



## A randomized split-mouth double-blinded comparative study of preoperative versus postoperative administrations of 120 mg etoricoxib in mandibular third molar surgery

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### Abstract

The pre-emptive efficacy of etoricoxib has reduced immediate postoperative pain in impacted third molar surgery; however, data comparing pre- and post-operative administration is lacking. The objective of this split-mouth, double-blind, randomized-controlled clinical trial was to assess and compare the efficacy of preoperative versus postoperative administrations of single-dose etoricoxib 120 mg for the management of acute postoperative pain in mandibular impacted third molar surgery. A total of 31 patients were included in this study. Each patient underwent two operations of bilaterally symmetrical third molar surgery based on allocation assigned by simple randomization technique into experimental (Preoperative administration: etoricoxib 120 mg) and control (Postoperative administration: etoricoxib 120mg) groups with washout period of one month. The postoperative assessment of pain was performed by using the 11-point Numerical Rating Scale (NRS) for two days and the total rescue analgesic requirement for seven days. The average pain scores and total analgesics rescue analgesics were compared by using Wilcoxon signed-rank test. P-value <0.05 was considered a significant difference. The preoperative administration of etoricoxib resulted in lower mean pain scores at 4, 6, 8, 12, 16, 20, and 48 hours after surgery when compared with the control group with a significant difference ( $p<0.05$ ). The mean value of the total rescue analgesic requirement was not significant between the experimental and control groups ( $p>0.05$ ). The preoperative administration of etoricoxib 120 mg revealed a significant difference in pain when compared to the same amount of drug administered postoperatively after four hours of local anesthesia deposition in mandibular third molar surgery. The mean rescue analgesic requirement was not statistically significant between both groups in the postoperative evaluation period.

**Keywords:** analgesia, etoricoxib, preoperative, third molar surgery, postoperative complication

### 1. Introduction

Third molars are the frequently impacted teeth that present with around 24 % of the global prevalence rate (Carter & Worthington, 2016). Surgical removal of impacted third molars are warranted because of its association with either pathology, cyst, infection, or periodontal disease and for prophylactic purpose such as prosthetic, orthognathic, orthodontic, or radiation therapy reasons (Campbell, 2013; Friedman, 2007).

The incidence of impaction is greater with mandibular than maxillary third molars (Carter & Worthington, 2016). Third molar surgery, like many other surgical procedures, is invasive and comes with risks and potential complications. Acute pain, facial swelling, and mouth opening restriction are all temporary but unavoidable side effects of third molar surgery (Coulthard et al., 2014). The overall postoperative complication rate was 16 % in a large prospective cohort study involving 8,700 third molar extractions in over 4,000 participants (Chuang, Perrott, Susarla, & Dodson, 2007).

Following impacted mandibular third molar surgery, a considerable proportion of patients experienced moderate-to-severe pain, which, along with swelling and trismus, accounts for the sudden deterioration in their overall well-being and quality of life (Duarte-Rodrigues et al., 2018). Peripheral nociceptors are sensitized by surgery-induced tissue injury and inflammation, resulting in pain hypersensitivity (Basbaum, Bautista, Scherrer, & Julius, 2009). If untreated, acute pain can lead to central sensitization. A pre-emptive analgesia is a pharmacological approach involving the administration of an analgesic agent before surgery (Dahl & Moïniche, 2004). The knowledge behind this technique is to suppress various noxious stimuli that generate intraoperatively due to the surgical process which contributes to acute and persistent postoperative pain.



Etoricoxib, a second-generation COX-2 inhibitor is effective in controlling moderate-to-severe pain (Laine, Curtis, Cryer, Kaur, & Cannon, 2007). A single dose of etoricoxib 120 mg has been shown to have analgesic efficacy analogous to a single dose of ibuprofen 400 mg (Clarke, Derry, & Moore, 2014). Oral administration of etoricoxib 120 mg has a long duration of analgesic efficacy which allows for once-daily dosing (Clarke et al., 2014). The pre-emptive analgesic efficacy of etoricoxib in various doses (90, 120, and 240 mg) in mandibular fracture and third molar surgery has been reported in the literature with significant benefit in reducing pain (Clarke et al., 2014; Daniels et al., 2011; Goswami et al., 2020; Malmstrom et al., 2004). The use of a higher dose like 120 mg can reduce acute pain in the clinical model like third molar surgery with fewer adverse effects (Albuquerque et al., 2017; Costa et al., 2015; Xie, Li, & Shang, 2021). A study compared 90 mg and 120 mg of etoricoxib with placebo and paracetamol (Brown et al., 2013). The study found significant mean pain reduction on day 2 follow-up compared to placebo and active comparator group. Also, the patient taking 120 mg doses resulted in less requirement of rescue analgesic drug on day 2 when compared with other comparative groups. A split-mouth randomized controlled trial found significant pain reduction and few rescue analgesics requirements with the pre-emptive administration of 120 mg etoricoxib after third molar surgery compared to the placebo group (Costa et al., 2015).

