

A COMPARATIVE STUDY ON EFFICACY OF AMOXICILLIN AND AZITHROMYCIN IN PREVENTION OF POSTOPERATIVE SEQUELAE FOLLOWING THIRD MOLAR SURGERY

Shakya-Gurung R¹, Bimb K², Shrestha D¹

¹Department of Pharmacology, ²Oral and Maxillofacial Surgery, Nepal Medical College Teaching Hospital, Attarkhel, Gokarneshwor-8, Kathmandu, Nepal

ABSTRACT

Amoxicillin is the commonly prescribed antimicrobial for prevention of post-operative complications following surgical extraction of mandibular third molar. However recently, the use of macrolide antibiotics had been encouraged in dentistry. The aim of this study was to compare the efficacy of Amoxicillin and Azithromycin in preventing post-operative sequelae following third molar surgery. An open- labeled randomized controlled study was carried out in Department of Oral and Maxillofacial surgery, college of Dental Sciences and Hospital, Nepal Medical College (CODSH-NMC), Attarkhel, Kathmandu, Nepal from May 2018 to June 2019. One hundred and twenty patients undergoing surgical extraction of impacted mandibular third molar were randomized by lottery method into two groups: Group A received Amoxicillin and Group B received Azithromycin. Both the groups were assessed postoperatively on 1st, 3rd and 7th days for post-operative complications- pain, swelling, trismus and pus discharge. The present study revealed no significant differences between the efficacy of Amoxicillin and Azithromycin in preventing postoperative sequelae following surgical extraction of impacted third molar. Amoxicillin and Azithromycin were therefore found to be equally effective. Thus, Azithromycin can be used as an alternative drug to Amoxicillin in case of resistance and intolerance to Amoxicillin.

KEYWORDS

Amoxicillin, Azithromycin, surgical extraction, impacted mandibular third molar extraction

CORRESPONDING AUTHOR

Mrs. Rashmi Shakya Gurung,
Department of Pharmacology, Nepal Medical College
Teaching Hospital, Attarkhel, Gokarneshwor-8,
Kathmandu, Nepal
Email: shakya.rushmee@gmail.com
ORCID ID: 0000-0002-5213-7741

INTRODUCTION

Surgical extraction of impacted mandibular third molar is one of the most commonly performed procedures in oral and maxillofacial surgery.¹⁻³ The procedure is classified as “clean-contaminated” group of surgeries.⁴ Pain, trismus, swelling and infection are the common significant post-operative complications associated to it.^{1,2,5} These complications affect the patients quality of life in the first few days postoperatively.⁴ Their incidence have been documented to range from 2.3% to 88.9% for pain, 5.7% to 14.3% for trismus and 1.3% to 12.0% for swelling.^{6,7} Also, risk of infection has been reported to range from 1-12.6%.^{8,9} Antimicrobials are usually prescribed to minimize these complications. Amoxicillin is one of the most commonly and widely prescribed antimicrobial for this purpose.²

However in the last decade, the use of macrolide antibiotics has been encouraged in dentistry. The therapeutic benefits of Azithromycin in the management of odontogenic infections have been investigated by a number of workers.¹⁰⁻¹² The therapeutic advantages of this antimicrobial are: improved tissue distribution and low incidence of adverse effects. Also, because it has a long half-life and good tissue penetration it only needs to be taken once daily for three days.¹³ This improves the patient’s compliance as well. Hence, this study was conducted to compare the efficacy of Amoxicillin and Azithromycin in minimizing post-operative sequelae following surgical extraction of impacted mandibular third molars.

MATERIALS AND METHODS

This open-label randomized controlled trial was conducted in Department of Oral and Maxillofacial Surgery, College of Dental Sciences and Hospital Nepal Medical College (CODSH-NMC) and Department of Pharmacology, Nepal Medical College Teaching Hospital from May 2018 to June 2019 after prior approval from Institutional Ethical Committee.

One hundred and twenty patients aged 18-60 years undergoing surgical extraction of impacted mandibular third molar who met the inclusion criteria were included in the study. A written informed consent was obtained from each patient after explaining the nature and outcome of the procedure with possible consequences and complications. Patients with history of allergy and intolerance to Amoxicillin or Azithromycin, pre-existing periodontal disease and pathologies associated to impacted third molars, immunocompromised patients, pregnant females, smokers and patients on antimicrobials

two weeks prior to the study were excluded from the study.

