**Does a single dose of systemic antibiotic prevent postoperative inflammatory complications after lower third molar surgery? A randomized controlled trial**

**INTRODUCTION**

Following a protocol in healthy patients, surgical procedures in the oral cavity have up to 3% of risk for development of infection[1]. The polymicrobial flora in the oral cavity, greatly represented by anaerobes, has a significant impact on the development of odontogenic infections, in particular postoperatively [2,3]. The third molar surgery (M3) comprises more than a half of all the procedures in oral surgery. Although these procedures are classified as so called ‘clean’ surgery, a prophylactic application of antibiotics is occasionally carried out in previously diagnosed pericoronitis or apical inflammation[1]. The operative procedure causes a damage to the surrounding bone and soft tissue, which can lead to an imbalance of microorganisms in the oral cavity and the development of postoperative complications. These complications are commonly related to the age, sex and general health of the patient, the grade of impaction and the duration of the surgical procedure, previous infections, condition of the tooth, hygiene of the oral cavity, other pathological changes in the immediate vicinity of the third molar, the surgeon’s experience etc. [4-6]. Inflammatory reactions as pain, swelling, limitations in mouth opening, increased body temperature and general weakness of the patient are possible postoperative complications after M3 surgery. In some of the cases, postoperative hemorrhage or local purulent inflammation can appear, and may cause bacteremia which can then lead to a septic condition.

The pain following a surgical removal of the lower M3 has been the subject of investigation for decades, with the aim of improving the quality of life of patients in the postoperative period. The studies reviewed have not pointed to the effectiveness of the routine use of systemic antimicrobial drugs in preventing or reducing postoperative pain after the removal of impacted third molars in normal circumstances [7-8].

The aim of the presented study was to evaluate the effectiveness of a single prophylactic dose of amoxicillin in the prevention of local and systematic complications after lower third molar removal. The aim was also to propose clinical guidelines with respect to anantibiotic regimen.

**METHODS**

**Study design and sample description**

The study was registered via Clinical Trials (www.clinicaltrials.gov) with reference number ID of this study NCT03130933 and name of the trial register „Complications after lower third molar surgery“.

This prospective study was performed at the Department of Oral Surgery of the Clinical Hospital Dubrava, Zagreb, Croatia, in the period from April 2010 to November 2016. All patients voluntarily agreed to participate in the study and signed informed written consents.  The study was approved by the Ethics Committee of the School of Dental Medicine, Zagreb, Croatia (81-2009), according to the Declaration of Helsinki –Ethical principles for medical research involving human subjects. The identity of the subjects was protected in all phases of the study.

The exclusion criteria in this study were systematic diseases with increased risk for local infections, current smoking, pregnancy, lactation, usage of oral contraceptive drugs and any antibiotic coverage and sensitivity to penicillin.

The sample consisted of systematically healthy subjects between the ages of 18 to 40 (both genders) and having semi-impacted lower third molars indicated for surgical removal randomly divided into two main groups of patients. Unlike the patients from the second group, the first group of patients had never been diagnosed an inflammation in third molar area prior to the surgical procedure. The main test groups were further divided in two subgroups (control and tested): the tested subgroup (100 patients) received a prophylactic single dose of 2 grams of amoxicillin an hour prior to the procedure, while the second control subgroup (100 patients) received a placebo. No one knew what they have received, except researcher. The selection of the third molars for control and study subgroup was made according to the Pederson difficulty index [9]. According to this index (Table 1), the patients were classified into three groups: easy, moderate and difficult. The patients from this study who were classified into a difficult group were excluded from the study, due to a longer and more complicated surgical procedure with an expected prolonged recovery period and possible postoperative complications.

