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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

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Abstract. Pain after third molar extraction has been considered the most suitable pharmaceutical model to evaluate acute pain. This study aimed to evaluate the pre-emptive analgesic/anti-inflammatory efficacy of etoricoxib 120 mg following mandibular third molar surgery. A split-mouth, randomized, triple-blind, placebo-controlled study was conducted with patients undergoing the surgical removal of mandibular third molars. All volunteers were allocated randomly to receive either etoricoxib 120 mg or placebo 1 h preoperatively, and inflammatory events were evaluated. An estimated sample of 18 surgical units per group was required based on a pilot study (95% confidence level and 80% statistical power). Rescue medication was analyzed by Kaplan–Meier method through log-rank Mantel–Cox test and Pearson linear correlation ($P < 0.05$). Pre-emptive etoricoxib reduced postoperative pain scores significantly in comparison to placebo ($P < 0.001$), with a pain score peak at 6 h after surgery ($P < 0.001$). The mean rescue medication consumption was lower in the etoricoxib group compared to the placebo group over the study period ($P < 0.05$). There was no statistically significant difference between groups related to swelling and trismus. The pre-emptive administration of etoricoxib 120 mg significantly reduced the postoperative pain intensity and the need for rescue medication, but did not reduce swelling or trismus.

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Key words: pre-emptive analgesia; third molar; non-steroidal anti-inflammatory drugs; etoricoxib.

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Introduction

Third molar surgeries are common procedures that significantly affect patient quality of life, especially in the 3 days following surgery, due to the intensity of the pain experienced[1,2] and the inflammatory events caused by this type of surgical intervention.[3] Compared to similar procedures in the maxilla, the removal of mandibular third molars usually expresses a higher degree of surgical trauma and pain, requiring the removal of greater amounts of bone secondary to the presence of more complex levels of dental impaction. In addition to pain, the most commonly observed postoperative complications associated with the removal of mandibular third molars are trismus and swelling as a result of the local inflammatory process.[4]

In this context, pre-emptive analgesia represents an anti-nociceptive treatment that prevents the establishment of an altered afferent input process, something that would amplify postoperative pain.[5] According to Al-Sukhun et al.,[6] this pharmacological strategy provides increased patient comfort and reduces the ingestion of analgesic medications for pain control in the postoperative period, reducing the patient recovery time. Pre-emptive analgesia has become one of the most promising strategies for pharmaceutical pain management.[7,8]

Several pharmacological methods to obtain pre-emptive analgesia have been described, such as regional blocks with local anaesthetics, the administration of intravenous opioids, and the use of *N*-methyl-D-aspartate receptor antagonists, corticosteroids, and non-steroidal anti-inflammatory drugs (NSAIDs).[5,9–13] NSAIDs inhibit prostaglandin synthesis and are commonly prescribed for pain relief and the control of swelling after oral surgery.[14] Although some adverse effects related to the use of NSAIDs such as gastrointestinal bleeding, renal function disturbances, a reduction in platelet function, shortness of breath, and profound hypotension have been described in the literature,[5,13] the oral intake of NSAIDs has been recommended by some authors as an efficient pre-emptive therapeutic regimen.[6,15,16] A recent study has demonstrated etoricoxib to be an efficient drug for the management of acute pain secondary to primary dysmenorrhoea and oral and orthopaedic surgeries,[17] and etoricoxib at 120 mg has shown efficacy in several non-dental clinical trials as a pre-medication to control acute postoperative pain.[18–22] Two recently published Cochrane reviews evaluated the analgesic efficacy of a single postoperative dose of etoricoxib in a dental pain model.[23,24] However, evidence of the efficacy of pre-emptive analgesia after third molar surgery remains scarce, and to date, there has been only one non-placebo controlled study that has evaluated the pre-emptive analgesic effect of this drug in third molar surgery.[12] Etoricoxib is a potent and selective cyclo-oxygenase 2 (COX-2) inhibitor with few gastrointestinal side effects[17] and with favourable pharmacological properties, and may thus be considered a promising drug for pre-emptive analgesia.

Therefore, the aim of the present placebo-controlled and triple-blind study was to evaluate the pre-emptive analgesic and anti-inflammatory efficacy of etoricoxib 120 mg following mandibular third molar surgery, using a split-mouth study design.

Materials and methods

Study design and sample

This study was approved by the Ethics Committee of the Academia Cearense de Odontologia and was performed in accordance with the Helsinki statements. The research protocol followed a prospective, single-centre, split-mouth, randomized, triple-blind, placebo-controlled study design, and it was conducted on patients recruited from the Division of Oral and Maxillofacial Surgery, Walter Cantídio University Hospital, Federal University of Ceará (Brazil), who required lower third molar extraction. Patient recruitment was conducted between April 2011 and September 2012 according to the CONSORT statement.[25] The sample unit used in the present study was the surgical site.

Healthy subjects (American Society of Anesthesiologists (ASA) classification I) of both genders, aged 18–35 years, with a clear indication for removal of two lower third molars, were invited to participate in this study. In order to control for the level of traumatic injury inflicted on the patient, the following inclusion criteria were also applied: (1) full coverage of lower third molars by osseous tissue, requiring bone removal and/or tooth sectioning for their extraction, and (2) similar patterns of root formation, position, and degree of impaction between the right and left impacted third molars for all study subjects. Other inclusion criteria were the absence of periodontal disease, swelling, hyperthermia, and trismus prior to surgery. Enrolment in the study required the ability and willingness to cooperate with the research protocol and the provision of appropriate written informed consent.