Patients were randomly divided into two groups of 60 patients in each using lottery method of randomization. A total of 120 pieces of paper corresponding to each member of sample population were taken; on half of these papers (60) Amoxicillin were written and on the other half (60) Azithromycin were written in order to create two sample groups: Group A and Group B. These pieces of paper were then folded and mixed thoroughly into a box. The researcher picked the folded pieces of paper randomly from the box and the patients were prescribed with the drug accordingly. Thus, cases were randomized into two groups: Group A patients were prescribed with post-operative dose of 500 mg Amoxicillin three times a day for five days and Group B patients were prescribed with postoperative dose of 500 mg Azithromycin once a day for three days. Both the treatment groups were also prescribed with analgesics in the form of Ibuprofen 400mg two times a day for three days.

All the extraction procedures were performed under local anesthesia (2% lignocaine with adrenaline ratio of 1: 2,00,000) under aseptic condition by the same Oral and Maxillofacial surgeon with identical standard technique. Then proper postextraction instructions and medications were explained to the patient.

Both the groups were assessed preoperatively and postoperatively on 1st, 3rd and 7th days for four different variables namely facial swelling, degree of mouth opening, pain and pus discharge. These variables were assessed as follows:

1. Facial swelling was assessed as present or absent.
2. Degree of mouth opening was assessed by measuring the distance between the incisal edges of upper and lower incisors at the maximum mouth opening in millimeters using caliper.
3. Pain was assessed by using a four point verbal rating scale where 0= no pain, 1= mild pain, 2 = moderate pain and 3= severe pain.
4. Pus discharge was considered as a sign of infection. It was assessed and categorized as present or absent.

Variables were assessed by the same surgeon who performed the extraction procedures and data were recorded in a preformed evaluation sheet. The recorded data was compiled, processed and analyzed by SPSS version 16.0 for windows. Comparison of swelling and pus discharge between the study groups were analyzed using chi-square test. Shapiro-Wilk test was used to test

the normality of data distribution. Mann-Whitney U test was used to compare median interincisal distance and pain between the groups. P value less than 0.05 was considered as statistically significant.

RESULTS

Out of 120 patients, 54.2% (65/120) were female and 45.8% (55/120) were male. In Group A, 51.7% were female and 48.3% were male while in the Group B, 56.7% were female and 43.3% were male.

The mean age of the total patients was 30.40 ± 9.25 years (range 18-58years). In group A, the mean age was 30.38 ± 9.34 years (range 20-56 years) while in the group B; it was 30.40 ± 9.26 years (range 18- 58 years).

The most commonly occurring pattern of impacted mandibular third molar based on Winter`s classification¹⁴ according to angulation was found to be mesioangular (33.3% in group A and 40% in group B) in both groups. This was followed by horizontal (26.7% in group A and 33.3% in group B), vertical (20% in group A and 16.7% in group B) and distoangular (20% in group A and 10% in group B) type of impactions.

Table 1: Comparison of median inter-incisal distance (mm) between the study groups, Mann-Whitney U test

Assessment time	Group	Median ± QD	Minimum	Maximum	P value
Pre-op	A	35 ± 1.5	20	40	0.35
	B	35 ± 1	28	38	
POD ₁	A	32 ± 1.5	15	36	0.21
	B	33 ± 1	21	36	
POD ₃	A	34 ± 1	18	37	0.05
	B	34 ± 1	21	45	
POD ₇	A	34 ± 1	23	43	0.05
	B	35 ± 0.5	26	45	

