day for the first five days postoperatively. Owing to this design, the three groups could only be formed upon the study completion after consulting the codebook used to provide the correct film-coated tablets for use in the postoperative period. At this point, it was revealed that, among the 157 individuals who completed the study period, 52 belonged to the Group M (receiving moxifloxacin), 53 formed the Group C (receiving cefixime), and the remaining 52 formed the Group P (the placebo control group).

All surgical interventions were performed under local anesthesia, using 2% lidocaine with adrenaline 1: 80,000 in a total 4 mL volume (2 mL solution for injection contained 40

mg lidocaine hydrochloride in the form of lidocaine hydrochloride monohydrate and 0.025 mg adrenaline in the form of adrenaline tartrate, Lidocaine 2% – adrenaline, 40 mg + 0.025 mg, Galenika, Serbia). In all participants, the surgery involved a triangular mucoperiosteal flap design, sutured using synthetic multifilament non-absorbable suture material (black silk 3–0).

In the case of impacted teeth, the wound was sutured with individual sutures *per primam*, while in the case of partially erupted teeth, part of the wound healed *per secundam*. Sutures were removed on the seventh postoperative day. Subjects were advised to take an analgesic containing 200 mg ibuprofen and 325 mg paracetamol (Metafex® tablets, Pharmaceutical Works Polpharma SA, Poland) after surgery, as required.

Data related to intervention duration (from the first incision to the placement of the last suture) and its course (the need for tooth separation and mechanical bone manipulation) were entered into the research protocol. Participants were assessed on the first, second, and seventh day following surgery. In the postoperative period, patients were monitored for the occurrence and intensity of postoperative inflammatory sequelae (pain, edema, and trismus), as well as dry socket, and based on these indicators, potential favorable effects of the applied medication were evaluated. The degree of postoperative pain was established based on the number of analgesics having taken each postoperative day (till the suture removal). The extent of postoperative edema was determined by measuring the distance between selected reference points (chin tip-tragus) using a flexible ruler immediately before surgery (providing a baseline for subsequent comparisons), as well as 24 h, 48 h, and 7 days after surgery. The postoperative edema coefficient (Ec) for each of these periods was calculated according to the modified Carrillo et al. [23] formula (Ec = [postoperative distance – preoperative distance] ×100 / preoperative distance). Similarly, the degree of postoperative trismus was assessed 24 h, 48 h, and 7 days after surgery by measuring the distance (in cm) between the mesial incisal angles of the upper and lower central incisors at the maximum mouth opening ability. The dry socket was diagnosed based on reported severe pain in the wound area, accompanied by a specific local clinical appearance of the operative wound and absence of pus.

The SPSS 20.0 software package (IBM Corp. released 2011, IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY) was used for all data processing and statistical analyses. For descriptive data, absolute and relative values were used, along with the central tendency (arithmetic mean) and dispersion (standard deviation, percentiles) measures. Statistical analyses included parametric difference tests (ANOVA) and nonparametric tests (Kruskal-Wallis test, Fischer's test, and Pearson's χ^2 test), with the significance level set at 0.05.

Results

The study included 157 participants, of whom 52 comprised the Group M (moxifloxacin), 53 the Group C (cefixime), and 52 the Group P (placebo).

However, due to the circumstances beyond the researchers' control (due to the double-blind study design), the surgical intervention in the Group M was more than twice as long as in the other two groups (Figure 1). Although this discrepancy could have resulted in marked differences in the sequelae that occurred in the postoperative period, subsequent analyses revealed that this was not the case.

Postoperative pain was assessed by analyzing the number of tablets of the recommended analgesic taken daily during the postoperative period. The results showed that the subjects in the Group M used the fewest analgesics, even though the surgery in this group of patients, on average, lasted longer. The greatest number of analgesic tablets was taken by patients in the Group P, especially on the first and second postoperative day, but also later in the postoperative period, sug-