Patients were excluded if they fulfilled any of the following criteria: were smokers, pregnant or breast-feeding, using medications that could potentially interact with the drugs used in the study, had orthodontic bands on the second molars, had a known allergy to NSAIDs, had a systemic chronic disease, had signs of any pre-existing acute inflammatory or infectious condition, or had used NSAIDs within the past 21 days. Individuals who did not express an interest in participating in this clinical trial during subject recruitment were also excluded. Patients were removed from the study if there was intolerance to the pharmacological regimen, if they were unable to follow the study protocol, if the surgical time exceeded a duration of 2 h, or if they presented a postoperative infection.

Data were recorded preoperatively according to a standardized clinical examination and included gender, age, systemic conditions, periodontal status, haemogram parameters, platelet count, international normalized ratio (INR), and plasma glucose. A panoramic radiograph was required to evaluate variables such as the tooth position according to the Pell and Gregory[26] and Winter[27] classifications, degree of tooth/root development, and level of impaction.

Patients were scheduled for surgery in two separate clinical sessions (one side at a time) at least 3 weeks apart. Subjects were allocated to one of two groups through a computer-generated randomization code (Microsoft Excel), according to the medication received 1 h before surgery: group 1, etoricoxib 120 mg; group 2, placebo. Antibiotic prophylaxis was not given to the patients. After surgery,

ibuprofen 300 mg at 8-h intervals was allowed in the case that a rescue analgesic medication was needed.

Sample size calculation

Initially, a placebo-controlled study with six patients (12 mandibular third molars) was performed to calculate the sample size required to conduct this clinical trial and statistically reject the null hypothesis with 80% power and a 95% confidence interval. Based on the mean pain scores of the pilot study (etoricoxib 0.3 ± 0.8 and placebo 2.3 ± 2.9), a minimum sample size of 18 surgical sites in each group was estimated.

Blinding

Information on the type of medication provided to each study subject was withheld from the patient, surgeon, clinical investigator (responsible for patient follow-up examinations and outcome measurements), and statistician. Prior to surgery, a list containing a randomized distribution of all surgical sites and pain medications to be administered was held in a sealed envelope by an external study collaborator, who was unaware of the study protocol and had no further participation in this clinical trial other than to guarantee a triple-blind study design. The statistical analysis was initially carried out with groups coded with the letter 'A' representing etoricoxib and 'B' representing placebo. The envelope decoding this information was only accessed once both the clinical trial and statistical analysis had been concluded. At this time, each patient and surgical site assigned to receive etoricoxib or placebo was identified.

Surgical overview

All patients underwent a standardized surgical technique performed in an outpatient setting under local anaesthesia, followed by strict biosafety control. One surgeon with 10 years of experience in oral and maxillofacial surgery performed all of the surgical procedures. The same surgical procedure was adopted for both sides of the mouth, aiming to reduce differences in the level of intraoperative trauma. The extraction of lower third molars was performed under local anaesthesia with mepivacaine 2% and epinephrine 1:200,000 (Mepivalem AD; Dentsply, USA), using two or three 1.8-ml cartridges. A full-thickness flap was raised, followed by bone removal using a drill cooled with bi-distilled water. The surgical wound was closed using a 4–0 silk suture.

Postoperative instructions were read and explained carefully to the patient, e.g. following a liquid and cold diet for 24 h, performing rigorous oral hygiene, and avoiding mouthwashes to prevent the occurrence of post-surgical bleeding. Patients were informed that they must contact the surgeon by telephone in the case of persistent bleeding or any other complications such as fever. In addition, patients were also asked to report any physical symptoms experienced during the study period, e.g., nausea, vomiting, dizziness, headache, insomnia, and signs of infection.

Outcome measures

The primary outcome of the study was the occurrence of postoperative pain. Measurements of this outcome considered pain intensity and the need for rescue analgesia. Postoperative pain intensity was measured using a 10-cm visual analogue scale (VAS), which consisted of an interval scale ranging from 0 (absence of pain or discomfort) to 10 (maximum pain or discomfort).[12,14,17,28,29] Before surgery, each patient received an explanation on how to measure pain intensity on the VAS. After surgery, patients received a standardized VAS form to record the values of postoperative pain, and it was required that this form be returned to the researcher on the day of suture removal. Study participants were asked to record the pain intensity score at 0, 2, 4, 6, 8, 10, 12, 24, 48, and 72 h and on days 5 and 7 following surgery. Additional analyses included the length of time elapsed until the intake of a rescue analgesic by the patient.[30] The number of patients requiring a rescue analgesic was also recorded.

