Preventive Efficacy of Antibiotics after Impacted Mandibular Third Molar Surgery

Rongxin Sun, Xiaojie Zhang, Xiaolong Zang and Zhiyong Li

Department of Oral and Maxillofacial Surgery, Zhejiang University School of Medicine, Stomatology Hospital, Hangzhou, China

ABSTRACT

Objective: To explore the preventive efficacy of antibiotics following surgical removal of the impacted mandibular third molars and screen the potential risk factors.

Study Design: A cohort trial.

Place and Duration of the Study: Department of Oral and Maxillofacial Surgery, Zhejiang University School of Medicine, Stomatology Hospital, Hangzhou, China, from August 2021 to 2022.

Methodology: Cases with impacted mandibular third molar were divided into two groups based on antibiotics use. The primary outcome variable post-operative infection, secondary clinical parameter analgesics intake, and other variables (the operative time, the history of pericoronitis, and wound closure) were documented.

Results: The post-operative infections occurred in 3.64% (n = 12) of the 330 cases (n = 330); 3.01% in the antibiotic group (n = 166) and 4.27% in the control group (n = 164, OR = 1.44, 95% CI: 0.49 to 4.06; p = 0.54). Concerning secondary outcome measures, the analgesics that the antibiotic group took was 5.40, and the control group took was 5.95 (95% CI = -0.21 to 1.30; p = 0.16). For those with post-operative infections, the average operative time was 22.83 minutes, whereas for those without post-operative infections it was 14.87 minutes (95% CI = -0.26 to 15.67; p = 0.04). When the operative time was greater than or equal to 15 minutes, it was related to more analgesics use (95% CI: -0.43 to 1.93; p <0.05), also was the history of pericoronitis (95% CI = 0.04 to 1.54; p = 0.04).

Conclusion: Antibiotics are unnecessary for preventing post-operative infections or minimising analgesic requirements following extraction of the impacted mandibular third molars; operative time and pericoronitis showed a suppressive influence on post-operative recovery.

Key Words: *Impacted molars, Antibiotics, Analgesics, Operative time, Pericoronitis.*

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INTRODUCTION

Impacted mandibular third molar (IMTM) extraction, the most prevalent oral and maxillofacial surgical intervention, is associated with a spectrum of potential complications. Literature reveals that patients may encounter post-operative issues, including oedema, pain, and bleeding with reported frequencies ranging from 4.5 to 10%.[1,2] Post-operative infection may exacerbate other complications, significantly impacting patients' daily life, such as speaking, eating, and sleeping. Notably, compromised oral hygiene due to post-operative limitations can further fuel the infection risk.[3]

Antibiotics are commonly employed by dentists worldwide to prevent post-extraction infections following IMTM removal.[4] However, the efficacy of antibiotics as prophylactic measure remains uncertain, as a recent randomised controlled trial found that a single dose of 2g amoxicillin administered one hour prior to surgery did not significantly reduce the risk of post-operative infections after IMTM extraction.[1] Furthermore, the systematic reviews were unable to reach an agreement on this topic.[5]

Worldwide, the escalating issue of antimicrobial resistance (AMR), fuelled by the excessive and inappropriate use of antibiotics, has emerged as a pressing global health concern that merits immediate attention.[6,7] A recent study has highlighted the alarming rise of AMR in neonatal sepsis.[8] Actions must be taken to deal with the post-operative complications of IMTM surgery, not only relying on antibiotics. This research may offer a clinical basis for standardised medication administration in oral surgery, thereby fostering better patient outcomes. The aim of this study was to value the necessity of antibiotic therapy after the extraction of IMTM, and more crucially, to screen the potential risk factors impacting post-operative recovery.

METHODOLOGY

This cohort study was methodically carried out in the Zhejiang Province, China, under the strict adherence to the principles outlined in the Declaration of Helsinki. The Zhejiang Stomatology

Correspondence to: Dr. Zhiyong Li, Department of Oral and Maxillofacial Surgery, Zhejiang University School of Medicine, Stomatology Hospital, Hangzhou, China
E-mail: hxlzy2002@zju.edu.cn

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Hospital's Ethics Committee gave its approval to the current study (Approval No: 2023009), with informed patient consent. The sample size was calculated using OpenEpi 3.01. The absolute precision was held at 5% and the level of confidence was maintained at 95%. The patients who sought surgical removal of IMTM at the Department of Oral and Maxillofacial Surgery in Zhejiang University School of Medicine, Stomatology Hospital, from August 2021 to 2022 were considered as the participants in this study. According to Pell and Gregory's classification, the impacted teeth were categorised based on their position and class. The study included participants who were non-smokers, with a confirmed IMTM diagnosis through either panoramic radiography or cone-beam computed tomography (CBCT), and met Pell and Gregory II classification for the extraction. The participants were excluded who had a recent history of acute local infection, cyst, or tumour, had used antibiotics within the previous week, were breastfeeding or pregnant females, or had co-existing systemic diseases or known allergies to cephalosporins or non-steroidal anti-inflammatory drugs (NSAIDs).