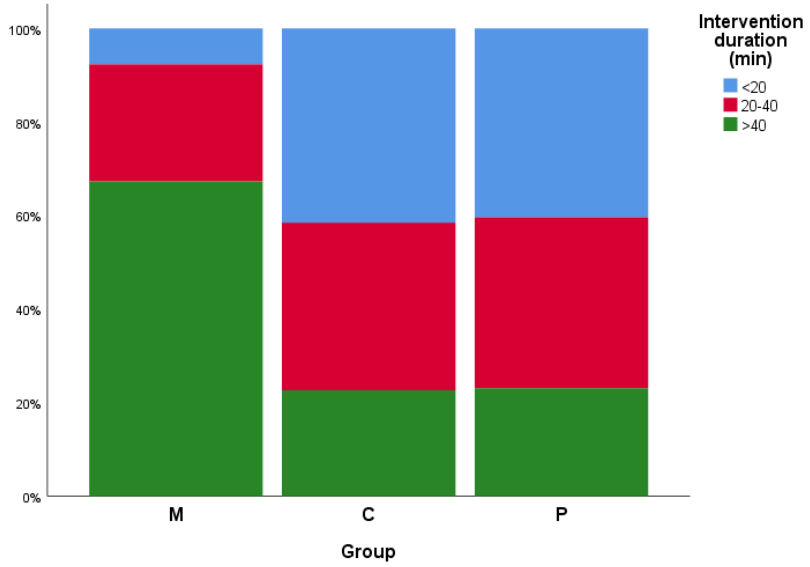


Fig. 1 – Comparison of the three research groups in terms of surgery duration. Group M – patients who received maxifloxacin; Group C – patients who received cefixime; Group P – patients who received placebo.

gesting that participants who were given a placebo experienced the strongest postoperative pain (Table 1). Analysis of changes in pain intensity as a function of time indicated a marked difference between the last and the first postoperative day in all three groups. However, the changes were least pronounced in the Group M, while pain intensity declined considerably in the Group C, and especially in the Group P, in which the pain was particularly intense on the first and second postoperative day.

Comparative analysis of postoperative pain intensity in the two study groups (M and C) and the control group (P), based on the same criterion (number of analgesic tablets taken daily), showed that the participants in the Group M experienced statistically significantly lower pain levels in all observation periods compared to those in the Group C (except on the last postoperative day) and the control group P (Table 2).

The mean value of the tragus-chin tip distance changed in all research groups during the postoperative period, most notably on the second postoperative day but also on the first, whereby this value was close to the baseline (preoperative) values on the seventh postoperative day. However, changes in the tragus-chin tip distance were less pronounced in the Group M than in the other groups, as shown in Figure 2.

When the postoperative edema values measured on the seventh postoperative day were compared to the baseline, a statistically significant difference was observed between the Group M and C, as well as between these study groups and the control group (Group P).

Table 1

Postoperative pain intensity at three follow-ups, based on the number of analgesic tablets taken daily

Group	Patients (n)	Tablets (n), mean ± SD
M		
1st postoperative day	52	0.9 ± 0.9
2nd postoperative day	52	0.2 ± 0.6
7th postoperative day	52	0.0 ± 0.0
C		
1st postoperative day	53	3.9 ± 0.9
2nd postoperative day	53	3.2 ± 0.8
7th postoperative day	53	0.5 ± 1.2
P		
1st postoperative day	52	4.5 ± 0.9
2nd postoperative day	52	4.3 ± 1.1
7th postoperative day	52	1.8 ± 1.8

Group M – patients who received maxifloxacin;
Group C – patients who received cefixime;
Group P – patients who received placebo;
SD – standard deviation.

Table 2

Statistical comparison of pain intensity at three follow-ups, based on the number of analgesic tablets taken daily

Follow-up appointment	Group M (*p*-value)	Group C (*p*-value)
1st postoperative day		
Group C	< 0.001	
Group P	< 0.001	0.025
2nd postoperative day		
Group C	< 0.001	
Group P	< 0.001	0.001
7th postoperative day		
Group C	0.051	
Group P	< 0.001	< 0.001

Group M – patients who received maxifloxacin;
Group C – patients who received cefixime;
Group P – patients who received placebo.