**Surgical procedure**

Before the surgery all patients were informed in detail about the surgical procedure, its side effects, potential complications and possible risks. The surgical procedure was performed by the oral surgeons with more than 5 years of experience, in order not to influence the trauma level by the therapist’s surgical experience. All surgical procedures were performed under local anesthesia (alveolar nerve block) with 2% lidocaine chloride, 1.8 ml, containing 1:80000 adrenaline (Belupo, Koprivnica, Croatia). Local anesthetic quantity in each procedure was two ampoules per patient. Before the procedure, every patient was asked to rinse the mouth with 0.2% chlorhexidine.  The incision was of sufficient size in order to allow good visibility. The full-thickness mucoperiosteal flap was raised using a buccal approach, an adequate osteotomy was done using micromotorhandpiece and bur, and third molar removal was finished using elevating instruments in the appropriate direction. The removal of bone dust, granulation tissue and broken tooth fragments was done in order to wound toileting. Gentle, sterile saline irrigation was done in the end. Primary closure of the surgical area was performed using 3-0 silk sutures (Silkam, B.Braun, Spain). No dressings or haemostatic agents were used after procedures. The average duration of the procedure was approximately 30 minutes per patient.The sutures were removed on the seventh postoperative day at the clinical follow-up. The patients received identical postoperative instructions and were advised to avoid smoking, exertion and to limit their activity for at least the rest of the day. They were asked to apply ice to their face for the first 24 hours and to keep their face elevated in order to reduce swelling. Rinsing and irrigating of the wound was not allowed for the first two days. They were instructed to brush their teeth, but to avoid brushing near the surgical wound for two days.

**Post-operative evaluation**

The patients were recalled for follow-ups on post-operative days one and seven. In all tested groups, the data was obtained by using identical questionnaires. The following symptoms were assessed: pain, swelling, wound healing- alveolar osteitis (AO), infection at the surgical site (SSI) , maximum range of inter-incisal opening of mouth, increased body temperature and hemorrhage. A postoperative follow-up was always done by the same surgeon. Patients evaluated their postoperative pain with the grades ranging from 0-10 according to the visual analogue scale (VAS)  The surgeon evaluated the type of post-extraction alveolus healing as normal healing, acute inflammation followed by infected alveolus or dry socket. The surgeon who assessed wound swelling did not know which group the patient was allocated to. The method of assessing the swelling was described in our previous study. The post-operative swelling was assessed on postoperative days one and seven, using a four-point scale as follows: 0=no swelling, 1=mild swelling, 2=moderate swelling, 3=severe swelling [10].

The maximum inter-incisal opening of the mouth was calculated from the mesioincisal angle of the ipsilateral mandibular central incisor to the mesioincisal angle of the ipsilateral mandibular central incisor using digital caliper (Caliper-Digital; Salvin Dental Specialties, Inc, Charlotte, NC).

Increased body temperature was measured by each patient at home during the postoperative period of seven days. The body temperature within 36.0ºC and 37.0ºC was evaluated as normal. The body temperature higher than 37.0 ºC was evaluated as increased. All temperatures were measured at the same time of the day, between 9:00 and 11:00 a.m.

Hemorrhage was observed by patients during the next seven days after the surgical procedure. It was classified as absent or present through the following days. Present hemorrhage was classified as light or intense.

The outcome variable was the presence or absence of an inflammatory complication after third molar surgery (SSI or AO). A diagnosis of SSI was identified by purulent discharge from the surgical site at any point postoperatively, fever, lymphadenopathy, pain and oedema warranting surgical intervention and/or systematic antibiotics). Alveolar osteitis was diagnosed in the cases of an empty alveolar socket, increased pain lasting for more than two days after surgery, and exposed alveolar bone tissue [11-13].

**Statistical analysis**

The statistical analysis was performed using *Statistica*10.1 (StatSoft Inc., Tulsa, USA). The choice of the measure of central tendency and the measure ofvariability for age, sense of pain and duration of pain was determined by Kolmogorov-Smirnov’s test. A comparative statistical analysis for age between the examined groups was determined by Kruskal-Wallis test, and Mann-Whitney test was used in a *post-hoc*analysis.  A comparison of the duration and intensity of pain including all the examined parameters, i.e. swelling, hemorrhage and increased body temperature was done by using one-way ANOVA test. Tukey’s test was used in the *post-hoc* analysis. The difference in the intensity of pain was evaluated by using the VAS and it was determined in the end of anesthesia, 24 hours after applying local anesthesia and seven days postoperatively. For that purpose, Freedman’s test and Wilcox’s test were used in the *post-hoc* analysis. The prevalence of the patients with specific characteristics (gender) was shown by the frequencies and percentages and the significance of the difference in the frequency of prevalence between the groups and were tested by chi-square test. The*post-hoc* analysis was carried out by t-test of the difference in proportions. The level of statistical significance was set at a *P* value less than or equal to 0.05.