Considering the efficacy of single-dose etoricoxib at 120 mg dose in previous studies, a technique to administer only one dose after surgery and compare it with the same single dose before surgery has not been conducted yet in the available literature. There is insufficient knowledge on whether preoperative or postoperative administration of etoricoxib 120 mg is advantageous in managing acute postoperative pain after third molar surgery.

Therefore, we aimed to assess and compare the efficacy of preoperative versus postoperative administration of single-dose etoricoxib 120 mg for the management of acute postoperative pain in mandibular impacted third molar surgery.

## 2. Objectives

1. To assess and compare the postoperative pain between preoperative and postoperative administration of etoricoxib 120 mg in mandibular third molar surgery.
2. To assess and compare the rescue analgesic drug requirement between preoperative and postoperative administration of etoricoxib 120 mg in mandibular third molar surgery.

## 3. Materials and Methods

### 3.1 Study design and study site

A double-blinded, split-mouth, randomized, controlled trial was conducted at the Department of Oral and Maxillofacial Surgery, Faculty of Dentistry, Mahidol University, Bangkok, Thailand from July 2020 to January 2021.

### 3.2 Sample Size

A study found a significant difference in mean postoperative pain between the intervention (etoricoxib 120 mg) and placebo (Costa et al., 2015). The sample size was calculated using G\* power statistics (version 3.1) using the 2 independent means of the visual analogue scale. A total of 54 samples (27 in each group) was required to detect an effect size of 0.92 as calculated from mean postoperative pain and standard deviation at the 10th hour, at 95% power, and 5% type I error.

### 3.3 Study participants

#### **Inclusion criteria:**

- American Society of Anesthesiologists (ASA): class I or II



- Patients with the presence of asymptomatic, bilaterally similar partially or totally impacted lower third molars as classified by the inclination (according to the Winter classification), class, and position (according to the Pell and Gregory classification) that require flap opening, bone removal, and tooth separation during the operation
- Age: 18 – 30 years

**Exclusion criteria:**

- Patients with any history of allergy to non-steroidal anti-inflammatory drugs
- Pre-existing acute infection and inflammation
- Patients with a history of narcotics or alcohol abuse
- Chronic opioid analgesic use
- Pregnancy and lactating mother
- The surgical time exceeding 120 minutes or any surgical complications occurred that would render the procedures non-comparable
- Unable to follow the instructions or refusal to the follow-up appointments

### 3.4 Randomization and Blinding

A simple random technique was used to allocate the patients into the experimental and control group. Initially, a Computer-generated random number sequence was generated. The allocation concealment was done using the sealed envelope technique which contained the code (A and B) for the purpose of intervention of each participant. Each participant was assigned to two interventions for the operation of two bilaterally symmetrical mandibular third molars. Code A represents the assignment to the experimental group in which etoricoxib (Arcoxia<sup>®</sup>, MSD, Thailand) is administered preoperatively while Code B represents the control group to which the drug is administered postoperatively. The codes are placed in specific boxes according to the groups allocated by a nurse who did not participate in the study other than this period. All participants had similar bilateral lower impacted third molars (LITMs); therefore, the investigator or operator randomly divided the sides of impaction into two equal groups.

For maintaining the blinding in this study, two empty identical capsules were filled with either etoricoxib 120 mg (Arcoxia<sup>®</sup>, MSD, Thailand) or crushed Vitamin B12 as a placebo. During the first operation of one side of the jaw, if code A was allocated, then the capsule containing etoricoxib was given preoperatively and identical capsule with vitamin was given in the postoperative period. Then, on the second operation on the opposite side of the jaw, the experimental drug and placebo were administered reversely.

Both patient and operating surgeon or investigator were blinded to the type of medication given because of the identical capsule. The envelope was decoded once both the clinical trial and statistical analysis had been concluded. The investigator was responsible for patient follow-up examinations and outcome measurements.

### 3.5 Ethical consideration

The study protocol followed the Declaration of Helsinki on medical protocol and was approved by the Faculty of Dentistry/ Faculty of Pharmacy institutional review board (protocol No. 2020/DT006), and registered in the Thai Clinical Trials Registry (TCTR20210726002).

### 3.6 Study procedure and assessments

All patients underwent preoperative screening for the consultation to the removal of the third molar. Before surgery, the consent of the patient was obtained to enroll in the research by the investigator. All patients were explained the objectives, implications, and possible complications of this clinical trial. In addition, Numerical Rating Scale (NRS) was also described to the patient.

