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Use of antibiotics after lower third molar surgery – useful or harmful procedure? A randomized, double-blind, placebo-controlled trial

Примена антибиотика после хируршког вађења доњег трећег молара – корисна или штетна процедура?
Рандомизована, двоструко-слепа, плацебо-контролисана студија

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SUMMARY

Introduction/Objective The aim of the present study was to investigate the effects of moxifloxacin and cefixime in preventing postoperative infection following mandibular third molar surgery.

Methods Double-blind study was completed by 157 patients undergoing surgical removal of mandibular third molars. Patients were randomly assigned to three groups: moxifloxacin (M), cefixime (C) and placebo (P). Patients in each group were classified into two subgroups: subgroup (a) without previous history of pericoronitis and subgroup (b) with previous history of pericoronitis. All patients were evaluated at the postoperative follow-ups on the first, second and seventh postoperative day.

Results Postoperative infections were registered only in patients with history of pericoronitis. Antibiotic prophylaxis with cefixime, and moxifloxacin, reduced the occurrence of postoperative infection. Overall incidence of postoperative infections was 6.4%. All postoperative infections were registered in placebo-group, where the incidence of postoperative infection was 19.2%. Microbiological tests verified the clinically obtained results. Isolated microflora was resistant to penicillin-derived antibiotics in 50% of cases.

Conclusion Prophylactic use of antibiotics after third molar surgery should be weighted against potential risks and benefits and could be considered in cases with previous history of pericoronitis, when complicated surgical extraction is performed.

Keywords: third molar surgery; antibiotic prophylaxis; postoperative complications; drug resistance; microbial susceptibility tests

САЖЕТАК

Увод/Циљ Циљ студије био је да се испита ефекат моксифлоксацина и цефиксима на сузбијање инфекције након хируршког вађења доњих трећих молара.

Метод Двоструко-слепа студија спроведена је на 157 пацијената којима су хируршки уклоњени доњи трећи молари, а који су насумично распоређени у једну од три групе: моксифлоксацин (М), цефиксим (Ц) или плацебо (П). Пацијенти из сваке групе распоређени су у две подгрупе: подгрупу (а) без претходне историје перикоронтиса, и подгрупу (б) са претходном историјом перикоронитиса. Пацијенти су контролисани на постоперативним прегледима првог, другог и седмог постоперативног дана.

Резултати Постоперативна инфекција регистрована је искључиво код пацијената са претходном историјом перикоронитиса. Антибиотска профилакса цефиксимом или моксифлоксацином смањила је појаву постоперативне инфекције. Укупна инциденца постоперативних инфекција била је 6,4%. Сви случајеви постоперативне инфекције регистровани су у групи која није примала антибиотике већ плацебо, где је инциденца инфекција била 19,2%. Микробиолошке анализе потврдиле су клинички добијене резултате. Изолована микрофлора била је резистентна на деривате пеницилина у 50% случајева.

Закључак У склопу профилактичке примене антибиотика после хируршког вађења доњих трећих молара треба узети у обзир потенцијане ризике и бенефите, а може се сматрати сврсисходном у случајевима са претходном историјом перикоронитиса, као и у случају компликованијих хируршких екстракција.

Кључне речи: хирургија трећих молара; антибиотска профилакса; постоперативне компликације; резистенција на лекове; тестови осетљивости микроорганизама

INTRODUCTION

Amoxicillin (alone or in combination with clavulanic acid), as well as clindamycin and metronidazole, have long history of success in treatment of odontogenic infections. These are still the most commonly used antibiotics in oral surgery due to the fact that oral microorganisms are mostly susceptible to them. Therefore, it's not surprising that majority of published studies related to the use of antibiotics in oral and maxillofacial surgery, both for prophylaxis and treatment of odontogenic infections, were done with amoxicillin or antibiotics of similar antimicrobial spectrum [1].