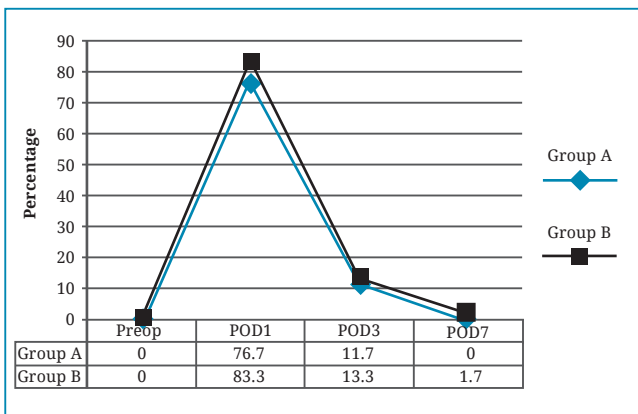


Fig 1: Comparison of swelling between the study groups

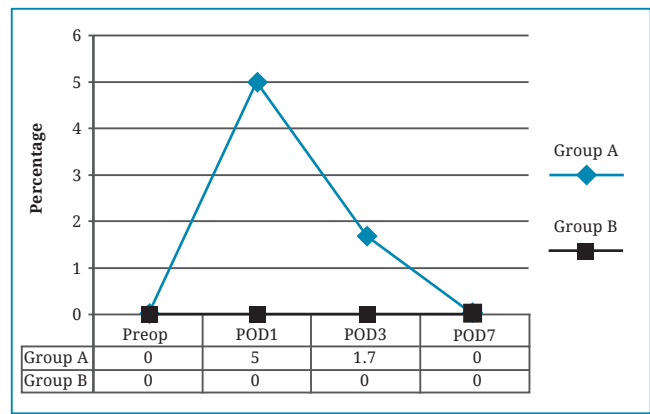


Fig 2: Comparison of pus discharge between the study groups

Table 2: Comparison of pain assessment between the study groups, Mann-whitney U test

Assessment time	Group	No pain	Mild pain	Moderate pain	Severe pain	P value
POD ₁	A	5	16	27	12	0.51
	B	0	26	13	21	
POD ₃	A	16	29	10	5	0.62
	B	21	22	14	3	
POD ₇	A	30	27	3	0	0.03
	B	45	7	8	0	

The mouth opening was found to be slightly more in Group B patients compared to Group A patients on post-operative day 1 (POD₁) and post-operative day 7 (POD₇). However, median interincisal distance in Group B patients was significantly more than Group A patients at post-operative day 3 (POD₃) and POD₇ (Table 1, $p=0.05$). The severity of pain as shown in Table 2 showed no significant differences between the study group on POD₁ and POD₃. However, on POD₇, pain score of Group B patients was found to be significantly lower as compared to Group A patients (Table 2, $p=0.03$).

No significant difference was observed between the two groups while assessing pus discharge (Fig. 1, χ^2 value-POD₁= 0.79, POD₃= 0.31, POD₇>0.05) and swelling (Fig. 2, χ^2 value - POD₁= 0.361, POD₃= 0.783, POD₇= 0.315)

DISCUSSION

Common significant post-operative complications associated with the extractive surgery requiring bone removal are pain, trismus, swelling and infection.^{1,2,5} Indentistry, Amoxicillin is the common drug used for the treatment and prevention of infections. However, the development of resistance to this drug has become common. Therefore, the search for a good alternative to Amoxicillin is necessary. Very few studies are present which have compared Amoxicillin with other antimicrobials in dentistry.¹⁵⁻¹⁷ The present study is aimed to compare the efficacy of Azithromycin to Amoxicillin in healthy subjects undergoing surgical extraction of impacted mandibular third molars.

In this study, higher incidence of mandibular third molar impaction was found in females (54.2%) which is corroborated by studies done by Upadhyaya *et al*¹⁸ and Khanal *et al*.¹⁹ This can be attributed to differences in growth pattern between males and females. Females have less incremental and a shortened duration for growth of mandible compared to males.²⁰ Moreover, by the time 3rd molars begin to erupt, growth in females is already ceased. All these factors presumably lead to hindrances in tooth eruption.

In the present study, mesioangular was found to be the most common pattern of mandibular third molar impaction in terms of angulation followed by horizontal, vertical and distoangular. Several authors have mentioned similar observation.^{18,19}

Pus discharge was found statistically insignificant between the two study groups. Data from this study showed the incidence of infection at 5% in POD₁ and 1.7% in POD₃ for Amoxicillin group and nil for Azithromycin group. Iglesias *et al*¹⁵ and Sissalli *et al*¹⁶ have also showed similar findings.^{15,16}

Study on the infection rates with Azithromycin has shown to be as low as 0%.¹⁷ These all point out that prophylactic antimicrobial agents indeed decrease the infection rate.