**RESULTS**

There were significantly more females in relation to the total number of males (54.3% vs. 45.7%; p=0.015). The results of the statistical analysis showed that in the group without previous inflammation, the two subgroups did not differ significantly (p=0.817), as well as in the group with previous inflammation (p=0.439), regarding age of patients. No significant difference between the subgroups within the first tested group (without inflammation) was determined in the stage of limited mouth opening and hemorrhage (p>0.05). Statistically significant differences were determined for the degree of swelling and increased body temperature (p<0.05) (Table 2). A significantly greater number of subjects treated with placebo had increased body temperature (p=0.42, p=0.012). When statistical significance was determined by chi-square, a *post-hoc* analysis was necessary in order to determine the stage of swelling for which the differences were significant, as well as t-test for proportion. For stage 1 swelling, determined within 24 hours and seven days after the procedure, there was a significantly greater number of subjects in the subgroup with placebo compared to the number of subjects who received antibiotic (p=0.048, p=0.001) (Table 2). A statistically significant difference for hemorrhage between the subgroups within the second tested group (with inflammation) was determined (p<0.001) (Table 3). A significantly greater number of subjects in the placebo group had a marked hemorrhage in the first postoperative day, compared with the number of subjects in the subgroup with inflammation who received an antibiotic (25% *vs.* 3%, P<0.001). The same significance for this category was also recorded after 24 hours, although with different individual values. No statistically significant differences were determined for other factors (Table 3).

There were no statistically significant differences between the incidence of AO and SSI in tested groups (p=0.156, p=0.668).

With regard to pain, no statistically significant difference in pain intensity was determined between the two subgroups in the group with no inflammation (Table 4).

 In the group with previous inflammation, the subjects who received antibiotic showed statistically significant less pain expressed on the VAS scale, compared to the subjects who received a placebo with grade 2 swelling (p=0.013),  grade 3 swelling (p=0.049) and with hemorrhage within 24 hours (p=0.003).

In the group with previous inflammation, no significant differences were determined for pain intensity after 24 hours between the subjects who received antibiotic compared to the subjects who received a placebo (both p>0.05), although after seven days the pain intensity experienced by the subjects with a placebo was statistically significantly greater compared to the subjects who received antibiotics (p=0.001). A significant difference was also determined for the duration of pain. The average duration of pain in the subjects with inflammation who received a placebo was seven days, while in the subjects who received antibiotic it was four days. Pain in the group with placebo lasted significantly longer (p<0.001).

**DISCUSSION**

The objective of this study was to determine whether the use of a single preoperative prophylactic dose of antibiotic, when compared to placebo, decreased the frequency of postoperative complications. Additionally, we tried to determine whether the previous inflammation associated with impacted M3 had an impact on postoperative complications. Reports concerning the type, dosage, administration or duration of antibiotics have been very heterogeneous and there is no consensus regarding the use of antibiotics in preventing postoperative complications in M3 surgery [14-21]. This topic remains controversial, because unnecessary application of antibiotics could promote bacterial resistance or some kind of adverse reaction, which is commonly reported in the literature [22-23]. However, a single prophylactic dose of antibiotics has never resulted in the development of resistance [24].

Postoperative risk factors include increasing age (older than 24 years), female gender, smoking, surgical trauma, length of surgery (longer than 30 minutes), level of impaction and surgeon’s experience [25-27]. To standardize postoperative recovery, all procedures in the presented study were done by the same oral surgeon, Class 3 third molars according to Pederson difficulty index were excluded and all patients were healthy.

The results of statistical analysis of the age of patients showed that there was no statistical significance in groups. In the whole study group there were significantly more females in relation to the total number of males (54.3% vs. 45.7%; p=0.515). In similar studies there were also significantly more women than men. Blondeau and Daniel [28], in a sample of 327 patients had 58% female and 42% male patients, and in a sample of 366 patients, presented by Waite and Cherai [29], the difference was even greater: 61% ofwomen compared to 39% men. Blondeau and Daniel [28] showed that the rate of postoperative complications and the risks of permanent sequelae increase with age. They recommend that, once a decision has been made to extract an impacted mandibular third molar, the surgery should be carried out as soon as possible and well before the age of 24 years, especially for women.