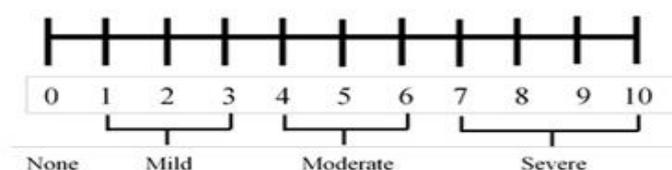
Initially, a panoramic radiograph was obtained to examine the tooth position, inclination, and level of impaction of LITM. Vital signs including blood pressure and pulse rate were assessed before surgery. The surgical procedure was initiated, which involved inferior alveolar nerve and buccal nerve block by



using 4% articaine with epinephrine 1:100,000. After the subjective and objective anesthetic symptoms were perceived, incision and the reflection of the mucoperiosteal flap followed by osteotomy, tooth section, and removal of impacted tooth were done. The surgical wound was sutured with black silk sutures after adequate hemostasis was ensured. All patients were given postoperative advice.

In the experimental group (A), a capsule of etoricoxib 120 mg (Arcoxia®, MSD, Thailand) was administered orally 30 minutes before the operation and the identical capsule containing vitamin was given to ingest 4 hours after the time of injection of local anesthesia. This delay in postoperative administration was done to the wearing off of the effect of local anesthesia used during surgery. On the other hand, the patient in the control group (B) was administrated with a capsule of vitamin, 30 minutes before the operation and the same identical capsule containing etoricoxib 120 mg tablet 4 hours after the injection of local anesthesia. Each participant underwent two surgical procedures performed by the same surgeon, with a washout period of four weeks between them. The nurse involved in the allocation recorded the data in sheets that were kept blinded and revealed to the investigator for data analysis only after the completion of all data collection.

Postoperative drug prescription included amoxicillin 500 mg three times a day for five days as antibiotics and paracetamol 500 mg tablet as a rescue analgesic drug to be taken at 6-hour after meal orally for the control of pain. Patients were told that if they experienced persistent bleeding or any other complications, such as a fever, nausea, and signs of infection they should call the surgeon.



**Figure 1** Numerical rating scale (NRS) is a means of recording subjective pain

Pain severity was assessed by using the Numerical rating scale (NRS). All patients were explained about the NRS to describe the pain as 0 represents no pain and 10 is the worst possible pain at the time of consent. NRS was categorized as 1-3 (mild pain), 4-6 (moderate pain), and 7-10 (severe pain). The total duration of the operation was recorded from the time of the first incision to the final closure of the surgical wound. Pain assessment was started after the completion of surgery. The initial assessment was done when suturing was completed which is considered as 0 hour, then at 2, 4, 6, 8, 12, 16, 20, 24, and 48 hours postoperatively. Following the surgery, all patients were given a standardized NRS form to record the values of postoperative pain. This form had to be returned to the researcher on the 7th day of surgery when the sutures were removed. All patients were asked to record the analgesic consumption in a postoperative data collection sheet. If any adverse effects related to the drugs were presented, then it was also recorded.

### 3.7 Study variables and data collection

Demographic data including age at the time of the operation and sex were recorded. Operative variables included degree and depth of impaction, duration of operation, the requirement of tooth sectioning, total amount of local anesthesia use, and intraoperative complication. All the data were registered and recorded in proforma by using NRS.

#### Outcomes:

1. Comparison of postoperative pain between the experimental and control group
2. Comparison of total rescue analgesic requirements between the experimental and control group



3.8 Statistical analysis

Wilcoxon signed-rank test was used to compare the means of variables between the two intervention groups. SPSS Statistics for Windows, version 18.0 (IBM Corp, Armonk, NY), was used for the statistical analysis. P <0.05 was considered statistically significant.