Swelling is also a common complication following surgical trauma caused by inflammation and edema. It reaches the maximum level on the second or third post operative day and completely resolves by the seventh day.¹¹ In the present study too, maximum amount of swelling was observed in POD₃ and gradually normalized by POD₇ in both the study groups. Also no significant difference was observed between them in terms of postoperative swelling. Several authors have made similar observation.^{1,11,15}

One of the hallmark of bacterial infection is local pain. Also pain following third molar surgery is believed to be associated with the process of inflammation. This in turn depends on various factors such as age of the patient, amount of bone removal, difficulty of extraction, surgeon's experience, pre-existing infection, duration and technique of extraction.^{5,21-23} The general pattern of post-operative pain, regardless of antimicrobial use in the present study had shown that the pain was severely maximum on POD₁ which decreased on POD₃ and became nil at POD₇. Pain score on POD₇ was lower in patients of Azithromycin group compared to Amoxicillin group which was statistically significant. Also patients with no pain were more in Azithromycin group. The healing of pain in the present study, however, cannot be attributed solely to the use of antimicrobials because of the use of Ibuprofen, which is an analgesic drug. Being a non-analgesic drug, antimicrobials might have a role in controlling pain by controlling the bacterial infection and swelling. Hence, antimicrobials might have indirect addictive effect with analgesics in controlling pain.

Oral function postoperatively indirectly expresses the intensity of certain local complications such as pain, swelling or trismus. A majority of patients declare that the most severe limitation following third molar extraction involves mastication.²⁴ Intraoperative direct trauma to the temporomandibular joint or postoperative inflammation of masticatory muscles can cause reduced mouth opening. This is secondary to pain and swelling. In this study, an appreciable mouth opening was observed in patients who received Azithromycin compared to those who received Amoxicillin. This was statistically significant on POD₃ and POD₇. Azithromycin in addition of being an antimicrobial is also known to have well-documented anti-inflammatory properties.²⁵ The macrolides have long been associated with anti-inflammatory benefits in patients

with inflammatory disorders.²⁶ This shows that Azithromycin appears to have a biphasic effect, where it enhances the immune system's response to bacteria initially and once the bacteria have been eradicated, thereby eliminating the inflammatory response as quickly as possible. This explains the quicker response in healing of pain and swelling in the patients receiving Azithromycin.

The present study found both Amoxicillin and Azithromycin to be equally effective in minimizing postoperative sequelae following surgical extraction of impacted mandibular third molar. Thus, Azithromycin can be used as an alternative drug to Amoxicillin in case of resistance and intolerance to Amoxicillin.

Moreover, it has several merits with high tissue distribution, anti-inflammatory action, sustained serum concentrations, long half-life, low incidence of adverse effects and better patient compliance due to shorter regimen.

ACKNOWLEDGEMENT

We would like to express our sincere gratitude to Dr. Sumit Singh, Dental surgeon for his valuable help during sample collection and Prof. Dr. Neeraj Panta, Head of Department, Department of Oral and Maxillofacial Surgery, CODSH-NMC for the support he has provided. We would also wish to thank all the participants who participated in the study.