Postoperative pain after surgical removal of the third molar occurs after the effect of the anesthesia ceases and pain intensity increases up to a maximum after 6-8 hours.  If untreated, the pain on average lasts for 24 hours, after which it gradually decreases. The average duration of pain in the present study was significantly longer in the subjects who received a placebo (seven days), compared to antibiotic subgroup (four days) in the inflammation group. How could a single dose of amoxicillin reduce the intensity of pain and how can this mechanism be explained? Is it possible that in the subjects who reacted more intensely, apart from reactive inflammation and additional factors, there was the additional effect of microorganisms which increased the reaction of tissue, while in the group with prophylactic dose of antibiotic these factors were reduced? Some answers can be found in the data showing that there were statistically significantly more subjects with increased body temperature during seven postoperative days (p=0.012) in the subgroup of the same tested group who had received a placebo before the procedure. Similar results were found for pain, swelling and postoperative hemorrhage in the placebo subgroup with previous inflammation. If we compare the results of a study by Pavić [30] who applied a prophylactic dose of 500 mg amoxicillin and obtained a negative response with regard to its efficacy on postoperative complications, then the question arises whether the prophylactic dose of 2 g of amoxicillin applied in the present study was responsible for the partially positive results. Can surgical procedures, in which impacted M3 are removed, be classified as clean contaminated procedures, or are they clean procedures with a minor risk of postoperative infection? Classification of the sample into two examined groups and the different results of the study in these groups could provide the answer to this question. Surgical procedures of all M3 which had previously caused episodes of pericoronal inflammation or periradicular lesions can be classified in the group of clean contaminated procedures and can therefore also contribute to the duration of the surgical procedure and the extent of the removed tissue. With regard to the difficulty in mouth opening, this commonly follows the two previously mentioned factors and is associated with them. Greater swelling and intensity of pain can be associated with more expressed difficulty in mouth opening. In our study, grade 1 difficulty of mouth opening was more marked in the subgroups without previous inflammation, while grade 2 and 3 difficulty mouth opening were more intense in the subgroups with previous inflammation, although in relation to other parameters no statistically significant differences which could be emphasized were found. A similar result for the incidence of difficulty in mouth opening after a prophylactic dose of 500 mg amoxicillin was also obtained in a study which does not recommend a routine usage of antibiotics before lower M3 surgery [30], but suggests that a combination of medical therapy with methylprednisol and ibuprofen proves to be a statistically significant effective treatment [31].

In the case of the development of local complications, the pain may last for several days, and a clinical examination of the wound and surroundings indicates the development of local inflammation. Many publications are focused on the correlation between prophylactic application of antibiotics and the incidence of the most common postoperative complications of SSI and AO following M3 surgery. The results of some studies [24,32,33] showed that a single preoperative dose of amoxicillin significantly decreased the incidence of SSI and AO.  In this study, the overall rate of AO was 4.25 % and the rate of SSI was 1.75%, which is consistent with other publications [34-36]. In our study a prophylactic single dose of antibiotics did not have a statistically significant effect on postoperative infections in the inflammation group which is in agreement with previous study [37]. Previous studieswith preoperative and postoperative administration of amoxicilin, found statistically significant lesser occurrence of pain, infection of the wound, temperature, dysphagia and other side-effects in the groups who received amoxicillin before and after lower M3 surgery in relation to the group who received a placebo [38-40]. It was also observed that antimicrobial efficacy was more expressed in the group who received therapy postoperatively than in those who received a prophylactic therapy[38].

**CONCLUSION**

According to the results of the study, a single preoperative dose of amoxicillin have a statistically significant effect on certain postoperative complications in M3 surgery and it is recommended as routine method when M3 are removed in healthy patients with episodes of previous pericoronal inflammation. Significant difference was determined for the duration of pain, bleeding and body temperature.

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