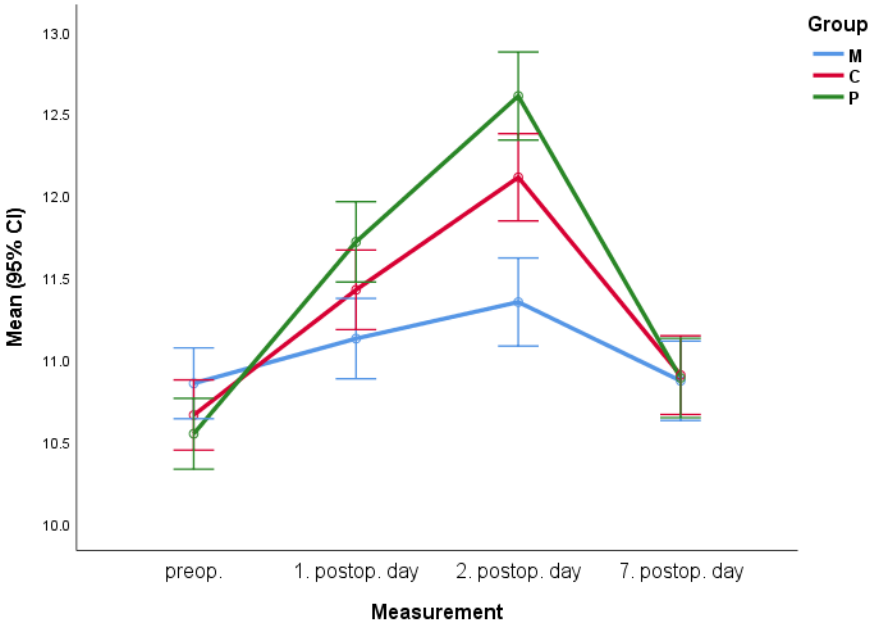


Fig. 2 – Postoperative edema progression, measured as the tragus-chin tip distance in the two study groups (M and C) and the control group (P).
Group M – patients who received maxifloxacin; Group C – patients who received cefixime; Group P – patients who received placebo; CI – confidence interval.

The postoperative Ec, calculated according to the modified Carrillo formula, further revealed that already on the first postoperative day, there was a statistically significant difference among the three groups, which persisted in the following days (Table 3). Moreover, the existence of statistically significant differences across the entire postoperative period was confirmed by comparison between individual groups (Table 4).

The degree of postoperative trismus, indicated by the interincisal distance between the upper and the lower central incisors expressed in centimeters, was measured preoperatively, as well as on the first, second, and seventh postoperative day (Table 5).

It is evident that, in all three groups, the degree of postoperative trismus was the greatest on the first postoperative day and gradually declined until the seventh postoperative day. Moreover, statistical analyses revealed that, relative to the baseline value, the trismus on both the first and second postoperative day was significantly lower in the Group M as well as compared to the Groups C and P. In addition, the degree of postoperative trismus in the Group C was statistically significantly lower compared to the Group P on the first as well as the second postoperative day. On the seventh postoperative day, the measured distance approached the baseline value in the Group M, and the differences in relation to the values measured in the other two groups were less pronounced.

The graph shown in Figure 3 indicates that postoperative trismus was least pronounced in the Group M and that the greatest differences in its degree were recorded on the first postoperative day, with a gradual tendency toward the baseline values by the seventh postoperative day.

The average incidence of dry socket in this study was 12.73%. The comparison of the three groups, however, revealed that none of the subjects in the Group M developed

Table 3

Postoperative edema assessment based on the edema coefficient (Ec) for the tragus-chin tip distance

Follow-up appointment	Patients (n)	Ec (mean ± SD)
1st postoperative day		
Group M	52	2.51 ± 3.18
Group C	53	6.99 ± 5.05
Group P	52	9.00 ± 5.02
2nd postoperative day		
Group M	52	4.13 ± 3.99
Group C	53	13.55 ± 6.83
Group P	52	17.37 ± 6.64
7th postoperative day		
Group M	52	0.13 ± 0.51
Group C	53	2.17 ± 2.26
Group P	52	3.28 ± 2.30

Group M – patients who received maxifloxacin;
Group C – patients who received cefixime;
Group P – patients who received placebo;
SD – standard deviation.

Table 4

Statistical comparison of the postoperative edema coefficient (Ec) measured for the tragus-chin tip distance among the three study groups

Follow-up appointment	Group M (*p*-value)	Group C (*p*-value)
1st postoperative day		
Group C	< 0.001	
Group P	< 0.001	0.036
2nd postoperative day		
Group C	< 0.001	
Group P	< 0.001	0.021
7th postoperative day		
Group C	< 0.001	
Group P		

Group M – patients who received maxifloxacin;
Group C – patients who received cefixime;
Group P – patients who received placebo.