The occurrence of postoperative inflammatory events was the secondary outcome measure adopted in the present study. Measurements (Fig. 1) were performed to assess postoperative facial swelling on the side of surgery, including the distance from the mandibular angle to (1) the tragus (distance MA–Tr), (2) the external corner of the eye (distance MA–ECE), (3) the nasal border (distance MA–NB), (4) the labial commissure (distance MA–LC), and (5) the soft pogonion (distance MA–SP). Differences between preoperative values (baseline) and those obtained at 24 and 72 h and at 5 and 7 days after surgery were compared. In order to estimate trismus, the maximum mouth opening ability was measured pre- and postoperatively (after 24 h, 72 h, 5 days, and 7 days), by assessing the distance between the upper and lower central incisors in millimetres using a calibrated ruler.

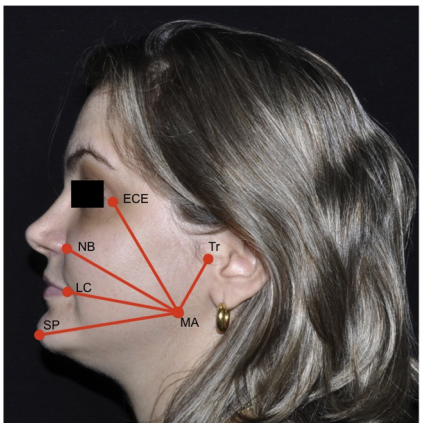

Fig. 1. Facial measurements for the assessment of postoperative swelling: mandibular angle to tragus (distance MA–Tr), mandibular angle to external corner of the eye (distance MA–ECE), mandibular angle to nasal border (distance MA–NB), mandibular angle to labial commissure (distance MA–LC), and mandibular angle to soft pogonion (distance MA–SP).

Statistical analysis

Data were initially submitted to the Kolmogorov–Smirnov normality test. Parametric data were analyzed by one-way or two-way analysis of variance (ANOVA)/Bonferroni test. Non-parametric data were analyzed with the Mann–Whitney or Wilcoxon and Friedman/Dunn post hoc tests. Quantitative variables were expressed as the mean ± standard deviation of the mean (SD). The Kaplan–Meier method was used to evaluate the rescue medication through the log-rank Mantel–Cox test. Pearson linear correlation was applied to correlate the total number of rescue medications taken and the sum of pain scores. All analyses were performed with GraphPad Prism 5.0 software (GraphPad Software Inc., San Diego, CA, USA). The level of significance was set as $P < 0.05$ for all of the evaluations.

Results

A total of 626 patients were screened for study eligibility (Fig. 2); 604 individuals were excluded because they did not meet the study criteria. Four subjects were removed from the study sample for the following reasons: one participant developed a postoperative infection following the first surgery and three participants missed the follow-up visits. The final