All patients were given 2% lidocaine (Tianfeng Pharmaceuticals Co., Ltd., Guangdong, China) block anaesthesia plus 4% articaine (Primacaine, Acteon, France) infiltration anaesthesia of relevant nerves before the operation. Following the administration of anaesthesia, the surgery was carried out by an expert surgeon, adhering to a standardised protocol. The procedure involved the use of a surgical handpiece equipped with a fissure bur for osteotomies when required. Tooth sectioning was performed to clear any obstructions with continuous sterile cooling liquid ensuring a minimal trauma. The mandibular third molar was extracted using a minimally invasive dental elevator. Prior to wound closure, a thorough examination confirmed the complete removal of the tooth, excluding any remnants such as fragments, bone, or root. Soft tissue wound closure was performed with 5-0 absorbable sutures (Covidien, Beijing, China), and no other sponges were placed in the extraction sockets. Another dentist explained the post-operation precautions and instructions. All the patients were given concentrated tinidazole gargles (Hangkang Pharmaceuticals Co., Ltd., Zhengjiang, China) on the following seven days, acetaminophen (Bayer Healthcare, Shandong, China) that was taken, if necessary. All patients were suggested to take cefuroxime axetil (Shenzhen Zhijun Pharmaceuticals Co., LTD, Guangdong, China) for the following three days (125mg, bid).

Non-compliance with antibiotic therapy was observed in a subset of the patients, who were consequently assigned to the control group. The antibiotic group received cefuroxime axetil. All the participants underwent re-evaluation 7 to 10 days post-surgery, with the wound healing assessed and pain medication usage queried. Prompt intervention was ensured for any post-operative complications that arose.

The primary outcome was post-operative infection, encompassing alveolar osteitis, and surgical site infection. A surgical site infection was diagnosed when any of the following criteria were met: (A) the presence of purulent drainage or an abscess; B) isolation of pathogenic micro-organisms from the affected area; and C) unexpected wound dehiscence in the patients displaying at least one of the following symptoms: Elevated body temperature (above 38°C), spontaneous pain, localised swelling, facial redness, or local heat. Additionally, a severe, antibiotic-responsive pain lasting for a week, accompanied by mild-to-moderate intraoral swelling and/or erythema, was also considered as a manifestation of the infection.[1]Diagnosis of alveolar osteitis was established upon the patients' presentation with intense, unrelieved pain (radiating to the ear, temporal region, mandibular area, or occiput) commencing the 2-3 days post-tooth extraction. The affected socket was noted to be empty or filled with gangrenous, foul-smelling necrotic clots, indicating the severity of the condition, and the ineffectiveness of standard analgesics.

The secondary outcome was the analgesic intake frequency, assessed using a four-point verbal rating scale (VRS). This scale categorised pain into four grades: 0 denoted no pain; 1 indicated mild pain but tolerable, without sleep disturbance; 2 represented moderate pain, unbearable with sleep disruption, and requiring analgesic; and 3 represented severe pain, intolerable, necessitating analgesics, severe sleep disturbance, and potential autonomic dysfunction. Pain levels of grades 2 and 3 necessitated analgesic use, whereas grades 0 and 1 did not. Additionally, the data on operative time, history of pericoronitis, and wound closure were recorded.

The statistical analyses were conducted using SPSS version 23.0 (IBM Corporation, Armonk, NY). Descriptive statistics were presented as frequencies and percentages for categorical data, while mean ± standard deviation (SD) was employed for continuous variables. To assess the statistical significance, the unpaired t-test was employed for comparing the two groups' operative time and analgesics intake, analgesics intake between two groups (15min and above), and the association between pericoronitis history, wound closure, and analgesic intake. Fisher's exact test was utilised to examine the relationship between wound closure and infectious complications. The Chi-square test was used to analyse the association between the two groups' infections, the history of pericoronitis, and infectious complications. Additionally, the Welch's t-test was employed to compare the operative times between the infectious and non-infectious groups. The significance was determined at a p-value threshold of $p < 0.05$.

RESULTS

A total of 330 cases of IMTMs from 310 patients were included in this clinical trial as the research objects. Antibiotic group (n = 166) included subjects who took cefuroxime axetil and the control group included (n = 164) subjects who did not take cefuroxime axetil. No significant differences were found between the arms in the baseline participants' characteristics. As only the Pell and Gregory II type was selected, there was no difference in the degree of difficulty of the extraction between the two groups. The patient's basic features are summarised in Table I. None of the subjects reported serious adverse events.

Table I: Clinical and demographical features.