Table 5

Mean postoperative trismus values relative to the baseline and the measurements obtained on each follow-up

Group	Patients (n)	mean ± SD
M		
baseline (preoperative) value	52	4.54 ± 0.61
1st postoperative day	52	3.55 ± 0.62
2nd postoperative day	52	3.92 ± 0.59
7th postoperative day	52	4.59 ± 0.60
C		
baseline (preoperative) value	53	4.67 ± 0.61
1st postoperative day	53	2.99 ± 0.88
2nd postoperative day	53	3.32 ± 0.87
7th postoperative day	53	4.18 ± 0.83
P		
baseline (preoperative) value	52	4.59 ± 0.59
1st postoperative day	52	2.44 ± 0.71
2nd postoperative day	52	2.65 ± 0.75
7th postoperative day	52	3.50 ± 0.93

Group M – patients who received maxifloxacin;
Group C – patients who received cefixime;
Group P – patients who received placebo;
SD – standard deviation.

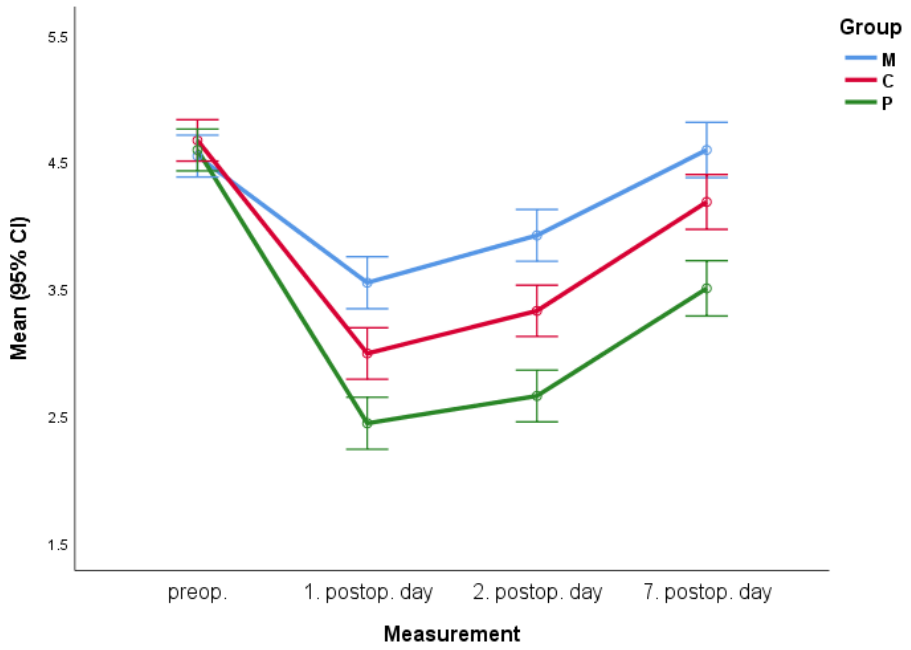


Fig. 3 – Postoperative trismus progression in the two study groups (M and C) and the control group (P). Group M – patients who received maxifloxacin; Group C – patients who received cefixime; Group P – patients who received placebo; CI – confidence interval.

Table 6

Dry socket incidence in the three researched groups

Group	Dry socket, n (%)	
	no	yes
M	52 (100.0)	0 (0)
C	46 (86.8)	7 (13.2)
P	39 (75.0)	13 (25.0)
Total, n (%)	137 (87.3)	20 (12.7)

Group M – patients who received maxifloxacin;
Group C – patients who received cefixime;
Group P – patients who received placebo.

Table 7

Statistical comparison of the significance of difference in dry socket incidence among the three researched groups

Group	M	P
C	0.013[b]	0.124[a]
P	< 0.001[b]	

[a]Pearson's χ^2 test; [b]Fisher's test.
Group M – patients who received maxifloxacin;
Group C – patients who received cefixime;
Group P – patients who received placebo.

dry socket, while 7 and 13 cases were recorded in the Groups C and P, respectively (Table 6). By subjecting findings pertaining to the three groups to the Fisher's nonparametric test, it was shown that the dry socket incidence was statistically significantly lower in the Group M in relation to the other two groups (Table 7).