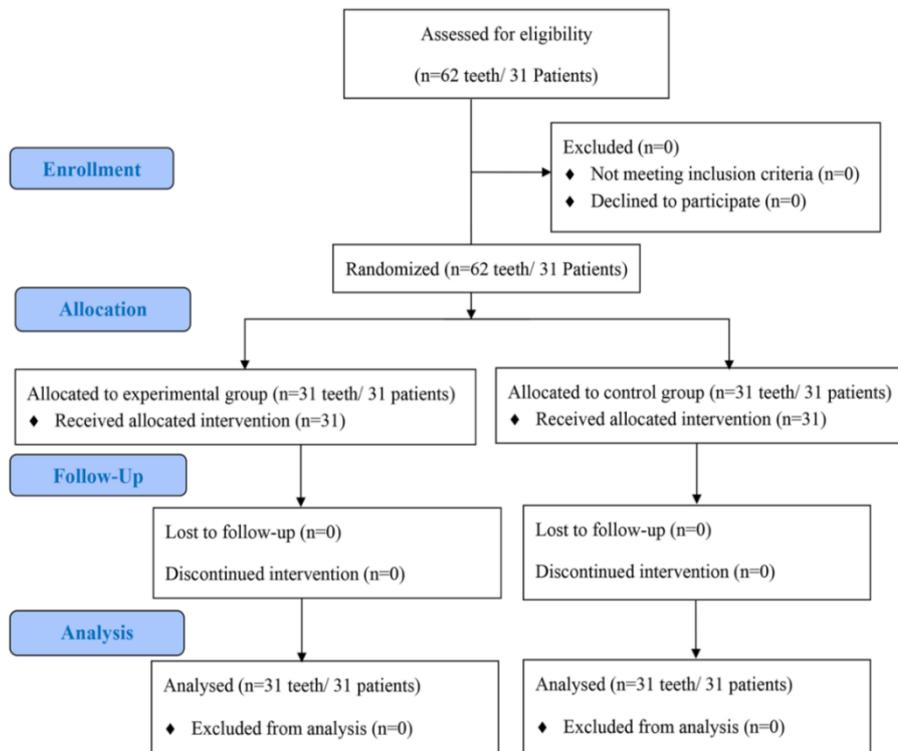
**Table 1** Analgesic consumption

Day after the operation	Amount of drug (Tablets)
Day 0	
Day 1	
Day 2	
Day 3	
Day 4	
Day 5	
Day 6	
Day 7	
Total (Tablets)	

4. Results

4.1 Participants and surgical characteristics

31 patients were included in this study (Figure 1) out of which 5 were male (16.1%) and 26 female (83.9%) with a mean age of 24.77 years (range: 20 to 29 years) (Table 1).



**Figure 2** Consort flow diagram of this study

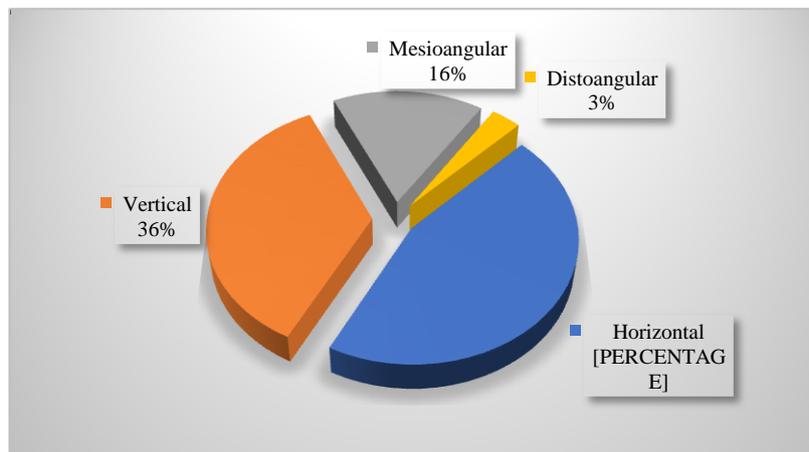
**Table 2** Participants and surgical characteristics

Variables Mean (SD)	Experimental group (E-P)	Control group (P-E)	p-value
Age (in years)			
Min = 20 years	24.77 (2.55)		-
Max = 29 years			
Sex			
Male	5		-
Female	26		
Duration of surgery (mins)	31.77 (7.14)	32.42 (6.57)	0.521
Amount of local anesthesia (ml)	3.73 (0.68)	3.73 (0.68)	1.000

Abbreviations: E-P, etoricoxib administered preoperatively-placebo administered postoperatively; P-E, placebo administered preoperatively-etoricoxib administered postoperatively; SD, standard deviation; Min, minimum; Max, maximum; Mins, minutes; ml, milliliters; Wilcoxon signed-rank test; Significant relationship ( $p < 0.05$ )

**Table 3** Type of mandibular third molar impaction based on Pell and Gregory classification

Class	I	Position	II	A	BI	C
	14		2	14	10	0
	10		5	2	5	0
	0		0	0	0	0
Total (%)	24 (77.42)		Total (%) 7 (22.58)	15 (51.61)	15 (48.39)	0

**Figure 3** Angulation of impacted lower third molars of the participants based on Winter classification

The mean duration of surgery was 31.77 minutes in the experimental group and 32.42 in the control group with no significant difference (Table 1;  $p > 0.05$ ). The mean total amount of local anesthesia (4% articaine) used in the experimental and control group was 3.73 and 3.73 milliliters respectively. However, there was no significant difference between the groups (Table 1;  $p > 0.05$ ). Furthermore, all



patients were operated on with incision followed by flap refection, osteotomy around the impacted tooth, and tooth sectioning for the removal of the impacted tooth.

The class, position, and angulation of the impacted third molar in this study are shown in Table 2 and Figure 2. The highest frequency was observed as Class I impaction in 77 % of total patients and horizontal angulation in 45% of total patients.

#### 4.2 Postoperative pain

The administration of etoricoxib before the impacted third molar surgery did not show a significant difference in mean pain score when compared with the postoperative administration at 0, 2, and 24 hours after surgery (Table 3; all p-value >0.05). However, preoperative administration of etoricoxib resulted in lower mean pain scores at 4, 6, 8, 12, 16, 20, and 48 hours after surgery when compared with the control group with a significant difference (Table 3; all p-value < 0.05). The mean pain level peaked at 4 hours after surgery in both groups while the lowest mean pain score was observed at 24 and 48 hours in both groups. In addition, the overall mean pain score within 48 hours of the evaluation was significantly lower in the experimental group compared to the control group ( $p < 0.05$ ).