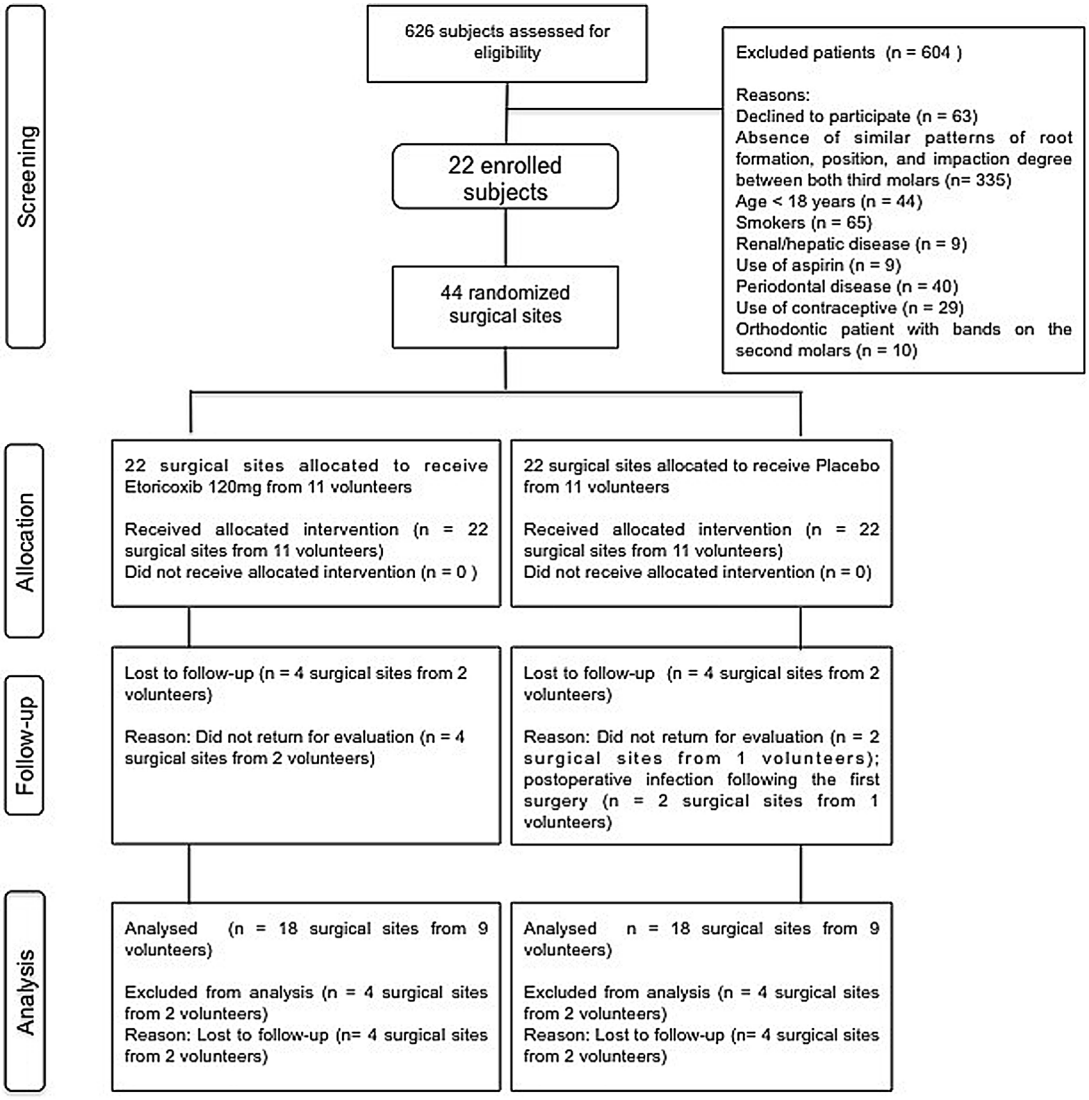

Fig. 2. Flow chart of patient recruitment into the study groups, according to the CONSORT statement.

sample consisted of 18 volunteers (8 males (44.4%) and 10 females (55.6%)), rendering 36 surgical sites.

Surgical and radiographic characteristics did not differ between the groups (Table 1). Local anaesthetic (mepivacaine 2% and epinephrine 1:200,000) was injected at all appropriate sites before surgery, and the total amount of local anaesthetic injected at each surgical site was measured based on the total number of dental cartridges used per procedure. The mean number of dental cartridges did not differ between groups (etoricoxib 2.2 ± 0.4, placebo 2.1 ± 0.2; $P = 0.265$). The average duration of the surgical procedure was 16.2 ± 9.4 min for the etoricoxib group and 16.7 ± 9.5 min for the placebo group, and no statistically significant difference was detected between the groups ($P = 0.839$).

Table 1. Comparison of the surgical and radiographic characteristics between the placebo and etoricoxib groups.

	Placebo	Etoricoxib	*P*-value
Duration of surgery, min	16.7 ± 9.5	16.2 ± 9.4	0.839*
Bone removal, yes/no	18/0	18/0	1.000†
Tooth sectioning, yes/no	9/9	12/6	0.310†
Number of dental cartridges	2.1 ± 0.2	2.2 ± 0.4	0.265*
Postoperative bleeding, yes/no‡	6/84	5/85	1.000†
Day 0	0/18	0/18	1.000†
Day 1	4/14	5/13	1.000†
Day 3	1/17	0/18	1.000†
Day 5	0/18	0/18	1.000†
Day 7	1/17	0/18	1.000†
Pell and Gregory position, I/II/III	10/8/0	8/10/0	0.505†
Pell and Gregory position, A/B/C	0/15/3	0/15/3	1.000†
Winter position, mesioangular/vertical	18/0	18/0	1.000†

* Wilcoxon test; data expressed as the mean ± standard deviation.

† χ^2 test or Fisher's exact test; data expressed as the absolute frequency.

‡ Day 0 = day of surgery; day 1 = first postoperative day; day 3 = third postoperative day; day 5 = fifth postoperative day; day 7 = seventh postoperative day.

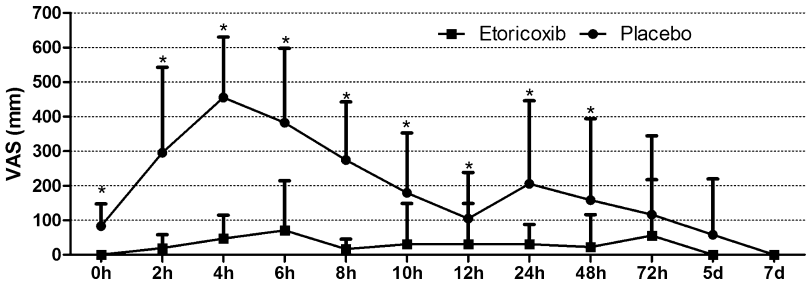

Fig. 3. VAS pain intensity (mm) in the placebo and etoricoxib groups recorded at specific postoperative time intervals. Data are expressed as the mean ± standard deviation. *$P < 0.05$ compared to the placebo group (Mann–Whitney test).

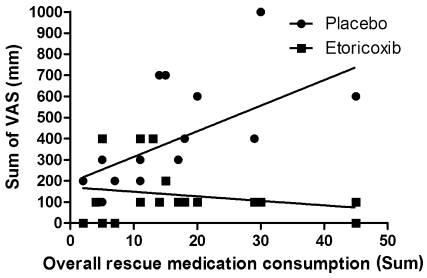

Fig. 4. Pearson correlation analysis of the number of ingested ibuprofen capsules (rescue medication) and the sum of pain scores during the 7-day evaluation period in the placebo group ($P = 0.007$, $r = 0.377$) and the etoricoxib group ($P = 0.410$, $r = -0.109$).