Discussion

At present, as a part of the impacted mandibular third molar surgery, especially in private dental practice settings, antibiotics are often routinely prescribed due to the prevalent view (which is not based on scientific evidence) that this promotes a safer postoperative course, with fewer postoperative sequelae that commonly accompany this intervention. However, such potentially unnecessary use of antibiotics may lead to adverse consequences (development of resistant microorganism strains and increased risk of allergy to prescribed antibiotics). Thereby, many researchers do not support routine antibiotic use following mandibular third molar surgery unless preoperative infection (pericoronitis) is diagnosed [14–18]. Therefore, the aim of the present double-blind prospective study was to evaluate the efficacy of antibiotic prophylaxis in mitigating discomfort (inflammatory sequelae and dry socket) that most frequently occur after the impacted mandibular third molar surgery.

Due to the fact that many patients are allergic to antibiotics from the penicillin group [24, 25] (commonly prescribed in oral surgery), we investigated two non-penicillin antibiotics (moxifloxacin and cefixime) as potentially useful alternatives for all patients who are allergic to synthetic penicillin or are intolerant to other so-called "first line" antibiotics typically prescribed to treat oral infections (such as macrolides). Nevertheless, it is known that beta-lactam antibiotics, penicillin and its derivatives may have a cross-allergic reaction with cephalosporins (10–30%) and should, therefore, be administered with caution. Still, the latest research shows that the cross-allergic reaction is significantly lower and even negligible with cephalosporins of the second and especially the third generation [26, 27]. Although research on the use of moxifloxacin or cefixime in oral surgery is scant, it is interesting to note that in the few existing investigations, moxifloxacin was shown to be more effective in shortening the recovery period following the surgi-

cal extraction of mandibular third molars than amoxicillin with clavulanic acid [28]. Therefore, moxifloxacin (one of the newer fourth-generation fluoroquinolones used orally) and cefixime (one of the third-generation cephalosporins, also used orally) were examined in this study. Both antibiotics exhibit desirable activity against oral Gram-negative and multidrug-resistant Gram-positive bacteria [29, 30]. In addition, it was particularly advantageous that both antibiotics were manufactured in visually identical tablets and were used once a day, which facilitated the adoption of a double-blind design. Besides, the placebo tablets used by the patients in the control group also had the same appearance as the used antibiotics.

Nonetheless, owing to the double-blind study design, it was impossible to know in advance whether the research groups would be mutually comparable. After opening the codebook, we found that all three groups were comparable in terms of the number of subjects but differed in average intervention duration. This was a potential cause for concern, given that it could influence the incidence of postoperative inflammatory sequelae (pain, edema, trismus) [31, 32], which were the focus of the present investigation. Specifically, in the Group M, on average, the interventions lasted the longest, which indicates more difficult surgical procedures. However, the fact that the percentage of postoperative inflammatory sequelae was the lowest in this group suggested that the prophylactic use of moxifloxacin had a more influential effect on the postoperative course than the case complexity.

The greatest pain intensity, estimated by the number of analgesics used daily, was recorded on the first postoperative day, when pain was statistically significantly greatest in the control group (Group P), followed by the study group where cefixime was prescribed (Group C). Pain intensity gradually decreased during the postoperative period in all groups, as expected, due to the process of successful surgical wound healing. Subsequent comparison of the postoperative pain intensity across the groups revealed that the most favorable results were achieved in the Group M, as patients in this group took analgesics sporadically and only for the first two days, significantly less than in the other two groups.

Moxifloxacin is rarely used in the prophylaxis and therapy of odontogenic infections, which is surprising given that, for example, comparing moxifloxacin with the "gold standard" (amoxicillin with clavulanic acid), Limeres et al. [28] found that moxifloxacin significantly shortened the postoperative recovery time of subjects who underwent mandibular third molar surgery, with faster recovery of oral functions and decreased postoperative pain intensity. However, as the study design did not allow a placebo control group, further verification of the reported findings was needed.

When the three groups in our study were compared with respect to the extent of postoperative edema, a statistically significant difference between the study groups and the control group was noted. Moreover, postoperative edema was least pronounced in subjects who received moxifloxacin. The postoperative edema peaked between the first and the second day following surgery in all three groups, but the values measured at each follow-up were statistically significantly lower in the Group M relative to the other two groups.

In the only study identified during the literature search in which moxifloxacin was used prophylactically following mandibular third molar surgery, postoperative edema was not considered [28]. In other, much more numerous studies, some authors reported a significant reduction in postoperative edema after a course of amoxicillin or amoxicillin with clavulanic acid [12, 33], while others failed to observe such a beneficial effect [34–36].