The pain score data perceived from patients showed no significant difference between 0 and 2 hours in the experimental and control group because the duration of action was 4% articaine with epinephrine 1:100,000.

The pain score data perceived from patients showed no significant difference at 24 hours while the pain was reduced significantly in the control group. This may be because of the increased effect of etoricoxib given after surgery.

**Table 4** Comparison of mean Numerical Rating Scale scores for pain between the study groups

Evaluation time	Mean (SD)		p-value
	Experimental group	Control group	
Immediately after surgery (0 hr)	0.87 (1.59)	0.87 (1.59)	1.000
2 hr	2.39 (2.22)	2.39 (2.22)	1.000
4 hr	4.35 (2.68)	5.06 (2.49)	0.009
6 hr	2.13 (1.98)	4.13 (1.88)	<0.001
8 hr	1.71 (1.88)	3.35 (1.74)	<0.001
12 hr	1.13 (1.47)	2.48 (1.46)	0.001
16 hr	0.84 (1.44)	1.87 (1.41)	0.001
20 hr	0.90 (1.33)	1.32 (1.14)	0.021
24 hr	0.81 (1.25)	0.77 (0.84)	0.855
48 hr	0.74 (1.13)	0.35 (0.61)	0.010
Total	1.18 (1.23)	2.26 (0.99)	0.001

Abbreviations; SD, standard deviation; hr, hour; Wilcoxon signed-rank test; Significant relationship ( $p < 0.05$ )

The mean number of postoperative rescue analgesic drug intake by the experimental group of patients who received preoperative etoricoxib did not differ significantly when compared to the control group of patients administered with postoperative etoricoxib in mandibular third molar surgery at all follow-up periods (all p-value >0.05). The overall mean total analgesic requirement was not significant between the experimental and control groups.

**Table 5** Comparison of the mean total number of analgesics taken in the period of evaluation between the study groups

Evaluation Days	Mean (SD)		p-value
	Experimental group	Control group	
operation day (day 0)	1.10 (1.01)	1.48 (1.06)	0.16
postop day 1	1.10 (1.10)	1.13 (1.38)	0.99
postop day 2	1.00 (1.12)	0.94 (1.48)	0.85
postop day 3	0.55 (1.03)	0.77 (1.28)	0.57
postop day 4	0.48 (0.93)	0.52 (1.03)	0.98
postop day 5	0.35 (0.76)	0.45 (0.93)	0.64
postop day 6	0.23 (0.67)	0.35 (0.75)	0.49
postop day 7	0.13 (0.56)	0.16 (0.45)	0.66
Total	4.94 (5.59)	5.8 (6.86)	0.95

Abbreviations; SD, standard deviation; postop, postoperative, Wilcoxon signed-rank test; Significant relationship ( $p < 0.05$ )

#### 4.3 Adverse effects

All included patients had no postoperative complications that might have affected the pain score. Wound healing was uneventful in both the study group. Furthermore, none of the patients had adverse effects related to the intervention drug used in this study. All patients were able to carry out their normal activities from the next day of surgery.

## 5. Discussion

The preoperative administration of etoricoxib 120 mg showed significant clinical benefit in pain reduction in the postoperative administration in the mandibular third molar surgery. However, rescue analgesic requirement in the postoperative period was not statistically different between the study groups. Preventing and managing postoperative complications after lower third molar surgery is an important part of clinical practice; as a result, anti-inflammatory drugs have been used to try to reduce these complications. The analgesic effects of NSAIDs are well-documented; however, the exact guidelines to recommend the safer analgesic drug are still under investigation. The principal mechanism of NSAIDs involves the inhibition of the cyclooxygenase pathway that further inhibits Prostaglandin (PGE<sub>2</sub>), Interleukin-1 beta (IL-1 $\beta$ ), and Interleukin-6 (IL-6), Interleukin-8 (IL-8), and Tumor necrosis alpha (TNF- $\alpha$ ) that elicits pain response. Etoricoxib is a selective COX-2 inhibitor that provides analgesia in the acute pain model with faster onset and longer duration of action. In addition, because of the mechanism of selective COX -2 inhibition, it has fewer gastrointestinal effects and also does not affect platelet function. In comparison with other NSAIDs, etoricoxib has shown better efficacy in the reduction of pain after third molar surgery (Brown et al., 2013). Etoricoxib has been administered preoperatively or postoperatively, with either single or daily doses, in various dose formulations like 60, 90, 120, or 240 mg for pain management in dental surgery. Studies have found a significant benefit of using single-dose etoricoxib preoperatively (Costa et al., 2015; Xie et al., 2021) or postoperatively (Malmstrom et al., 2004) in postoperative pain reduction when compared with placebo alone. A study by Brown et al. in 2013 (one dose daily) compared 90 mg and 120 mg of etoricoxib with placebo and paracetamol. The study found significant mean pain reduction on day 2 follow-up compared to placebo and active comparator group. Also, the patient taking 120 mg doses resulted in less requirement of rescue analgesic drug on day 2 when compared with other comparative group.