REFERENCES

- Sharma R, Reddy PB. Efficacy of postoperative prophylactic antibiotic therapy in third molar surgery. *J Clin Diagn Res* 2014; 8: 14-6.
- Martin MV, Kanatas AN, Hardy P. Antibiotic prophylaxis and third molar surgery. *Br Dent J* 2005; 198: 327-30.
- Blondeau F, Daniel NG. Extraction of impacted mandibular third molars: postoperative complications and their risk factors. *J Can Dent Assoc* 2007; 73: 325.
- Olurotimi AO, Gbotolorun OM, Ibikunle AA, Emeka CI, Arotiba GT, Akinwande JA. A comparative clinical evaluation of the effect of preoperative and postoperative antimicrobial therapy on postoperative sequelae after impacted mandibular third molar extraction. *J Oral Maxillofac Res* 2014; 5: 1-6.
- Rabi A, Maheswari R, Srinivasan B, Warad LP, Suvarna CC, Tank KS. Effectiveness of antimicrobial therapy after extraction of impacted mandibular third molar: a randomized clinical trial. *J Contemp Dent Pract* 2018; 19: 81-5.
- Odai DE, Obuekwe NO. Mandibular third molar disimpaction: indications and associated complications. *Annals Med Surg Prac* 2016; 1: 44-8.
- Jerjes W, El-Maaytah M, Swinson B *et al.* Experience versus complication rate in third molar surgery. *Head Face Med* 2006; 2: 14-21.
- Hochwald DA, Davies WH, Martinoff J. Modified distolingual splitting technique for removal of impacted mandibular third molars: incidence of postoperative sequelae. *Oral Surg Oral Med Oral Pathol* 1983; 56: 9-11.
- Nordenram A, Syndnes G, Odegaard J. Neomycin-bacitracin cones in impacted third molar sockets. *Int'l J Oral Surg* 1973; 2: 279.
- Lo Bue AM, Sammartino R, Chisari G, Gismondo MR, Nicoletti G. Efficacy of azithromycin compared with spiramycin in the treatment of odontogenic infections. *J Antimicrob Chemother* 1993; 31: 119-27.
- Sefton AM, Maskell JP, Beighton D *et al.* Azithromycin in the treatment of periodontal disease. Effect on microbial flora. *J Clin Periodontol* 1996; 23: 998-1003.
- Varvara G, D' Arcangelo C. The evaluation of the clinical efficacy and tolerance of azithromycin in odontostomatological infections. *Minerva Stomatol* 1998; 47: 57-62
- Graziani F, Corsi L, Fornai M *et al.* Clinical evaluation of piroxicam-FDDF and azithromycin in the prevention of complications associated with impacted lower third molar extraction. *Pharmacol Res* 2005; 52: 485-90.
- Winter GB. The principles of Exodontia as applied to the impacted third molar. St. Louis: American medical book co 1926; 241-79.
- Iglesias F, Garcia AG, Yanez-Vico, R *et al.* Comparative trial between the use of amoxicillin and amoxicillin clavulanate in the removal of third molars. *Med Oral Patol Cir Bucal* 2014; 1: e612-5.
- Sissalli U, Lalli C, Carone L. Amoxicillin and clavulanic acid vs ceftazidime in the surgical extraction of impacted third molar: a comparative study. *Int'l J Immunopathol Pharmacol* 2012; 25: 771-4.
- Ishihama K, Kimura T, Yasui Y, Komaki M, Ota Y. Azithromycin as prophylaxis for the prevention of postoperative infection in impacted third molar surgery. *J Infect Chemother* 2006; 12: 31-5.
- Upadhyaya C, Chaurasia NK, Neupane I, Srivasta S. Incidence and pattern of impaction of mandibular third molars: a single institutional experience in Nepal. *Kathmandu Univ Med J* 2017; 15: 67-70.
- Khanal P, Dixit S, Singh R, Dixit P. Difficulty index in extraction of impacted mandibular third molars and their post-operative complications. *J Kathmandu Med Coll* 2014; 3: 14-20.

20. Ochoa B, Nanda R. Comparison of maxillary and mandibular growth. *Am J Orthod Dentofac* 2004; 125: 148-59.
21. Mansuri S, AbdulkayumAM. Age as a factor in the complications rate after removal of mandibular third molars: a review of literature. *J Evolution Med Dent Sci* 2013; 2: 7994-8001.
22. Paul CK, Rahman QB, Alam S, Kundu GC, Uzzaman H. Effect of age on immediate postoperative tissue reaction following surgical extraction of impacted mandibular third molar. *Bangabandhu Sheikh Mujib Med Univ J* 2014; 7: 120-8.
23. Olojede OA, Gbotolorun OM, Ibuikunle AA, Emeka CI, Arotiba GT, Akinwande JA. A comparative clinical evaluation of the effect of preoperative and postoperative antimicrobial therapy on postoperative sequelae after impacted mandibular third molar extraction. *J Oral Maxillofac Res* 2014; 5: 1-6.
24. 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: 286-91.
25. Banjanac M, Munić Kos V, Nujić K et al. Anti-inflammatory mechanism of action of azithromycin in LPS-stimulated J774A.1 cells. *Pharmacol Res* 2012; 66: 357-62.
26. Amsden GW. Anti-inflammatory effects of macrolides—an underappreciated benefit in the treatment of community-acquired respiratory tract infections and chronic inflammatory pulmonary conditions. *J Antimicrob Chemother* 2005; 55:10–21.