Among the inflammatory sequelae that may arise following surgical extraction of mandibular third molar surgery, postoperative trismus is probably the most unpleasant for the patient. In our study, postoperative trismus was least pronounced in the Group M. Moreover, on the first and second postoperative day, the degree of postoperative trismus was also statistically significantly lower in the Group C compared to the Group P. These results can be attributed to the anti-inflammatory effect of the prescribed antibiotics.

Dry socket is probably the most challenging complication in wound healing after mandibular third molar surgery. In this study, the overall incidence of dry socket in the full sample was close to 13%, which is consistent with the results published elsewhere [37, 38]. However, it is interesting that the highest percentage of dry socket was, by far, recorded in the control group (in 25% of cases), while approximately half that percentage was recorded among the subjects who used cefixime (Group C), with no cases in the Group M (which received moxifloxacin).

Our findings have explicitly shown that both studied antibiotics (especially moxifloxacin) were effective in alleviating all inflammatory sequelae (pain, edema, and trismus) commonly occurring after surgical extraction of mandibular third molar surgery. This raises the question of the extent to which such a result can be attributed to the antimicrobial action of the applied antibiotics or their anti-inflammatory properties. It is well known that any trauma of soft and osseous tissue causes an acute inflammatory reaction and mobilization of several immune system cells. In this local defense mechanism, various mediators play a complex role, whereby pro-inflammatory cytokines [interleukin (IL)-1, IL-6, tumor necrosis factor (TNF)-α, TNF-β, and others] propagate inflammation through trauma-affected tissues and have been shown to have the capacity to activate prostaglandin secretion [39, 40]. It is noteworthy that fluoroquinolones, especially moxifloxacin, have an anti-inflammatory effect [41], thus influencing the production of IL-1, TNF-α, and IL-6. Hence, the stated anti-inflammatory properties of moxifloxacin can explain its favorable effect on the suppression of inflammatory sequelae after mandibular third molar surgery, as observed in our study.

Even though the results of this research point out favorable anti-inflammatory effects of antibiotics, as well as their positive impact on restoring oral functions in a shorter time and subsequently reduced morbidity, we should still

weigh these benefits against the risks of adverse effects of antibiotic use. To make relevant conclusions and solve the existing controversies, continuing research on this topic is necessary.

Conclusion

It is evident that the initial hypothesis guiding this investigation is largely confirmed. In fact, it is fully supported by the findings related to inflammatory sequelae, given that both antibiotics, especially moxifloxacin, had a pronounced effect on reducing pain, edema, and trismus as the most common postoperative complaints following mandibular third molar surgery. It is interesting, however, that both antibiotics, especially moxifloxacin, also contributed to reducing the incidence of dry socket in the postoperative period, which was unexpected because inflammation is not the cause of dry socket.