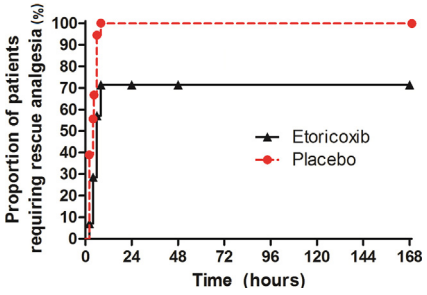

Fig. 5. Kaplan–Meier plot for etoricoxib and placebo groups, representing the proportion of patients in each group who required rescue analgesia ($P = 0.004$, log-rank Mantel–Cox test).

The postoperative peak pain score occurred at 4 h in the placebo group and 6 h in the etoricoxib group (Fig. 3), and a statistically significant difference was detected between the groups ($P < 0.001$). The mean pain score values immediately after ($P = 0.011$) and at 2 h ($P = 0.011$), 4 h ($P < 0.001$), 6 h ($P < 0.001$), 8 h ($P < 0.001$), 10 h ($P = 0.013$), 12 h ($P = 0.037$), 24 h ($P = 0.010$), and 48 h ($P = 0.048$) after surgery were significantly lower in the etoricoxib group (Table 2). The placebo group showed a significant reduction in pain at 12 h after surgery in comparison to the observed mean peak pain score observed at 4 h ($P = 0.003$), whereas the etoricoxib group demonstrated a significant reduction in pain at 8 h postoperatively when compared to the peak pain score at 6 h postoperatively ($P < 0.001$) (Table 2).

In the placebo group, the total number of ingested rescue capsules showed a direct statistical correlation with the sum of pain scores ($P = 0.007$, $r = 0.377$) (Fig. 4). However, this correlation was not observed in the etoricoxib group ($P = 0.410$, $r = -0.109$). In addition, the proportion of subjects requiring rescue analgesic medication was significantly higher in the placebo group at different times of observation ($P = 0.004$) (Fig. 5). At 8 h after surgery, all patients who had received placebo had consumed rescue analgesics, while 22.2% of patients who had received etoricoxib did not need rescue medication during the 7 days after surgery.

The time elapsed (mean ± SD) from the end of surgery to the intake of the first rescue medication differed statistically between the etoricoxib group (27.6 ± 48.7 h) and the placebo group (4.0 ± 1.9 h) ($P = 0.033$) (Table 3). The mean number of rescue capsules consumed on day 0 (placebo 1.4 ± 0.5 vs. etoricoxib 0.7 ± 0.6; $P = 0.003$) and on day 1 (placebo 1.3 ± 0.9 vs. etoricoxib 0.3 ± 0.4; $P < 0.001$), and the overall rescue medication consumption (placebo 4.0 ± 2.5 vs. etoricoxib 1.6 ± 1.3; $P < 0.001$) were significantly higher in the placebo group (Table 3).

Postoperative facial measurements did not differ between the groups at any given time. However, differences in individual facial measurements and in the overall sum of these measurements were observed within groups (Table 4). In addition, maximum mouth opening did not differ between the placebo and etoricoxib groups ($P = 0.662$) (Table 5).

Table 2. Comparison of the VAS postoperative pain intensity measurements (in centimetres) between the placebo and etoricoxib groups.

Period	Drug group		*P*-value
	Placebo	Etoricoxib	
0 h	0.8 ± 0.6*	0.0 ± 0.0	0.011
2 h	2.9 ± 2.5*	0.2 ± 0.4	0.011
4 h	4.5 ± 1.7*,†	0.5 ± 0.7	<0.001
6 h	3.8 ± 2.1*	0.8 ± 1.5†	<0.001
8 h	2.7 ± 1.6*	0.2 ± 0.1‡	<0.001
10 h	1.8 ± 1.7*	0.4 ± 1.3	0.013
12 h	1.0 ± 1.3*,‡	0.4 ± 1.3	0.037
24 h	2.0 ± 2.4*	0.4 ± 0.6	0.010
48 h	1.6 ± 2.4*	0.3 ± 1.0	0.048
72 h	1.2 ± 2.3	0.7 ± 1.8	0.285
5 days	0.6 ± 1.6	0.0 ± 0.0	0.406
7 days	0.0 ± 0.0	0.0 ± 0.0	1.000
Sum	17.1 ± 12.8*	3.2 ± 5.7	<0.001
P-value	<0.001	0.003	

VAS, visual analogue scale. Data are expressed as the mean ± standard deviation.
*$P < 0.05$ compared to etoricoxib (Wilcoxon test).
†$P < 0.05$ in relation to the immediate postoperative period (Friedman/Dunn test).
‡$P < 0.05$ in relation to the hour of peak pain (placebo at 4 h postoperative, etoricoxib at 6 h postoperative) (Friedman/Dunn test).

Discussion

The present study evaluated the efficacy of an oral NSAID, which represents a class of drugs commonly prescribed following oral surgery procedures.[31] For this purpose, mandibular third molar surgery was chosen as a clinical model. The different clinical models used to evaluate the efficacy of oral analgesics are based on the relative frequency of the expression of chronic (i.e. cancer patients), postpartum/episiotomy, and postsurgical (i.e. orthopaedic and dental surgery) pain.[32] According to Cooper,[33] models to

Table 3. Comparison of rescue analgesic consumption after surgical procedures in the placebo and etoricoxib groups.