However, due to the growing number of patients being allergic to penicillin derivatives [2] as well as the increasing occurrence of oral microorganisms resistant to penicillin and several other antibiotics [3], there is a growing need for research directed towards antibiotics that could be an alternative to amoxicillin and other antibiotics with similar antibacterial spectrum in prevention and treatment of oral infections. Among novel antibiotics, it seems that fluoroquinolones (especially moxifloxacin) and third generations of cephalosporins (especially cefixime) to be promising in that regard. Both are effective against many microorganisms resistant to other antibiotics, including amoxicillin [4, 5]. Moreover, they have different pharmacokinetic properties from penicillin derivatives and may demonstrate (especially moxifloxacin) some anti-inflammatory and immunomodulatory effects [6], which is desirable in prophylaxis or treatment of odontogenic infections.

On the other hand, inadequate prescribing accelerates the development of bacterial resistance to a large number of antibiotics, which could have unforeseeable consequences for health care worldwide in the future. Antibiotic resistance is currently one of the biggest public health problems today, resulting in significant decreases in infection treatment efficiency, an increase in multidrug-resistant bacterial strains, and increased morbidity and mortality, with repercussions for the health system as a whole [7]. The World Health Organization (WHO) report makes it clear that this is not a phenomenon in poor or developing countries - the problem of bacterial resistance is now being observed around the world [8].

We intended to test the efficacy of moxifloxacin and cefixime in preventing postoperative infection after mandibular third molar surgery [9, 10]. The goal of our study was to investigate whether prophylactic use of moxifloxacin and cefixime has significant impact on rate of

postoperative infections after third molar removal. Having an increased antibiotic resistance in mind, our goal was also to determine under what circumstances recommendations on their prophylactic use can be justified.

METHODS

This clinical research, approved by the Ethics Committee of the Dental Clinic of Vojvodina, with the decision number 01-33/8-2019 and registered of the NIH - ClinicalTrials.gov with ID NCT05027893, was carried out as a double-blind, prospective, placebo-controlled clinical study. All patients included in the study were ≥18 years old, indicated for surgical removal of the impacted mandibular third molars, with good systemic health (classified as ASA I and ASA II) [11]. Exclusion criteria: hypersensitivity to study drugs; history of systemic antibacterial therapy within 6 months prior to randomization; pregnancy or breastfeeding; fluoroquinolone-related tendon disorder; clinically relevant cardiac conditions or current use of QT interval prolonging drugs; severe hepatic insufficiency (Child–Pugh C); cases where, in addition to removing the impacted mandibular third molar, some other oral surgical procedure was performed; patients with currently present pericoronitis.

It was assumed that the percentage of infection in prophylactic groups would be similar and no more than 1%, while in the placebo group, it would be higher, approximately 15%. Sample size was calculated as a difference between two proportions (1% and 15%). Using 80% power and alpha=0.05, 56 patients per group was determined sufficient to achieve 80% to detect significant differences between groups.

Patients were randomly and equally assigned to treatment groups. Randomization was performed using a complete randomization algorithm (R software for Windows, package "randomizeR"), allocation ratio 1:1:1 and sample size 165 (55 per group). Randomization list was created with three groups and consequent numbers from 1 to 165. The medication boxes were marked using a specific ID consisting of 3 digits and 2 letters, generated by R software. The IDs were randomly assigned to the randomization list numbers and the final randomization list consisted of ID and list number. Consecutive patients were assigned to a specific group by reading the list number and giving the medication box with specific ID for that number. Only

third party members, who were not involved in patient care, had all lists in one place and could identify the medication (to be used for emergency unblinding purposes if needed). That person was available 24/7 via mobile phone number provided to the participants.

The manufacturers (Hemofarm DOO, Vršac, Serbia and Alkaloid DOO, Skopje, North Macedonia) created the boxes for medications to be identical by instruction of the research team. The boxes with film-coated tablets were the same shape, size, color, and taste. Placebo tablets were created using the same instructions (PhytoNet DOO, Belgrade, Serbia).

After the screening, all participants that fulfill the enrollment criteria (inclusion/exclusion) were blindly assigned to a specific group by randomization list. Eight patients were classified as dropouts due to either non-compliance (n=4) or failure to appear for the control visit (n=4).