	Antibiotic group	Control group	Total	Mean (SD)	95% Confidence Interval	p-value (unpaired t-test)
n	166 (50.30%)	164 (49.70%)	330	–		
Age (years)	26.27 ± 3.94	25.46 ± 3.97	–	25.87 ± 3.97		
Females (F)	106 (48.62%)	112 (51.38%)	218	–		
Males (M)	60 (53.57%)	52 (46.43%)	112	–		
Left third molar (L)	78 (49.37%)	80 (50.63%)	158	–		
Right third molar (R)	88 (51.16%)	84 (48.84%)	172	–		
Operative time*	15.86 ± 9.07	14.45 ± 6.99	–	15.16 ± 8.12	-3.17 to 0.34	0.11

**Surgery time measured in minutes starting from the first incision.*

Table II: Infections in the antibiotic group and the control group.

	No infectious complications	Infectious complications		Total
		Alveolar osteitis	Surgical site infection	
AG	161	2	3	166
CG	157	3	4	164
Total	318	5	7	330

OR = 1.44, 95% CI: 0.49 to 4.06; p = 0.54, AG: Antibiotic group; CG: Control group.

The post-operative infection rate was 3.64% (n = 12) among the 330 cases analysed. The rate was 3.01% in the antibiotic group and 4.27% in the control group, indicating no significant difference between the two treatment groups (p >0.05, Table II).

In terms of secondary outcome assessments, the antibiotic group consumed an average of 5.40 analgesic tablets (acetaminophen) per individual, compared to 5.95 for the control group. However, no significant disparity was observed between the two groups in terms of analgesic pill consumption (95% CI = -0.21 to 1.30; p = 0.16).

The mean operative time in this study was 15.16 minutes. A significant difference was observed between patients with post-operative infections (average time: 22.83 minutes) and those without (14.87 minutes, 95% CI = -0.26 to 15.67, p = 0.04). The study population was divided into two groups based on the operative duration: Group A (<15 minutes, n = 174) and Group B (≥15 minutes, n = 156). Group A consumed an average of 5.12 analgesic pills, while Group B took 6.30 pills. A significant difference between the two groups was discovered (95% CI = 0.43 to 1.93; p <0.05).

The history of pericoronitis was not related to the infectious complications (OR = 1.04, 95% CI = 0.32 to 3.37; p = 0.95), but was related to more analgesics' intake (95% CI = 0.04 to 1.54; p = 0.04). While the wound closure was not related to infectious complications (OR = 1.56, 95% CI = 0.18 to 1.84; p = 0.39), neither was the analgesics' intake (95% CI = -1.22 to 0.30; p = 0.24).

DISCUSSION

The findings of this study suggested that oral cephalosporin could decrease the incidence of post-operative infection following the extraction of impacted mandibular third molars in healthy participants, although no statistically significant difference was identified. The analgesic consumption patterns were indistinguishable between the antibiotic and the control groups. However, a significant difference in the analgesics' use was observed when the surgical duration exceeded 15 minutes or when the participants had a history of pericoronitis.

The discovery of antibiotics is a landmark event in the history of modern medicine. Millions of lives have been saved since Alexander Fleming discovered them in 1928, but the effectiveness of antibiotics has increasingly been challenged by the emergence of AMR.[9] AMR is a major cause of death, with an estimated 4.95 million global deaths in 2019 attributed to the bacterial AMR.[10] The excessive and inappropriate use of antibiotics is seen as the main reason for increasing the prevalence of drug-resistant bacteria,[11] and in the dentistry field, where antibiotics are frequently used in various treatment settings, such as periodontal and peri-implant infection,[12] dental implant surgery,[13] and the tooth extraction.[14] Doctors often aim to prevent infections through the use of antibiotics; however, the emergence of antimicrobial resistance poses a significant challenge, potentially leading to prolonged, chronic infections.[15] It has been observed that the widely used antibiotic treatments for bacterial illnesses have led to bacterial resistance worldwide and even the appearance of superbacteria.[16] Therefore, the primary objective of this investigation was to assess the necessity of antibiotic administration following the extraction of IMTM while striving to minimise the antibiotic usage.

In the present study, of the total 330 subjects included, 3.64% presented post-operative infections, the percentage is similar to a recent randomised controlled trial that enrolled 154 patients and reported 4.5% of infectious complications.[1] Additionally, there was no statistically significant difference between the groups' rates of post-operative complications, with 3.03% of the patients in the antibiotic group and 4.24% of the patients in the control group experiencing infectious problems. Similar findings were found in a recent study, which found that the incidence of the surgical site infections was 6% in the antibiotic-treated group and 16% in the control group, also without significant difference between the groups.[17] In this investigation, there was no sufficient evidence that prophylactic antibiotics may lower the risk of developing infections, which is consistent with the findings of an earlier research.[1,17] The study design distinguished itself by administering cefuroxime axetil post-extraction in contrast to the previous research that employed amoxicillin as a pre-surgical prophylactic agent.[1,17] However, Ramos *et al*.'s recent meta-analysis demonstrated a benefit to prescribing antibiotics,[18] but there

was no decisive evidence proving the benefits in healthy people, because patients may be at considerably higher risk of developing the antibiotic resistance and having negative side effects.[19] In the light of the evidence, it can be argued that antibiotics are generally unnecessary for preventing the post-operative infections following the IMTM extraction in healthy people, regardless of the timing of administration or the specific antibiotic type.