	Placebo	Etoricoxib	*P*-value
Side effects, yes/no	0/18	0/18	1.000*
Rescue medication intake, yes/no	18/0	14/4	0.104*
Time to first rescue medication, h	4.0 ± 1.9†	27.6 ± 48.7	0.033
Number of rescue medications consumed			
Day 0	1.4 ± 0.5†	0.7 ± 0.6	0.003
Day 1	1.3 ± 0.9†	0.3 ± 0.4‡	<0.001
Day 2	0.8 ± 1.2	0.2 ± 0.6	0.134
Day 3	0.3 ± 0.6‡	0.1 ± 0.4	0.389
Day 4	0.1 ± 0.2	0.1 ± 0.2	1.000
Day 5	0.1 ± 0.2	0.1 ± 0.2	1.000
Day 6	0.0 ± 0.0	0.1 ± 0.3	0.584
Day 7	0.1 ± 0.2	0.0 ± 0.0	0.791
Overall medication consumption	4.0 ± 2.5	1.6 ± 1.3	<0.001
P-value	<0.001	<0.001	

Day 0 = day of surgery; day 1 = first postoperative day; day 2 = second postoperative day; day 3 = third postoperative day; day 4 = fourth postoperative day; day 5 = fifth postoperative day; day 6 = sixth postoperative day; day 7 = seventh postoperative day. Data are expressed as the absolute frequency, or as the mean ± standard deviation.

* Fisher's exact test.

† $P < 0.05$ compared to etoricoxib (Wilcoxon test).

‡ $P < 0.05$ relative to the immediate postoperative period (Friedman/Dunn test).

evaluate different forms of dental pain can be divided into three oral surgery categories: complicated oral, periodontal, and impacted third molar removal. Since third molar surgery is associated with both moderate (40%) and severe (60%) postoperative pain,[34–36] this pharmacological model has become the most utilized in clinical trials involving acute pain, showing results comparable to non-dental postsurgical models, regardless of the analgesic tested.[37]

In the present model of acute pain, a split-mouth, triple-blind, randomized, placebo-controlled study was performed to control for individual biological variations and to reduce possible biases.[38] The split-mouth study design has the advantages of allowing the surgical sides to be 'mirrored', because of the similarity of radicular formation patterns and position/degree of dental impaction in the same individual, and of having a study subject

Table 4. Comparison of the facial swelling values measured pre- and postoperatively between the placebo and etoricoxib groups.

Facial measurements	Period*	Drug groups		*P*-value
		Placebo	Etoricoxib	
MA–Tr	Baseline	5.5 ± 0.8	5.6 ± 0.4	0.938†
	24 h	6.4 ± 0.7‡	6.3 ± 0.6‡	
	72 h	6.2 ± 0.7	6.1 ± 0.6	
	5 days	5.8 ± 0.7§	5.9 ± 0.6§	
	7 days	5.6 ± 0.7	5.7 ± 0.5	
MA–ECE	Baseline	9.8 ± 0.8	10.0 ± 0.6	0.807†
	24 h	10.8 ± 1.0‡	10.6 ± 0.9‡	
	72 h	10.4 ± 0.8	10.4 ± 0.7	
	5 days	10.1 ± 0.8§	10.0 ± 0.7§	
	7 days	9.9 ± 0.8	10.0 ± 0.6	
MA–NB	Baseline	10.3 ± 0.8	10.5 ± 0.6	0.878†
	24 h	11.4 ± 0.9‡	11.4 ± 0.8‡	
	72 h	11.1 ± 0.8§	11.0 ± 0.6§	
	5 days	10.5 ± 0.7	10.6 ± 0.5	
	7 days	10.3 ± 0.6	10.5 ± 0.5	
MA–LC	Baseline	8.3 ± 0.5	8.6 ± 0.7	0.731†
	24 h	9.2 ± 0.6‡	9.3 ± 0.9‡	
	72 h	9.1 ± 0.5	9.0 ± 0.8§	
	5 days	8.8 ± 0.7§	8.8 ± 0.6	
	7 days	8.4 ± 0.2	8.7 ± 0.8	
MA–SP	Baseline	9.9 ± 0.6	10.1 ± 0.8	0.722†
	24 h	11.1 ± 1.0‡	10.9 ± 1.1‡	
	72 h	10.6 ± 0.8§	10.3 ± 0.8§	
	5 days	10.2 ± 0.7	10.0 ± 0.7	
	7 days	9.9 ± 0.6	10.0 ± 0.7	
All measures	Baseline	8.8 ± 1.9	9.0 ± 1.9	0.993†
	24 h	9.8 ± 2.0‡	9.7 ± 2.0‡	
	72 h	9.5 ± 1.9§	9.3 ± 1.9§	
	5 days	9.1 ± 1.9	9.1 ± 1.8	
	7 days	8.8 ± 1.9	9.0 ± 1.8	

MA, mandibular angle; Tr, tragus; ECE, external corner of the eye; NB, nasal border; LC, labial commissure; SP, soft pogonion; ANOVA, analysis of variance. Data are expressed as the mean ± standard deviation.

* Baseline = preoperative value.