Mandibular third molar surgeries were performed by 5 oral surgeons (Figure 1). All surgeries performed under local anaesthesia, using 4 ml of 2% lidocaine with adrenaline 1:80,000. Flaps were elevated, bone removed with surgical burrs and third molars sectioned as needed to facilitate removal. All wounds sutured with non-resorbable 3-0 black silk sutures. The sutures were removed on the seventh postoperative day. Patients were advised to take an analgesic containing 200 mg of ibuprofen and 325 mg of paracetamol if needed.

All patients postoperatively received film-coated tablets with either 400 mg of moxifloxacin or 400 mg of cefixime *per os*. One third of patients received placebo-tablets containing indifferent substances with no antimicrobial action (99% microcrystalline cellulose, 0.5% silicon dioxide and 0.5% magnesium stearate). Surgeons who performed surgery were blinded to the type of tablet which patients received. All used film-coated tablets were administered for the first five days postoperatively, once a day, in a double-blind manner. All patients were evaluated at the postoperative follow-ups on the first, second and seventh postoperative day.

Postoperative infection was diagnosed based on the presence of local signs of inflammation and systemic signs of infection (elevated body temperature, accelerated erythrocyte sedimentation, leucocytosis).

Swab samples were obtained from surgical wounds of patients with signs of postoperative infection, and microbiologically analysed. The susceptibility of isolated microorganisms to moxifloxacin, cefixime and other antibiotics commonly used in oral and maxillofacial surgery was tested by culture on antibiotic-containing media. Regarding the susceptibility to antimicrobial drugs, bacteria were classified according to the growth inhibition zone, into three categories: susceptible (S), intermediate (I) and resistant (R).

After the study was completed and the codebook was opened, results were grouped by type of treatment into three groups: moxifloxacin (M), cefixime (C) and the placebo (P). Based on the previous history of pericoronitis, patients in each group were classified into two subgroups: patients without previous history of pericoronitis (a) and patients with previous history of pericoronitis (b).

The manuscript was reported in accordance with the CONSORT statement [12]. Primary outcome was identified as occurrence of postoperative infection. Secondary outcomes were subgroup analysis (previous history of pericoronitis or not) and identified as susceptibility of isolated microorganisms to antibiotics (in cases where swab samples were obtained).

Results are presented as count and percent (where appropriate). Group comparisons were performed using Fisher's Exact test. P values less than 0.05 were considered significant. All data were analyzed using SPSS 20.0 (IBM corp.) statistical software.

RESULTS

The clinical study included 165 patients who were indicated for surgical removal of impacted mandibular third molar. Eight patients were excluded from the study due to non-compliance with the postoperative instructions or not showing up to follow-up exams. The template for the CONSORT flow diagram [12] is shown in Figure 2. The study, in accordance with the described method, was completed by a total of 157 patients, so that the first study group, group (M), consisted of 52 patients (subgroup (a) of 39 patients, subgroup (b) of 13 patients), the second study group (C) 53 patients (subgroup (a) of 39 patients, subgroup (b) with of 14 patients), and the control group (P) 52 patients (subgroup (a) of 39 patients, subgroup (b) of 13 patients). Mean patient age was 26.7 with standard deviation 8.85 in group M; 24.2

with standard deviation 5.11 in group C, and 25.5 with standard deviation 5.44 in group P. Gender distribution in groups was as follows: group M (59.6% female, 40.4% male); group C (73.6% female, 26.4% male), group P (75% female, 25% male).

In our study, the overall incidence of postoperative infections was 6.4%. Interestingly, we did not register any *de novo* infection - all cases of postoperative infection occurred in patients who had preoperative history of pericoronitis (subgroup b), and all these cases belonged to the placebo-group P (Table 1).

The difference between each of the study groups (groups M and C) and the control placebo-group (group P) regarding the occurrence of postoperative infection was confirmed with Fisher's test of exact probability ($p < 0.001$).

There is a statistically significant difference in the predisposition to infection with previous history of pericoronitis (Table 2). Patients of the group P, subgroup (b), had a postoperative infection in 77% of cases (10/13 patients). Patients without previous history of pericoronitis remained infection-free following surgery (0%, 0/39 patients).