The mean operative time (15.16 minutes) found in this study is comparable to the 11.03 minutes found in Lopez-Carriches *et al*.,[20] differing from the 22.63 minutes found in Bello *et al*.[21] This variation could be attributed to differences in surgeons' expertise and the definition of the operative time. This study found that the post-operative infections were related to more operative time. Furthermore, when the operative time exceeded 15 minutes, it was related to more analgesics' use. In a single-blinded randomised controlled trial including 38 patients, Agarwal *et al.* reported a correlation between the operative time and the need for rescue analgesia.[22]

Besides, Bello *et al.* discovered that the intensity of discomfort, trismus, and oedema steadily worsened with longer operative time, the surgical procedures were exclusively performed by a single surgeon, suggesting that operative time could potentially reflect the procedural complexity and the duration of tissue exposure to potential trauma. Inflammation, following tissue injury, is closely intertwined with reparative mechanisms.[23] Consequently, with the extended operative time, more inflammatory mediators are released, indicative of the postoperative response. Given that, this study suggested that the long operative time could be a risk factor for IMTM surgery. When operative time exceeds 15 minutes, or when specific procedures extend beyond the typical surgical time, it underscores the necessity for heightened focus on the post-operative recovery following the IMTM surgery. This situation highlights the significance of employing proficient surgical techniques for oral surgeons.

Following the removal of IMTM, a variety of analgesics have been used to manage the post-operative discomfort, such as ibuprofen, codeine, acetaminophen, and so on.[24] In the present study, all the patients were given acetaminophen prescriptions. The average pills of analgesics taken was nearly six, with no difference between the antibiotic group and the control group. This was different from the previous research that antibiotic prophylaxis was associated with a reduced need for rescue analgesia.[1] The discrepancy may be caused by the evaluation of pain management. According to the authors' current knowledge, no research has been conducted to explore the connection between the history of pericoronitis and post-operative pain. A noteworthy finding from this study revealed that the patients with a history of pericoronitis tend to require higher analgesic consumption post-surgery. This observation highlights the need for a heightened focus on pain management for individuals with a pericoronitis background. The study's findings collectively reinforce the notion that antibiotics may not be universally required and indicate the importance of analgesics, particularly for those with a history of pericoronitis.

The retrospective cohort design of this study introduced inherent biases, as it relied on the self-reported antibiotic usage of the patients at the clinical centre. Although all the patients were advised to take antibiotics, approximately half voluntarily chose not to, due to concerns about the side effects. This limitation stems from the non-randomised selection of antibiotics by the patients. Future randomised controlled trials (RCTs) could potentially address this issue and mitigate this bias, enhancing the study's validity. Besides, the results of this study are limited to specific demographic, healthy adults. A focus on investigating specific subgroups of dental patients, particularly those with prevalent systemic chronic diseases like diabetes and coronary heart disease,[25] would be of significant interest. These patients are at a heightened risk for infectious complications, and studying the potential benefits of preventive antibiotics in this context could contribute valuable insights to the field. A large-sample prospective RCT is needed to further investigate the effectiveness of antibiotics in patients with systemic disease in order to overcome the limitations of this study.

CONCLUSION

Antibiotics are unnecessary for preventing post-operative infections or minimising analgesic requirements following the IMTM. Instead, the use of analgesics and medical mouthwash is advised. In addition, the operative time and the history of pericoronitis showed a suppressive influence on post-operative recovery. Clinicians should individually assess each patient's need for prophylactic antibiotic therapy after dental extraction.

ETHICAL APPROVAL:
Ethical approval was granted by the Ethics Committee of Zhejiang Stomatology Hospital, Hangzhou, China (Approval No: 2023009).

PATIENTS' CONSENT:
Patients' consent was not required in this study as the data were taken from the patients' records without mentioning the patients' details or pictures.

COMPETING INTEREST:
The authors declared no conflict of interest.

AUTHORS' CONTRIBUTION:
RXS: Conception, design, data collection, and manuscript writing.
XJZ: Data analysis and interpretation.
XLZ: Manuscript correction and data analysis.
ZYL: Conception, design, and supervision.
All authors approved the final version of the manuscript to be published.

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