† $P < 0.05$, repeated-measures ANOVA–two-way/Bonferroni.

‡ $P < 0.05$ relative to the baseline period, repeated-measures ANOVA–one-way/Bonferroni.

§ $P < 0.05$ relative to the first 24 h after surgery, repeated-measures ANOVA–one-way/Bonferroni.

Table 5. Comparison of maximum mouth opening values in the placebo and etoricoxib groups.

Period	Drug groups		*P*-value
	Placebo	Etoricoxib	
0 h	44.0 ± 5.0	47.2 ± 80	0.662*
24 h	34.9 ± 6.6†	38.4 ± 8.3†	
72 h	37.0 ± 6.0	42.0 ± 8.6†	
5 days	41.5 ± 8.2‡	45.1 ± 8.2	
7 days	43.7 ± 5.0	47.2 ± 8.3	

ANOVA, analysis of variance. Data are expressed as the mean ± standard deviation.
* $P < 0.05$, repeated-measures ANOVA–two-way/Bonferroni.
† $P < 0.05$ relative to the immediate postoperative period, repeated-measures ANOVA–one-way/Bonferroni.
‡ $P < 0.05$ relative to the first 24 h after surgery, repeated-measures ANOVA–one-way/Bonferroni.

as his/her own control for postoperative pain perception.[39] Data homogeneity between the two groups studied in the present research was found due to the absence of statistically significant differences in gender, age, number of surgical procedures, surgery duration, bone removal and/or tooth sectioning, postoperative bleeding, and tooth position.

NSAIDs have been considered effective drugs in the management of pain after third molar removal,[31] and have been used previously to test the efficacy of pre-emptive analgesia as a strategy for pain control.[12,29,38–41] Pharmacologically, NSAIDs act by reducing peripheral and central nociception, secondary to a reduction in the sensory inflow of nociceptive input from the peripheral to central nervous system.[10,13] Among NSAIDs, etoricoxib is considered a potent selective COX-2 inhibitor.[42] Toivonen et al.[22] and Boonriong et al.[18] demonstrated that etoricoxib 120 mg used as a pre-medication in patients undergoing arthroscopic shoulder surgery, significantly reduced postoperative pain. Puura et al.[20] and Sandhu et al.[21] reported the use of etoricoxib 120 mg as a pre-emptive analgesic to decrease postoperative pain after laparoscopic cholecystectomy. Liu et al.[19] concluded that pre-medication with etoricoxib 120 mg reduces the pain scores and need for postoperative fentanyl after minor gynaecological surgery, without significant side effects. In the context of dentistry, there have been no placebo-controlled studies to evaluate the efficacy of the pre-emptive analgesic effect of etoricoxib 120 mg after third molar surgery; thus, the pre-emptive analgesic value of etoricoxib 120 mg remains to be established in dental studies. To date, only one study has used preoperative etoricoxib; however, the results were compared with a group in which a corticosteroid was used.[12] In addition, no systematic reviews concerning the pre-emptive use of etoricoxib 120 mg have been conducted.[23,24]

In the present study, the intensity of postoperative pain was reduced considerably through the preoperative administration of etoricoxib. Morse et al.[29] compared the pre-emptive analgesic efficacy of ibuprofen, rofecoxib (NSAID selective COX-2 inhibitor), and placebo and observed that in all of the evaluation periods, ibuprofen provided pain relief significantly superior to placebo. Rofecoxib also provided similar results, except for the postoperative 1, 3, and 4-h periods, when pain relief was not inferior to placebo. In the present study, etoricoxib showed a statistically significant difference over a 48-h period when compared with placebo. However, Chiu and Cheung[40] performed a placebo-controlled study with pre-emptively administered ibuprofen and rofecoxib, and observed that rofecoxib showed significant pain reduction only in the first 6 postoperative hours in comparison with the preoperative use of placebo. In the present clinical research, the pre-emptive administration of etoricoxib showed a superior postoperative analgesic effect in comparison to placebo at 0, 2, 4, 6, 8, 10, 12, 24, and 48 h after third molar removal. In contrast, Sotto-Maior et al.[12] reported no significant difference in pain control when etoricoxib 120 mg was used 1 h before third molar surgery. Two recent systematic reviews that attempted to measure the postoperative efficacy of etoricoxib 120 mg, showed that 72% of participants involved in five different studies experienced significant pain relief with etoricoxib during the 4–6 h after dental surgery.[23,24]

There was a statistically significant difference in peak pain between the two groups. The etoricoxib group displayed a pain peak at 6 h after surgery, while the placebo group showed a pain peak at 4 h postoperatively. This delay in the onset of the pain peak reinforces the importance of pre-emptive analgesia and the efficacy of etoricoxib 120 mg when compared with placebo. In two studies evaluating the pre-emptive analgesic effect of a selective COX-2 inhibitor (rofecoxib),[29,40] the pain peak occurred 6 h after the surgical procedure, which is similar to the results of the present work. In the study by Sotto-Maior et al.,[12] the preoperative administration of etoricoxib showed a total VAS score number of 6 (±1.8); however, the authors did not mention information on the pain peak reported by patients.