Patients with diagnosed postoperative infection were under close supervision for three weeks after surgery. In cases where postoperative infection was diagnosed in the placebo group, standard therapy was administered – amoxicillin with clavulanic acid (or in case of allergy to amoxicillin, azithromycin was used). After the microbial identification of the causative agent(s), and in case of its resistance to amoxicillin with clavulanic acid or azithromycin, antibiotic therapy was modified in accordance with microbiological susceptibility.

Out of 23 analysed samples, 5 were taken preoperatively from the examinees from each of the study groups (M and C), who had history of pericoronitis (subgroups b). A total of 13 samples were taken from the control placebo-group P; 3 samples preoperatively around the tooth with history of pericoronitis, and 10 samples from the operative wound of the patients with signs of postoperative infection before giving antibiotic therapy. Samples were tested for susceptibility to the researched antibiotics, as well as to the other antibiotics usually used in oral surgery (Table 3).

As shown in Table 3, all the swabs were susceptible to moxifloxacin. It is interesting to note that three swabs with strictly pathogenic *Staphylococcus aureus* were resistant to ampicillin, amoxicillin, amoxicillin with clavulanic acid, and had intermediate susceptibility to clindamycin. Resistance to moxifloxacin was not observed in any of the samples taken, and resistance to cefixime was noted in only one case.

DISCUSSION

Justification for the use of antibiotics relative to mandibular third molar surgery has been a controversial topic. Lang et al. [13] found as many as 42 different protocols for antibiotic administration following this procedure (in terms of type, dose, timing, and mode of delivery). Many authors conducted prospective, placebo-controlled clinical trials, with similar methods, and in most studies the antibiotic in the study group was amoxicillin (with or without clavulanic acid), administered in single preoperative dose or three to five days after surgery. The conclusions are mainly reduced to the common consensus that there is sufficient evidence for use of these antibiotics for third molar surgery, because the benefit does not outweigh the risk of side effects [14]. Recently, Cervino et al. [15] proposed a modified protocol that is based on the administration of amoxicillin or amoxicillin with clavulanic acid before and after intervention, but, again, has left many questions unanswered. The conclusion was that it was necessary to find an alternative to existing, especially penicillin-derived antibiotics [15].

Chugha et al. [9] observed heterogeneity in the design of the studies and the method of antibiotics administration. Better evidence and justification are needed in this area, as many strong recommendations are currently made on the basis of weak evidence [16].

Moxifloxacin and cefixime have been labelled by many authors as a realistic therapeutic alternative to existing antibiotics widely used in oral and maxillofacial surgery [5, 17]. Cachovan et al. [18] demonstrated that moxifloxacin penetrates very well into oral tissues, reaches high concentrations in bone, and is well resorbed after oral administration. Moreover, moxifloxacin is very effective against oral pathogens, especially against the periopathogen *Aggregatibacter actinomycetemcomitans*, as well as against *Porphyromonas gingivalis*, *Prevotela intermedia* and *Tannerella forsythia* [19]. Efficacy of oral treatment with moxifloxacin and amoxicillin with clavulanic acid on oral function and quality of life after

third molar surgery demonstrated that moxifloxacin shortened the period of postoperative recovery [20].

In our study, the frequency of postoperative infection in control group P was extremely high (19.2%). Data on the frequency of infection after this surgery vary depending on the assessment method. Most studies indicate that the prevalence of postoperative infection is in 1-10% range, which is lower than in our study [21]. Patients with previous history of pericoronitis had postoperative infection in 77% of cases, while none of the patients without previous history of pericoronitis developed postoperative infection (0%). All the cases of postoperative infection occurred in the group that did not receive antibiotics postoperatively. Some studies suggest that randomized controlled trials should be performed and a cause-and-effect relationship between previous history of pericoronitis and more frequent postoperative infection after mandibular third molar surgery should be established [22], while others have shown that postoperative infection is statistically higher in patients with previous history of pericoronitis [23].