In this study, etoricoxib was chosen because of its greater potency, longer half-life, and faster onset of action. For the dose, we choose 120 mg as the minimum amount that has efficacy in reducing moderate to severe pain in the surgery of impacted teeth (Malmstrom et al., 2004). The participants and surgical characteristics like age, sex, type of impaction, and operation duration may all be important risk factors for postoperative morbidity, as they have been linked to the occurrence of complications in the past.



There was no statistically significant difference between the two groups' mean values in this study. As a result, in this study, these parameters had no significant effect on the comparison between the two groups.

In this study, postsurgical pain reduction was superior with the single dose of preoperative etoricoxib action with the same drug given after surgery. Rescue drug requirement was comparable between both groups on all postoperative days. There was no significant difference in mean pain score at 0 and 2nd hour postoperatively between the groups. This may be attributed to the fact that; the analgesic effect of local anesthesia used before surgery might have lowered the pain in the control group of patients. This assumption was based on the mean duration of operation which was around half an hour. Therefore, the pain scores were similar to the preoperative etoricoxib administration group. Whereas, both groups experienced peak elevated pain in the 4th hour after surgery but the drug given before surgery demonstrated significantly less mean pain compared to the control group. Overall mean pain score was mild between both groups which suggests that etoricoxib can give either preoperative (1 hour before surgery) or postoperatively. A statistically significant difference was observed at 4 hours after surgery. This time point was the intervention period for the control group at which the drug has not shown the maximum effect.

Currently, a concept of pre-emptive analgesia in clinical pain research is underway. Several studies have been conducted as pre-emptive analgesia with the use of etoricoxib in third molar surgery (Albuquerque et al., 2017; Costa et al., 2015; Hasanin & Sahar, 2021; Rodrigues É, Pereira, Vasconcelos, & Ribeiro, 2019; Xie et al., 2021). The mechanism of acute pain control in this pre-emptive analgesia is an inhibition of pro-inflammatory mediators at the surgical site before the nociceptive mechanism persuades. The drug needs to act before the surgical insult to the tissue to attain pre-emptive acute pain management. Proinflammatory cytokines such as tumor necrosis alpha (TNF- $\alpha$ ) and Interlukin-1 beta (IL-1 $\beta$ ) have often been described as important mediators in the process of pain and inflammation (Quinteiro, Napimoga, Mesquita, & Clemente-Napimoga, 2012; Vernal et al., 2008). Some experimental studies have demonstrated IL-1 $\beta$  is responsible for hyperalgesia in the acute pain model (Alstergren, Benavente, & Kopp, 2003; Watkins et al., 1994). TNF- $\alpha$  also stimulated the synthesis of proinflammatory cytokines like IL-1 $\beta$  and IL-6 which activating prostaglandin synthesis (Cunha, Poole, Lorenzetti, & Ferreira, 1992; Ke et al., 2007). A study analyzed TNF- $\alpha$  and IL-1 $\beta$  in patient administered with pre-emptive etoricoxib 120 mg and ibuprofen 400 mg compared to the placebo one hour before the third molar surgery (Albuquerque et al., 2017). Enzyme-linked immunosorbent assay of excised soft tissue at the surgical site resulted in a significant decrease of TNF- $\alpha$  in the etoricoxib group and both TNF- $\alpha$  and IL-1 $\beta$  in the ibuprofen group compared to placebo. Likewise, TNF- $\alpha$  and IL-1 $\beta$  were positively correlated with pain perception and rescue drug requirement. This indicates that the pre-emptive effect of etoricoxib is important in the control of pain postoperatively. Based on the result in this study and the previous experimental study, preoperative administration of etoricoxib at least 24 minutes (Onset) before a surgical injury can assist in the management of postoperative pain.

Acute postoperative pain after third molar surgery is primarily caused by tissue injury-induced inflammation. The extent of surgical trauma, the need for bone tissue removal, and the extent of periosteum displacement all influence the course of the condition. Inflammatory complications following third molar surgery are still a significant factor in patients' quality of life in the early postoperative period. To make postoperative recovery more comfortable for patients, operating surgeons should be aware of the various modalities for alleviating these complications.

Cold compression was instructed for all the patients in both groups for initial 24 hours after surgery only. It may help in an immediate reduction in swelling which might further help in pain control but it was given in both the group of patients; therefore overall pain reading and comparison between the groups is not affected.

