

## Comparison of Postoperative Pain Management after Third Molar Extraction with Two Anti-Inflammatory Drugs

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### Abstract

**Background:** The present study was aimed to investigate the pre-emptive analgesia attained with oral celecoxib compared with oral acetaminophen post mandibular third molar surgery.

**Methodology:** A double-blinded, randomized, placebo-controlled clinical trial was performed in order to examine patients having a mandibular third molar for extraction under local anesthesia. The patients were randomized for receiving a preoperative oral dosage of celecoxib or acetaminophen as the predictor parameter. The primary outcome parameter was postoperative pain assessed through a visual analog scale (VAS) at different time points. The secondary outcome parameter was the quantity of postoperative analgesics taken in both groups. Statistical analyses included descriptive statistics, the t test, and the Pearson c2 test. Significance was set at  $P < .05$ .

**Results:** 60 patients were divided randomly into either celecoxib receiving group or acetaminophen receiving group. The postoperative pain scores in the celecoxib group receiving were significantly lower than those in the acetaminophen receiving group at 4, 6, 8, and 12 hours ( $P = .078$ ,  $P = .0012$ ,  $P = .0211$ , and  $P = .011$ , respectively). The number of patients who didn't require any analgesics in the celecoxib receiving group was less than that in the acetaminophen receiving group ( $P = .0186$ ). The average amount of rescue analgesic medication in the celecoxib group (0.6 0.8 dose) was significantly lower than that in the acetaminophen group (1.3 1.0 doses) ( $P = .002$ ). The Kaplan-Meier curve (KM curve) was indicative of long-term survival of the patients receiving celecoxib compared to those who did not receive any rescue analgesic medication ( $P = .0055$ ).

**Conclusions:** Celecoxib, as the study reflects, has a significant pre-emptive analgesic effect, thus helpful in reducing the usage of postoperative analgesics after removal of the third molar.

**Keywords:** Tooth Extraction; Celecoxib; Acetaminophen; Pre-Emptive Analgesic Effect.

### Introduction

Disimpaction of mandibular third molars with patients administered local anesthesia involves damage to bone as well as muscle tissue that leads to postoperative pain, swelling, and sometimes trismus.<sup>1</sup> Inadequate postoperative pain management is a potent source of complications and a major cause of

decreased quality of life after surgery. Inflammatory mediators, such as prostaglandins, leukotrienes, and

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**How to cite this article:** Singh KT, Kumar M, Singh Nishu<sup>3</sup>, Ranjan S, Mishra V, Gourav R. Comparison of Postoperative Pain Management after Third Molar extraction with two Anti-inflammatory Drugs. Niger Med J 2021;62;(5): 238-242

platelet-activating factor, are released after operation-induced injury; vascular dilation and increased permeability occur, causing edema and enhancing interstitial tissue response.<sup>2</sup> Therefore, prophylactic analgesia is a recommended method for treating postoperative pain after third molar extraction.<sup>3</sup> Pre-emptive approaches focus on preventing postoperative algesic flare and moderating or blocking the occurrence of hyperalgesic states. Pre-emptive analgesic strategies aim to control or prevent central sensitization. The basic principles of therapeutic intervention include the following: 1) differentiating between analgesic states that eliminate all physiological pain and those that eliminate only abnormal hypersensitivity, 2) specifically targeting the induction or maintenance of central sensitization by particular treatments, and 3) preventing or reducing postoperative pain with strategies designed to inhibit the onset of central sensitization during surgery.<sup>4</sup> Pre-emptive analgesia can be achieved by administering local anesthetic injections or analgesic drugs (nonsteroidal anti-inflammatory drugs [NSAIDs] or opiates) before surgery.<sup>5-7</sup> Acetaminophen is a well-tolerated, effective, and customary analgesic used for pain management. Acetaminophen works through central processes, including pathways that affect the production of prostaglandins, serotonin, opioids, nitric oxide, and cannabinoids.<sup>8</sup> To date, acetaminophen has been used for pre-emptive analgesia, mainly relying on the summary of experiences. However, it is frequently implicated in intentional or unintentional overdoses because of its wide availability, thereby causing severe liver injury and even acute liver failure.<sup>9</sup> As one of the selective inhibitors of cyclooxygenase (COX) 2, celecoxib significantly reduces gastrointestinal toxicity, exhibits no effect on platelet aggregation, and elicits anti-inflammatory and analgesic effects by reducing prostaglandin formation.<sup>10</sup> The exact mechanism of action of celecoxib is clear. Therefore, it is suitable for perioperative use. Numerous studies have shown that celecoxib is effective in postoperative pain reduction by preoperative administration.<sup>11-13</sup> However, few studies have been conducted on the pre-emptive analgesia of low doses of celecoxib in the extraction of the mandibular third molar. Its effect is also unclear. This study aimed to compare the efficacy of the preoperative administration of celecoxib with that of acetaminophen on postoperative pain relief after mandibular third molar surgery.