In the present study, the time elapsed from the end of the surgical procedure to the first use of rescue medication differed statistically between the groups analyzed. The average time to the start of postoperative rescue medication in the etoricoxib group was statistically longer than for the placebo group; thus, those patients who used etoricoxib took longer to require postoperative analgesic medication. This fact may reflect the drug pharmacokinetics of the pre-emptive analgesic action. Etoricoxib is a drug that has a fast onset of action and acts for a long period in the organism.[43] The maximum plasma concentration is 1.36 μg/ml.[43] The time taken for etoricoxib to reach the maximum plasma concentration is 1 h and its elimination half-life is 24.9 h[43]; these are favourable pharmacokinetic properties for a drug used to produce long-lasting and effective pre-emptive analgesia in the oral surgery setting. Similarly, the postoperative etoricoxib-related dental studies evaluated by Clarke et al.[23,24] showed that the weighted mean of the median time required for the use of rescue medication exceeded 24 h.

The apparent analgesic efficacy of etoricoxib is also reflected in the reduced number of rescue medications consumed during the evaluation period. As expected, day 0 was the period with the highest rescue medication consumption for both groups, and during the overall postoperative period, the etoricoxib group ingested the lowest number of rescue medications when compared to the placebo group. Morse et al.[29] also noted that the pre-emptive use of NSAIDs significantly reduced the need for rescue medication. Chiu and Cheung[40] observed a smaller quantity of medication required by the patients who utilized a selective COX-2 inhibitor when compared with patients who utilized ibuprofen. In the present research, the pre-emptive analgesic efficacy of etoricoxib was reinforced by the observance of a positive correlation between average pain intensity and the

number of rescue medication capsules that were ingested in the placebo group. This finding is consistent with the results of the dental postoperative studies described by Clark et al.[23,24] The authors reported that 17% of participants in the etoricoxib 120 mg group and 68% of individuals in the placebo group required rescue medication within the initial 6 h after the respective ingestion of either etoricoxib or placebo. In addition, during a 24-h evaluation period, 50% of participants in the etoricoxib 120 mg group required rescue medication, compared with 89% of individuals in the placebo group, demonstrating a satisfactory analgesic efficacy with the use of etoricoxib 120 mg over placebo.

It is recognized that the inflammatory response is mediated by prostaglandins, and their synthesis is initiated by the release of arachidonic acid from the cellular membrane phospholipids through the action of cyclo-oxygenase. The consequences of this physiological process include interlinked events that are represented by pain, swelling, and trismus.[44] It is important to observe that in the present research, although the group treated with etoricoxib showed a significant reduction in pain scores, these individuals did not demonstrate a reduction in swelling or an improvement in maximum mouth opening. Hence, no direct correlation between pain and swelling/trismus was noted.

Similarly, the etoricoxib and placebo groups showed an apparently positive anti-inflammatory effect in some postoperative periods. This result may be explained as follows: (1) preoperative etoricoxib does not exhibit an important anti-inflammatory effect, and (2) since a reduction in inflammation was observed intra-group, without any significant differences between groups, this effect was probably due to ibuprofen alone. Since the prescribed rescue medication regimen consisted of ibuprofen 300 mg every 8 h (when required for pain control), the intake of ibuprofen was higher within the first 72 h (specially on day 0), and within these initial postoperative days patients would frequently consume two to three capsules (600–900 mg) at a time instead of following the regular prescription of one single capsule (300 mg), an anti-inflammatory effect generated by ibuprofen cannot at present be discarded. In both groups, all measurements showed a peak swelling at 24 h and the reduction in swelling was only significant from the fifth to the seventh postoperative day. Sotto-Maior et al.[12] did not observe a significant difference in swelling with the pre-emptive use of etoricoxib. In addition, these authors observed that during the first 48 h of the postoperative evaluation, there was an increase in facial swelling despite a reduction in trismus, which was not found in the present study.

In the present study there were no reported side effects with the use of etoricoxib. According to the published Cochrane reviews,[23,24] the use of etoricoxib 120 mg has been demonstrated to be relatively safe. Information related to adverse events collected 6 h to 14 days postoperatively showed no significant difference in the number of participants reporting at least one adverse effect in the etoricoxib and placebo groups. In addition, no serious adverse events were reported following the use of etoricoxib 120 mg. However, the Committee for Medicinal Products for Human Use of the European Medicines Agency has updated the previously existing contraindications to the use of etoricoxib and has issued a warning for non-adequately controlled hypertensive patients: (1) etoricoxib should not be used in patients with hypertension whose blood pressure is persistently elevated above 140/90 mmHg and has not been adequately controlled, and (2) blood pressure should be monitored for 2 weeks after the start of treatment and regularly thereafter.[45] In spite of the evidence suggesting that the benefits of this drug outweigh the risks, the US Food and Drug Administration has not yet approved the use of etoricoxib in the USA.[24]

In conclusion, etoricoxib significantly reduced the intensity of postoperative pain and the need for rescue medication compared to the placebo. However, etoricoxib did not show any significant anti-inflammatory effect on swelling or trismus in comparison to the placebo group.

Ethical approval

This study was approved by the Ethics Committee of the Academia Cearense de Odontologia (Fortaleza, Brazil; protocol No. 132), and was in agreement with the Helsinki statements.

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Competing interests

None.

Patient consent

Written patient consent was obtained.

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