REFERENCES

1. *Hupp JR*. Principles of Management of Impacted Teeth. In: *Hupp JR, Tucker MR, Ellis E,* editors. Contemporary Oral and Maxillofacial Surgery. Part II: Principles of Exodontia. 7th ed. St. Louis: Mosby-Elsevier; 2018. p. 161–83.
2. *Martin MV, Kanatas AN, Hardy P*. Antibiotic prophylaxis and third molar surgery. Br Dent J 2005; 198(6): 327–30.
3. *Löffler C, Böhmer F, Hornung A, Lang H, Burmeister U, Podbielski A,* et al. Dental care resistance prevention and antibiotic prescribing modification-the cluster-randomised controlled DREAM trial. Implement Sci 2014; 9: 27.
4. *Oliveira AS, Guerreiro MP*. Influences on antibiotic prescribing by dentists: Insights from a pilot study. Int J Clin Pharm 2015; 37(1): 180.
5. *Cope AL, Chestnutt IG, Wood F, Francis NA*. Dental consultations in UK general practice and antibiotic prescribing rates: A retrospective cohort study. Br J Gen Pract 2016; 66(646): e329–36.
6. *Arteagoitia MI, Ramos E, Santamaría G, Álvarez J, Barbier L, Santamaría J*. Survey of Spanish dentists on the prescription of antibiotics and antiseptics in surgery for impacted lower third molars. Med Oral Patol Oral Cir Bucal 2016; 21(1): e82–7.
7. *Moloney J, Stassen LF*. Pericoronitis: treatment and a clinical dilemma. J Ir Dent Assoc 2009; 55(4): 190–2.
8. *Rodrigues WC, Okamoto R, Pellizzer EP, dos Carrijo AC, de Almeida RS, de Melo WM*. Antibiotic prophylaxis for third molar extraction in healthy patients: Current scientific evidence. Quintessence Int 2015; 46(2): 149–61.
9. *Moreno-Drada JA, García-Perdomo HA*. Effectiveness of Antimicrobial Prophylaxis in Preventing the Spread of Infection as a Result of Oral Procedures: A Systematic Review and Meta-Analysis. J Oral Maxillofac Surg 2016; 74(7): 1313–21.
10. *Arteagoitia I, Diez A, Barbier L, Santamaría G, Santamaría J*. Efficacy of amoxicillin/clavulanic acid in preventing infectious and inflammatory complications following impacted mandibular third molar extraction. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2005; 100(1): e11–8.
11. *Halpern LR, Dodson TB*. Does prophylactic administration of systemic antibiotics prevent postoperative inflammatory complications after third molar surgery? J Oral Maxillofac Surg 2007; 65(2): 177–85.
12. *López-Cedrún JL, Pijoan JI, Fernández S, Santamaria J, Hernandez G*. Efficacy of amoxicillin treatment in preventing postoperative complications in patients undergoing third molar surgery: a prospective, randomized, double-blind controlled study. J Oral Maxillofac Surg 2011; 69(6): e5–14.
13. *Marcussen KB, Laulund AS, Jørgensen HL, Pinholt EM*. A Systematic Review on Effect of Single-Dose Preoperative Antibiotics at Surgical Osteotomy Extraction of Lower Third Molars. J Oral Maxillofac Surg 2016; 74(4): 693–703.
14. *Kaczmarzyk T, Wichlinski J, Stypulkowska J, Zaleska M, Panas M, Woron J*. Single-dose and multi-dose clindamycin therapy fails to demonstrate efficacy in preventing infectious and inflammatory complications in third molar surgery. Int J Oral Maxillofac Surg 2007; 36(5): 417–22.
15. *Prajapati A, Prajapati A, Sathaye S*. Benefits of not Prescribing Prophylactic Antibiotics After Third Molar Surgery. J Maxillofac Oral Surg 2016; 15(2): 217–20.
16. *Xue P, Wang J, Wu B, Ma Y, Wu F, Hou R*. Efficacy of antibiotic prophylaxis on postoperative inflammatory complications in Chinese patients having impacted mandibular third molars removed: a split-mouth, double-blind, self-controlled, clinical trial. Br J Oral Maxillofac Surg 2015; 53(5): 416–20.
17. *Sidana S, Mistry Y, Gandevivala A, Motwani N*. Evaluation of the need for antibiotic prophylaxis during routine intra-alveolar dental extractions in healthy patients: A Randomized double-blind controlled trial. J Evid Based Dent Pract 2017; 17(3): 184–9.
18. *Arteagoitia I, Ramos E, Santamaria G, Barbier L, Alvarez J, Santamaria J*. Amoxicillin/clavulanic acid 2000/125 mg to prevent complications due to infection following completely bone-impacted lower third molar removal: a clinical trial. Oral Surg Oral Med Oral Pathol Oral Radiol 2015; 119(1): 8–16.
19. *Oomens MA, Forouzanfar T*. Antibiotic prophylaxis in third molar surgery: a review. Oral Surg Oral Med Oral Pathol Oral Radiol 2012; 114(6): e5–12.
20. *Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, Schünemann HJ*. GRADE Working Group. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ 2008; 336(7650): 924–6.
21. *Moreira MR, Carneiro RP, Freire DR, Guimaraes T, Batista de Melo GG*. Antimicrobial Modulator of Inflammatory Response in Third Molar Surgery Compared with Conventional Medication. J Res Dent 2019; 7(5): 83–6.
22. *Dalhoff A*. Immunomodulatory activities of fluoroquinolones. Infection 2005; 33 Suppl 2: 55–70.
23. *Carrillo JS, Calatayud J, Manso FJ, Barberia E, Martinez JM, Donado M*. A randomized double-blind clinical trial on the effectiveness of helium-neon laser in the prevention of pain, swelling and trismus after removal of impacted third molars. Int Dent J 1990; 40(1): 31–6.
24. *Macy E, Romano A, Khan D*. Practical Management of Antibiotic Hypersensitivity in 2017. J Allergy Clin Immunol Pract 2017; 5(3): 577–86.
25. *Blumenthal KG, Lu N, Zhang Y, Walensky RP, Choi HK*. Recorded Penicillin Allergy and Risk of Mortality: a Population-Based Matched Cohort Study. J Gen Intern Med 2019; 34(9): 1685–7.
26. *Chaudhry SB, Veve MP, Wagner JL*. Cephalosporins: A Focus on Side Chains and β-Lactam Cross-Reactivity. Pharmacy (Basel) 2019; 7(3): 103.
27. *D'Errico S, Frati P, Zanon M, Valentinuz E, Manetti F, Scopetti M,* et al. Cephalosporins' Cross-Reactivity and the High Degree of Required Knowledge. Case Report and Review of the Literature. Antibiotics (Basel) 2020; 9(5): 209.
28. *Limeres J, Sanromán JF, Tomás I, Diz P*. Patients' perception of recovery after third molar surgery following postoperative treatment with moxifloxacin versus amoxicillin and clavulanic acid: a randomized, double-blind, controlled study. J Oral Maxillofac Surg 2009; 67(2): 286–91.