## Materials and Methods

The present study was a randomized, controlled, double-blind, crossover clinical trial performed in accordance with the guidelines of good clinical practice and the Declaration of Helsinki. The study got clearance from the local institutional ethical review board. Sixty healthy patients were recruited to participate in the study. These were male and female patients aged between 17 and 50 years who were scheduled to undergo surgical removal of an impacted horizontal mandibular third molar. The participants were given standardized participant information sheets. Subsequently, written informed consent was obtained from the participants before study commencement. Patients were excluded if they had any conditions that contraindicated the use of NSAIDs and COX-2 inhibitors; were pregnant or nursing; had serious diseases including liver, kidney, and cardiovascular diseases; had ulcers or bleeding in the digestive tract; were unable to express subjective discomfort symptoms; had caries or periapical periodontitis; or had periodontal disease involving the adjacent teeth. Patients were included if they were at least 17 years old, had horizontally impacted teeth, had no history of allergy to steroidal drugs, and had taken no analgesic and anti-inflammatory drugs for 1 week. Sixty patients were randomly divided into 2 groups by use of a series of random numbers, with 30 patients in each group. One group received an oral dose of 500 mg of acetaminophen, whereas the other group was administered 200 mg of oral celecoxib. The patient and the operator were blinded to the type of drug. Drug administration was performed 30 minutes before surgery. All operations were performed by the same oralmaxillofacial surgeon to minimize the differences between operators. The same local anesthesia techniques were performed in all patients. In particular, 2% lidocaine was used to block the inferior alveolar nerve, the lingual nerve, and the long buccal nerve. Local infiltration anesthesia was achieved by using 4% articaine and 1:100,000 epinephrine (Septanest; Septodont, Saint-Maur-des-Fosses, France). Both the acetaminophen and celecoxib groups underwent the same surgical procedure to reduce surgery-related bias. In brief, a buccal mucoperiosteal flap was raised, the bone was removed, and the tooth was sectioned. After the tooth was extracted, the alveolar tissue was scraped and rinsed with sterile saline solution. The wound was sutured with a No. 4-0 silk, and the suture was removed 1 week after surgery. An 11-point visual analog scale (VAS) score (from 0 to 10) was used to assess pain (0, showed no pain; 1- 3, showed mild

pain; 4 - 6, showed moderate pain; 7 - 9, showed severe pain; and 10, showed worst possible pain). Postoperative pain was recorded on the VAS at 2, 4, 6, 8, 12, and 24 hours after surgery. Ibuprofen (300 mg) was prescribed as the rescue drug only in the case of pain (VAS score > 3). Simultaneously, patients recorded their total ibuprofen consumption (number of tablets) within the first 24 hours (at 2, 4, 6, 8, 12, and 24 hours) and the time the first analgesic rescue medication was taken after the procedure was completed.

### Statistical analysis

Data were analysed using SPSS software version 22. Independent t tests and  $\chi^2$  tests were used to determine significant differences between the 2 groups. Parametric outcomes were further expressed as mean standard deviation. The Kaplan-Meier (KM) method was used for estimation of the survival curves, while log-rank test was applied for comparison of the differences between curves. A value of ( $P < .05$ ) was considered to be statistically significant.

### Results

Pain scores were obtained from 60 patients who were randomly divided into the 2 study groups. No side effects were reported for any of the medications used. The patients in the acetaminophen group consisted of 9 male and 21 female patients with an average age of  $28.8 \pm 5.3$  years and an average weight of  $59.3 \pm 10.5$  kg. The patients in the celecoxib group consisted of 13 male and 17 female patients with an average age of  $30.9 \pm 7.5$  years and an average weight of  $63.7 \pm 13.6$  kg. The average duration of the operation was  $15.3 \pm 5.3$  minutes in the acetaminophen group and  $15.7 \pm 5.4$  minutes in the celecoxib group. No differences in age, gender, weight, and duration of the operation were detected between the 2 groups.

### PAIN (VAS SCORE ANALYSIS)

The mean VAS pain score was  $2.7 \pm 1.7$  in the celecoxib group 4 hours after surgery. This value was lower than that in the acetaminophen group (mean VAS pain score,  $4.1 \pm 2.3$ ). This trend continued for 12 hours postoperatively.