We also observed three postoperative infections where *Staphylococcus aureus* was isolated from the sample; in all other cases we registered polymicrobial flora dominated by viridians streptococci. The results of microbiological analysis verified the results of clinical trials, because the microorganisms isolated from all swab samples were susceptible to moxifloxacin. All samples were susceptible to cefixime, except one case with coagulase-negative staphylococci (CoNS). Also, in 50% of the samples taken, resistance to ampicillin, amoxicillin and amoxicillin with clavulanic acid was registered, which is very concerning (Table 3). Microbiological analysis of samples obtained from odontogenic abscesses concluded that odontogenic infections are polymicrobial. Moxifloxacin had promising *in vitro* activity against odontogenic pathogens such as the viridans and hemolytic streptococci, *Strep. anginosus* and *Strep. mitis* group and *Neisseria spp.* [4]. Moxifloxacin was also effective against more than 90% of isolated strict anaerobes, predominantly *Prevotella spp.* [24]. Treatment of severe odontogenic infections comparing moxifloxacin, amoxicillin with clavulanic acid and clindamycin, in the mixed aerobic-anaerobic bacterial flora, showed at least one of the pathogens was resistant to penicillin in 50% of the patients, and a rate of increase in resistance to clindamycin was also noticeable [4, 25]. Due to its high tissue penetration and concentration in bone tissue, moxifloxacin has shown promising results [18, 24]. Because of the broader activity and reduced dosing frequency (administration only once daily), the use of

moxifloxacin instead of clindamycin in penicillin-allergic patients seems worth considering [4, 24].

Antibiotic prophylaxis with moxifloxacin and cefixime, reduced the occurrence of postoperative inflammatory sequelae (pain, swelling and trismus) . It is interesting, that both antibiotics, especially moxifloxacin, also contributed to reducing the incidence of postoperative dry socket, which is not provoked by inflammation [26].

Adequate antibiotic treatment comprises the administration of the appropriate antibiotic in optimal dose through the correct route of administration [27]. Nevertheless, antibiotics have been associated with considerable side effects, thus their use should be adequate and according to guidelines. Our finding that several patients in group P did not have postoperative infections confirms that antibiotics are not an absolute requirement in all surgical cases.

Side effects of fluoroquinolones include headaches, tendonitis, and transient neurological effects in elderly population [28]. In addition, some relatively benign side-effects are observed, such as nausea, vomiting and diarrhoea [29].

We did not include group with amoxicillin (with or without clavulanic acid) due to different dosing regimen which makes double-blind design impossible, and this is a relative limitation of the study. Another limitation of our study is a relatively small sample size, which should be considered when estimating the strength of data given here in. Finally, even though isolated microorganisms have demonstrated resistance to penicillin and its derivatives, we cannot claim with certainty that those species/strains have caused the infection, considering that all specimens contained polymicrobial flora.

Our study also indicates that antibiotics should not be prescribed generally in all cases. Over prescribing is fuelling a global increase in bacterial resistance, which is becoming a major public health challenge around the world [7]. Considering the increase in antimicrobial resistance, a growing awareness on the search for new antibacterial agents is essential, and the choice of moxifloxacin and cefixime to prevent posteperative infections after third molar surgery seems appropriate, not only because of the aforementioned benefits, but also because of the simplified dosing regimen, avoiding drug interactions in polymedicated patients (patients who use multiple medications), monotherapy options, and thus better compliance and adherence [30].

Ultimately, the decision to prescribe antibiotics, should be made on case-by-case basis, considering the complexity of the surgical case and well as risks and benefits of antibiotic prophylaxis.

CONCLUSION

We found a cause-and-effect relationship between previous history of pericoronitis and frequent postoperative infections after mandibular third molar surgery, while no infections were observed in patients without such history. This indicates that prior history of pericoronitis may be a decisive risk factor, and that prescribing prophylactic antibiotics may be unwarranted in cases where such a history is absent. Restraint and appropriate practices in antibiotics prescribing would be very helpful in limiting further spread of microbial resistance, and in maintaining efficacy of existing drugs. However, our study did not include the analysis of time elapsed between the last pericoronitis episode (in cases with history of pericoronitis) and date when surgery was performed, which may influence the relative risk of postoperative infection.

While strong recommendations require a more powerful study with a larger number of patients, our data provide evidence that in cases where prophylactic antibiotics are warranted, moxifloxacin and cefixime provide good protection against postoperative infection, and should be considered for use in that context.