29. *Shahbaz K.* Cephalosporins: pharmacology and chemistry. Pharm Biol Eval 2017; 4(6): 234–8.
30. *Pham TDM, Ziora ZM, Blaskovich MAT.* Quinolone antibiotics. Medchemcomm 2019; 10(10): 1719–39. D
31. *Yuasa H, Kawai T, Sugiura M.* Classification of surgical difficulty in extracting impacted third molars. Br J Oral Maxillofac Surg 2002; 40(1): 26–31.
32. *Blondeau F, Daniel NG.* Extraction of impacted mandibular third molars: postoperative complications and their risk factors. J Can Dent Assoc 2007; 73(4): 325.
33. *Ndukwe KC, Braimah RO, Owotade JF, Aregbesola SB.* Comparative Efficacy of Amoxicillin/Clavulanic Acid and Levofloxacin in the Reduction of Postsurgical Sequelae After Third Molar Surgery: A Randomized, Double-Blind, Clinical Trial in a Nigerian University Teaching Hospital. Niger J Surg 2016; 22(2): 70–6.
34. *Siddiqi A, Morkel JA, Zafar S.* Antibiotic prophylaxis in third molar surgery: A randomized double-blind placebo-controlled clinical trial using split-mouth technique. Int J Oral Maxillofac Surg 2010; 39(2): 107–14.
35. *Lacasa JM, Jiménez JA, Ferrás V, Bossom M, Sóla-Morales O, García-Rey C,* A, et al. Prophylaxis versus pre-emptive treatment for infective and inflammatory complications of surgical third molar removal: a randomized, double-blind, placebo-controlled, clinical trial with sustained release amoxicillin/clavulanic acid (1000/62.5 mg). Int J Oral Maxillofac Surg 2007; 36(4): 321–7.
36. *Monaco G, Tavernese L, Agostini R, Marchetti C.* Evaluation of antibiotic prophylaxis in reducing postoperative infection after mandibular third molar extraction in young patients. J Oral Maxillofac Surg 2009; 67(7): 1467–72.
37. *Bergdahl M, Hedström L.* Metronidazole for the prevention of dry socket after removal of partially impacted mandibular third molar: a randomised controlled trial. Br J Oral Maxillofac Surg 2004; 42(6): 555–8.
38. *Noroozi AR, Philbert RF.* Modern concepts in understanding and management of the "dry socket" syndrome: comprehensive review of the literature. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2009; 107(1): 30–5.
39. *Euler GJ, Miller GA, Hutter JW, D'Alessandro MM.* Interleukin-6 in neutrophils from peripheral blood and inflammatory periradicular tissues. J Endod. 1998; 24(7): 480–4.
40. *Balto K, Sasaki H, Stashenko P.* Interleukin-6 deficiency increases inflammatory bone destruction. Infect Immun 2001; 69(2): 744–50.
41. *Dalhoff A, Shalit I.* Immunomodulatory effects of quinolones. Lancet Infect Dis 2003; 3(6): 359–71.

Received on September 9, 2020
Revised on November 9, 2020
Accepted on November 19, 2020
Online First December, 2020