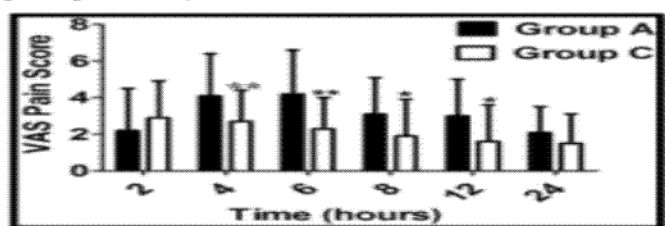


Figure 1: Pain scores at 2, 4, 6, 8, 12, and 24 hours after surgery as measured on visual analog scale (VAS) in acetaminophen group (group A) and celecoxib group (group C)

Table 1: Average Pain Measurements In Study Groups

Timing of VAS Pain Score, Hours	Acetaminophen receiving Group	Celecoxib receiving Group	P Value
2	2.2 ± 2.3	2.9 ± 2.0	.199
4	4.1 ± 2.3	2.7 ± 1.7	.008*
6	4.2 ± 2.5	2.3 ± 1.7	.001*
8	3.1 ± 2.1	1.9 ± 2.0	.021
12	3.0 ± 2.1	1.6 ± 2.1	.011
24	2.1 ± 1.4	1.5 ± 1.7	.084

Table 2: Comparison of Average dose and number of patients requiring rescue analgesic intake within 24 Hours between groups

Parameters	Acetaminophen Group ( n=30)	Celecoxib Group (n=30)	P Value
Patients who consumed first rescue analgesic medication during evaluation period (24hours)	22(73.3)	12(40)	.018*
Patients who required no rescue analgesic medication during evaluation period (24hours)	8(26.7)	18(60)	.018*
Total analgesic consumption (tablets) for 24 hours postoperatively	1.3T1.0	0.6T0.8	.002 <sup>y</sup>

### Discussion

Celecoxib, an NSAID, was the first specific inhibitor of COX-2 approved to treat patients with rheumatism and osteoarthritis. Celecoxib is an effective pre-emptive analgesic for patients undergoing periodontal surgery and hip surgery.<sup>11,15,17</sup> Liu and Wang<sup>12</sup> confirmed that the efficacy of 400 mg of preoperatively administered celecoxib is better than that of postoperatively administered celecoxib and showed that they have similar safety profiles in knee osteoarthritis patients undergoing total knee arthroplasty. However, information regarding the pre-emptive analgesic effectiveness of celecoxib at a low dose of 200 mg in the extraction of impacted teeth is limited.

Surgical removal of impacted mandibular third molars has been widely used as a model to evaluate analgesic drugs for acute pain. Treatment often leads to moderate to severe pain after surgery. To reduce postoperative pain, patients have to take analgesic drugs. Our results showed that celecoxib was superior to acetaminophen in relieving pain after surgical removal of the mandibular third molars.

The mean VAS score of the patients who received celecoxib before surgery was significantly lower than that of the patients who were given acetaminophen. This result indicated good postoperative pain management. Many studies have shown that the use of oral celecoxib before surgery can reduce postoperative pain. Pilatti et al<sup>11</sup> reported that

200 mg of celecoxib administered preoperatively and postoperatively can effectively reduce pain after open-flap debridement. In a randomized, double-blind, placebo-controlled, prospective clinical trial, 150 participants were randomly allocated to receive a standard oral dose of 200 mg of celecoxib, 400 mg of ibuprofen, or placebo containing lactose pre-emptively 1 hour before surgery.<sup>13</sup> The findings showed that celecoxib was more effective than ibuprofen in reducing pain after tooth extraction. Viswanath et al<sup>18</sup> verified that pre-emptive analgesia with intravenous ibuprofen is more effective than intravenous acetaminophen in reducing postoperative pain and opioid use during third molar surgery. Thus, celecoxib might be more effective than acetaminophen in relieving pain.

Our results indicated that celecoxib significantly relieved postoperative pain compared with acetaminophen at 4, 6, 8, and 12 hours after surgery. Studies investigating the clinical pharmacokinetics of celecoxib and acetaminophen have shown that 200 mg of celecoxib reaches its peak plasma drug concentration ( $t_{max}$ ) after 2.3 hours. Our data showed that the total analgesic consumption within 24 hours postoperatively in the celecoxib group was less than that in the acetaminophen group. Kang et al<sup>17</sup> proposed that the pre-emptive use of celecoxib provides additional pain relief until the fourth postoperative day, improves patient satisfaction at discharge, and reduces total narcotic consumption for postoperative pain management after hip hemiarthroplasty for hip fractures.

Our study similarly showed that the celecoxib group had a longer period until the consumption of the first analgesic tablet than the acetaminophen group. The data showed that 60% of the patients in the celecoxib group and 26.7% of the patients in the acetaminophen group did not require an analgesic during the evaluation period, indicating a significant difference. This outcome was related to the longer half-life of celecoxib than that of acetaminophen.

### Conclusion

In conclusion, celecoxib exhibits a significant pre-emptive analgesic effect, resulting in decreased use of postoperative analgesic medication. The results suggest that celecoxib is an alternative treatment for acute pain after surgical removal of the impacted mandibular third molar.

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