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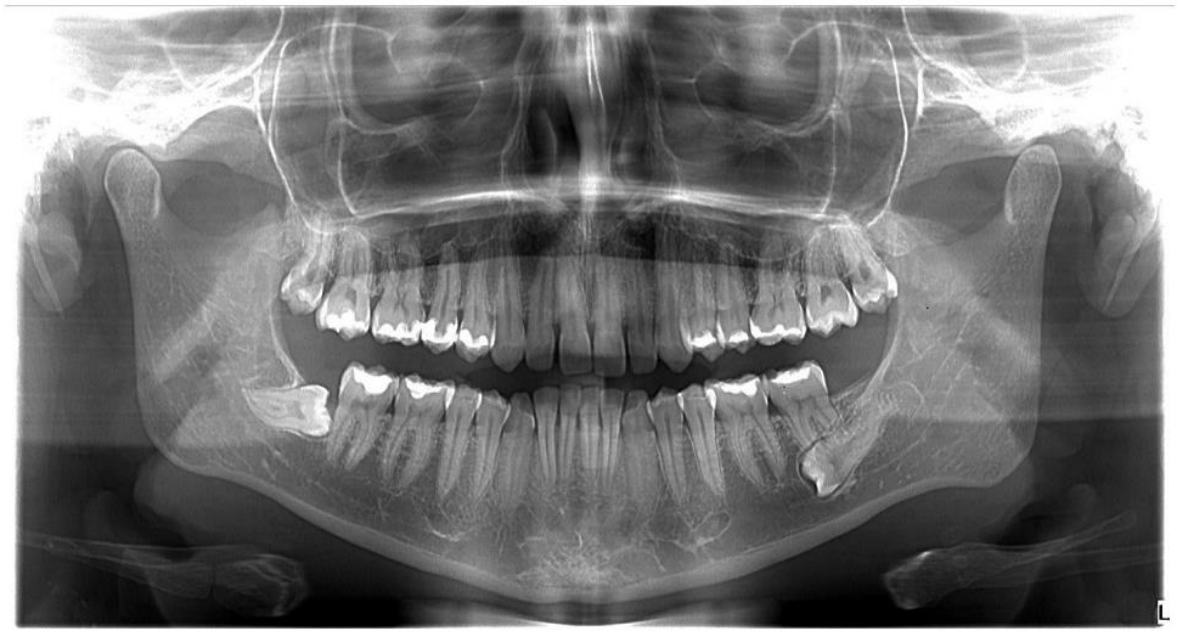

Figure 1. Panoramic radiograph of a patient included in this study (lower right third molar with previous history of pericoronitis was removed)