### **Strength and limitations of the study**

The result of this randomized split-mouth study augments the information in the literature on clinical pain management in mandibular third molar surgery. Possible bias in the study has been eliminated with the randomization and double-blinding of the study design. In addition, etoricoxib 120 mg is



recommended to other clinicians operating this type of surgery, particularly before the surgery based on the result of this study. This study limits the assessment of swelling and trismus after surgery which could have provided more information on inter-relationship with the postoperative pain. The determination of the exact time of the pre-emptive effect of etoricoxib was not possible in this study. A further trial is recommended in addition to laboratory research that will evaluate the time of the pre-emptive effect of the drug to suppress the surge of inflammatory mediators. The result of the quantitative evaluation of pain is not sufficient to provide a definitive recommendation for pain control. A further randomized trial in this type of clinical pain model requires qualitative assessment such as oral health-related quality of life.

## 6. Conclusion

Preoperative administration of etoricoxib 120 mg revealed a significant difference in pain when compared to the same amount of drug administered postoperatively after four hours of local anesthesia deposition in mandibular third molar surgery. The mean rescue analgesic requirement was not statistically significant between both groups in the postoperative evaluation period.

## 7. Acknowledgements

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## 8. References

- Albuquerque, A. F. M., Fonteles, C. S. R., do Val, D. R., Chaves, H. V., Bezerra, M. M., Pereira, K. M. A., & Costa, F. W. G. (2017). Effect of pre-emptive analgesia on clinical parameters and tissue levels of TNF- $\alpha$  and IL-1 $\beta$  in third molar surgery: a triple-blind, randomized, placebo-controlled study. *Int J Oral Maxillofac Surg*, 46(12), 1615-1625. doi:10.1016/j.ijom.2017.05.007
- Alstergren, P., Benavente, C., & Kopp, S. (2003). Interleukin-1 $\beta$ , interleukin-1 receptor antagonist, and interleukin-1 soluble receptor II in temporomandibular joint synovial fluid from patients with chronic polyarthritides. *Journal of Oral and Maxillofacial Surgery*, 61(10), 1171-1178. doi:https://doi.org/10.1016/S0278-2391(03)00678-5
- Basbaum, A. I., Bautista, D. M., Scherrer, G., & Julius, D. (2009). Cellular and molecular mechanisms of pain. *Cell*, 139(2), 267-284. doi:10.1016/j.cell.2009.09.028
- Brown, J. D., Daniels, S. E., Bandy, D. P., Ko, A. T., Gammaitoni, A., Mehta, A., & Peloso, P. M. (2013). Evaluation of multiday analgesia with etoricoxib in a double-blind, randomized controlled trial using the postoperative third-molar extraction dental pain model. *Clin J Pain*, 29(6), 492-498. doi:10.1097/AJP.0b013e318260c144
- Campbell, J. H. (2013). Pathology associated with the third molar. *Oral Maxillofac Surg Clin North Am*, 25(1), 1-10, v. doi:10.1016/j.coms.2012.11.005
- Carter, K., & Worthington, S. (2016). Predictors of third molar impaction: A systematic review and meta-analysis. *J Dent Res*, 95(3), 267-276. doi:10.1177/0022034515615857
- Chuang, S. K., Perrott, D. H., Susarla, S. M., & Dodson, T. B. (2007). Age as a risk factor for third molar surgery complications. *J Oral Maxillofac Surg*, 65(9), 1685-1692. doi:10.1016/j.joms.2007.04.019
- Clarke, R., Derry, S., & Moore, R. A. (2014). Single dose oral etoricoxib for acute postoperative pain in adults. *Cochrane Database of Systematic Reviews*(5). doi:10.1002/14651858.CD004309.pub4
- Costa, F. W., Soares, E. C., Esses, D. F., Silva, P. G., Bezerra, T. P., Scarparo, H. C., & Fonteles, C. S. (2015). A split-mouth, randomized, triple-blind, placebo-controlled study to analyze the pre-emptive effect of etoricoxib 120 mg on inflammatory events following removal of unerupted mandibular third molars. *Int J Oral Maxillofac Surg*, 44(9), 1166-1174. doi:10.1016/j.ijom.2015.06.012
- Coulthard, P., Bailey, E., Esposito, M., Furness, S., Renton, T. F., & Worthington, H. V. (2014). Surgical techniques for the removal of mandibular wisdom teeth. *Cochrane Database Syst Rev*(7), CD004345. doi:10.1002/14651858.CD004345.pub2