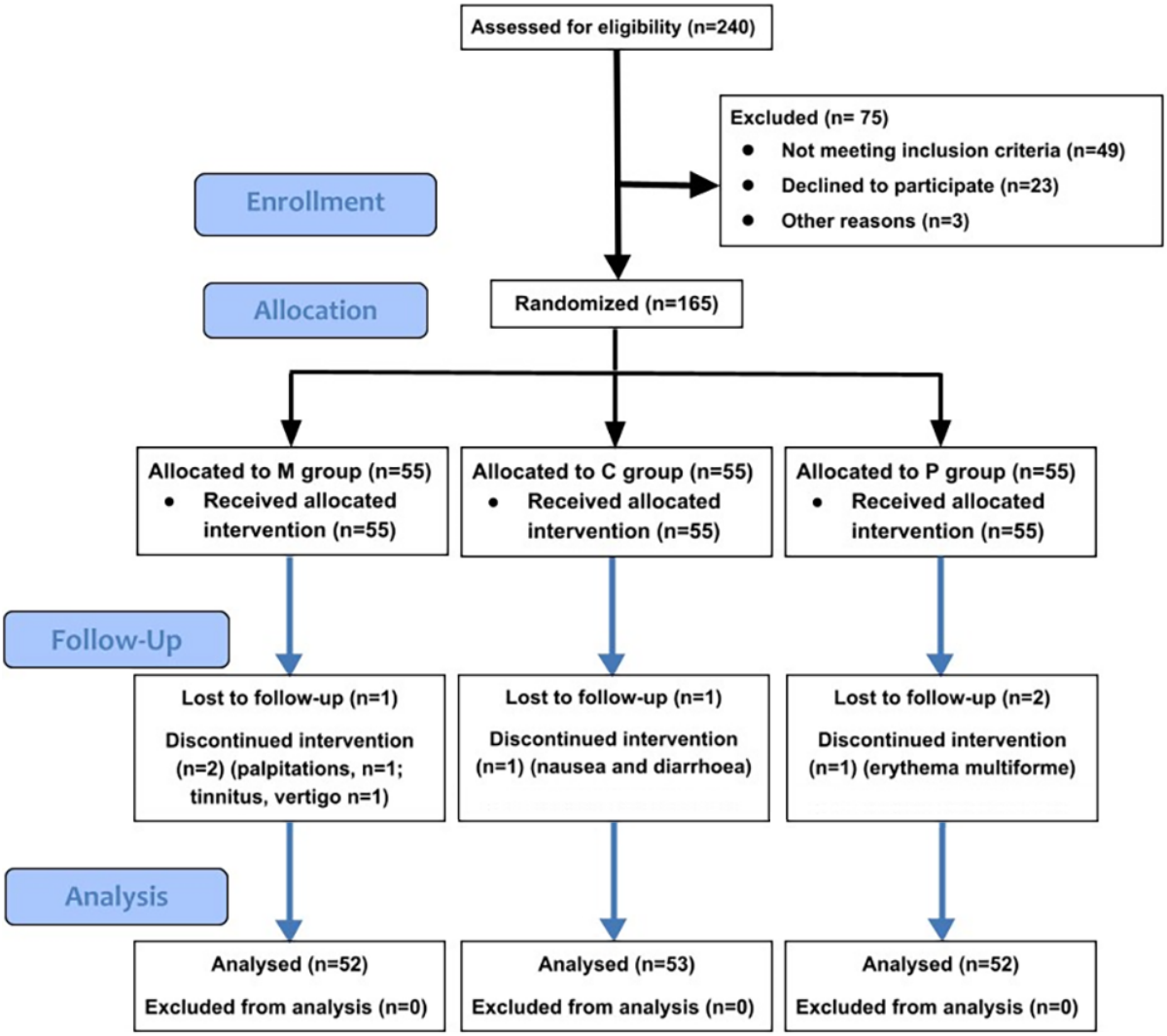

Figure 2. Flow diagram of the progress through the phases of a 3-group parallel randomized trial [12]; [downloaded Sep 2, 2021]; available from: http://www.consort-statement.org/

Table 1. Incidence of postoperative infection in the research groups

			Postoperative infection		Total
			no	yes	
Group	M	n	52	0	52
		%	100	0	100
	C	n	53	0	53
		%	100	0	100
	P	n	42	10	52
		%	80.8	19.2	100
Total		n	147	10	157
		%	93.6	6.4	100

Group M – research group receiving moxifloxacin;

Group C – research group receiving cefixime;

Group P – control group receiving placebo

Table 2. History of pericoronitis and postoperative infection

Parameter	Moxifloxacin (n = 52)	Cefixime (n = 53)	Placebo (n = 52)	p
History of pericoronitis	13 (25%)	14 (26.4%)	13 (25%)	0.982[a]
Postoperative infection	0	0	10 (19.2%)	< 0.001[b]

[a]Pearson χ^2;

[b]Fisher's exact test

Table 3. Susceptibility of samples obtained from the infected postoperative wounds or from the space around the tooth to test antibiotic

Antibiotic	Research Group												Total
	Moxifloxacin (M)			Cefixime (C)			Placebo (P)						
	History of pericoronitis			History of pericoronitis			History of pericoronitis			Postop. infection			
	S	I	R	S	I	R	S	I	R	S	I	R	
Moxifloxacin	5			5			3			10			23
Cefixime	5			5			2		1	9		1	23
Ampicillin	4		1	5			1		2	5		5	23
Amoxicillin	4		1	5			1		2	5		5	23
Amoxicillin + CA	4		1	5			2		1	6		4	23
Tetracycline	5			4		1			3	6		4	23
Clindamycin	5			4	1		3			8		2	23
Total samples	5			5			3			10			23

S – susceptible; I – intermediate; R – resistant; CA – clavulanic acid