- Cunha, F. Q., Poole, S., Lorenzetti, B. B., & Ferreira, S. H. (1992). The pivotal role of tumour necrosis factor  $\alpha$  in the development of inflammatory hyperalgesia. *British Journal of Pharmacology*, 107(3), 660-664. doi:<https://doi.org/10.1111/j.1476-5381.1992.tb14503.x>
- Dahl, J. B., & Møiniche, S. (2004). Pre-emptive analgesia. *Br Med Bull*, 71, 13-27. doi:10.1093/bmb/ldh030
- Daniels, S. E., Bandy, D. P., Christensen, S. E., Boice, J., Losada, M. C., Liu, H., & Peloso, P. M. (2011). Evaluation of the dose range of etoricoxib in an acute pain setting using the postoperative dental pain model. *Clin J Pain*, 27(1), 1-8. doi:10.1097/ajp.0b013e3181ed0639
- Duarte-Rodrigues, L., Miranda, E. F. P., Souza, T. O., de Paiva, H. N., Falci, S. G. M., & Galvão, E. L. (2018). Third molar removal and its impact on quality of life: systematic review and meta-analysis. *Qual Life Res*, 27(10), 2477-2489. doi:10.1007/s11136-018-1889-1
- Friedman, J. W. (2007). The prophylactic extraction of third molars: a public health hazard. *American journal of public health*, 97(9), 1554-1559. doi:10.2105/AJPH.2006.100271
- Goswami, D., Sardar, A., Baidya, D. K., Yadav, R., Bhutia, O., & Roychoudhury, A. (2020). Comparative evaluation of two doses of etoricoxib (90 mg and 120 mg) as pre-emptive analgesic for post-operative pain relief in mandibular fracture surgery under general anaesthesia: a prospective, randomised, double-blinded, placebo-controlled trial. *Turkish journal of anaesthesiology and reanimation*, 48(1), 24-30. doi:10.5152/TJAR.2019.54614
- Hasanin, A. M., & Sahar, S. A.-A. (2021). A Randomized case-controlled clinical trial of the effect of preemptive etoricoxib, prednisolone and a control group on of postoperative sequelae after surgical removal of impacted mandibular third molars. *Medico Legal Update*, 21(2), 563-571. doi:10.37506/mlu.v21i2.2742
- Ke, J., Long, X., Liu, Y., Zhang, Y. F., Li, J., Fang, W., & Meng, Q. G. (2007). Role of NF- $\kappa$ B in TNF- $\alpha$ -induced COX-2 expression in synovial fibroblasts from human TMJ. *Journal of Dental Research*, 86(4), 363-367. doi:10.1177/154405910708600412
- Laine, L., Curtis, S. P., Cryer, B., Kaur, A., & Cannon, C. P. (2007). Assessment of upper gastrointestinal safety of etoricoxib and diclofenac in patients with osteoarthritis and rheumatoid arthritis in the multinational etoricoxib and diclofenac arthritis long-term (MEDAL) programme: a randomised comparison. *Lancet*, 369(9560), 465-473. doi:10.1016/s0140-6736(07)60234-7
- Malmstrom, K., Sapre, A., Coughlin, H., Agrawal, N. G., Mazonko, R. S., & Fricke, J. R., Jr. (2004). Etoricoxib in acute pain associated with dental surgery: a randomized, double-blind, placebo- and active comparator-controlled dose-ranging study. *Clin Ther*, 26(5), 667-679. doi:10.1016/s0149-2918(04)90067-7
- Quinteiro, M. S., Napimoga, M. H., Mesquita, K. P., & Clemente-Napimoga, J. T. (2012). The indirect antinociceptive mechanism of 15d-PGJ2 on rheumatoid arthritis-induced TMJ inflammatory pain in rats. *European Journal of Pain*, 16(8), 1106-1115. doi:<https://doi.org/10.1002/j.1532-2149.2012.00114.x>
- Rodrigues É, D., Pereira, G. S., Vasconcelos, B. C., & Ribeiro, R. C. (2019). Effect of preemptive dexamethasone and etoricoxib on postoperative period following impacted third molar surgery - a randomized clinical trial. *Med Oral Patol Oral Cir Bucal*, 24(6), e746-e751. doi:10.4317/medoral.23095
- Vernal, R., Velásquez, E., Gamonal, J., Garcia-Sanz, J. A., Silva, A., & Sanz, M. (2008). Expression of proinflammatory cytokines in osteoarthritis of the temporomandibular joint. *Archives of Oral Biology*, 53(10), 910-915. doi:<https://doi.org/10.1016/j.archoralbio.2008.04.004>
- Watkins, L. R., Wiertelak, E. P., Goehler, L. E., Smith, K. P., Martin, D., & Maier, S. F. (1994). Characterization of cytokine-induced hyperalgesia. *Brain Research*, 654(1), 15-26. doi:[https://doi.org/10.1016/0006-8993\(94\)91566-0](https://doi.org/10.1016/0006-8993(94)91566-0)
- Xie, L., Li, Z., & Shang, Z. J. (2021). Preemptive oral etoricoxib on health-related quality of life after mandibular third molar surgery: a randomized, double-blind, placebo-controlled clinical trial. *Biomed Res Int*, 2021, 8888151. doi:10.1155/2021/8888151