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Effectiveness of Preventive Analgesia with Etoricoxib in Reduction of Postoperative Pain in Patients Undergoing Third Molar Extraction: A Review Systematics

Catalina Soledad Barrientos Soto[1]*, Fernanda Elena Vargas Magaña[1], Daniel Brevis[2], Pablo Ríos[3] and Lilian Herrera[3]

[1]*Avenida Alemania, pasaje los maquis 390, Frutillar, 5620005, Chile*

[2]*Dental Surgeon, Austral University of Chile, Valdivia campus, Chile*

[3]*Faculty of Medicine, Institute of Odontostomatology, Chile*

***Corresponding author:** Catalina Soledad Barrientos Soto, Avenida Alemania, pasaje los maquis 390, Frutillar, 5620005, Chile

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ABSTRACT

Objective: To determine the effectiveness of Etoricoxib used as preventive analgesia in reducing postoperative pain after third molar extraction.

Materials and Methods: A systematic review was conducted and registered in PROSPERO following the PRISMA 2020 guidelines. Eligibility criteria were established for randomized controlled trials. The Medline, Google Scholar, and Ovid databases were consulted, in addition to a manual search. This process was carried out independently by the two authors. The data and results were compiled and organized in an Excel spreadsheet for qualitative analysis, considering the heterogeneity of the studies. Risk of bias was assessed using the Cochrane RoB 2 tool. The certainty of the studies was assessed using the GRADE PRO tool.

Results: A total of four randomized controlled trials were included. A risk of bias assessment identified a high risk in one study. The remaining three trials were assessed as having a low risk of bias. Pain intensity was measured as the primary outcome in all included studies using the visual analog scale (VAS). All included trials demonstrated that 24 hours postoperatively, preventive analgesia with etoricoxib is capable of achieving a reduction in postoperative pain after third molar extraction, compared with placebo. Additionally, rescue analgesia medication was measured in all trials, and the proportion of patients requiring rescue analgesia and the amount of rescue analgesia was significantly lower in the etoricoxib group compared to the placebo group. Due to the methodological heterogeneity of the included trials, it was not possible to perform a meta-analysis.

Conclusion: Preoperative administration of Etoricoxib significantly reduces pain intensity compared to placebo, showing sustained effectiveness. Likewise, a lower need for rescue analgesia was observed. Qualitative analysis supports the effectiveness of Etoricoxib in this clinical context; However, methodological heterogeneity limits the possibility of performing a robust quantitative analysis and drawing definitive conclusions. Consequently, new randomized clinical trials with standardized methodologies are recommended to confirm these findings.

Keywords: Third Molar; Tooth Extraction; Third Molar Surgery; Preventive Analgesia; Etoricoxib

Abbreviations: NSAID: Nonsteroidal Anti-Inflammatory Drug; VAS: Visual Analog Scale; NRS: Numerical Rating Scale; VRS: Verbal Rating Scale; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RCTs: Randomized Controlled Trials; ITT: Intention-To-Treat

Introduction

Etoricoxib is a nonsteroidal anti-inflammatory drug (NSAID) selective cyclooxygenase-2 inhibitor (COX-2 inhibitor), developed to decrease the production of inflammatory substances. It is indicated for the relief of acute pain and inflammatory symptoms (Biase, et al. [1]). It is rapidly absorbed, reaching peak plasma levels after one hour, supporting its use for long-term analgesic coverage (Konuganti, et al. [2]). It has a prolonged half-life of up to 24 hours, reducing the risk of pain fluctuations, and presents a limited risk of drug-drug interactions (Shetty, et al. [3]). Etoricoxib provides pain relief with fewer renal adverse effects and a lower risk of gastric and duodenal ulcers because it does not inhibit the gastroprotective isoform of COX-1 (Matute Crespo, et al. [4]), compared to traditional nonsteroidal anti-inflammatory drugs (NSAIDs), although it increases cardiovascular side effects. Selective COX-2 inhibitors are safe in patients with asthma and do not impair platelet function (Shetty, et al. [3]). Postoperative pain, edema, and trismus are common after third molar extraction (Barbalho, et al. [5]). In dentistry, postoperative analgesia is used to manage these conditions, as poor postoperative pain control can negatively impact quality of life (Singh, et al [6]). Another alternative involves administering preoperative anti-inflammatory drugs before painful stimulation (Junior, et al. [7]), a technique known as preventive analgesia. Preventative analgesia is an antinociceptive treatment applied before tissue injury to prevent peripheral and central sensitization.

Therefore, it may be more effective than postoperative analgesia (Gately, et al. [8]). Several pharmacological methods can achieve this effect, including local anesthesia, corticosteroids, NSAIDs, analgesics, and combinations of these drugs (Junior, et al. [7]). The reason for studying this drug is based on the fact that it is able to achieve more effective and lasting analgesia for the relief of acute pain (Clarke, et al. [9]). Etoricoxib is a promising analgesic and anti-inflammatory alternative for patients suffering from gastrointestinal symptoms, asthma, and platelet dysfunction in other areas of medicine; an effect that can be extrapolated to preventive analgesia in third molar surgery, since it does not increase the risk of bleeding compared to non-selective NSAIDs (Shetty, et al. [3]), in addition to having a more stable analgesic and anti-inflammatory effect. On the other hand, an economic evaluation demonstrated that etoricoxib at all doses is a less cost-effective treatment than celecoxib (200 mg), and therefore has a superior cost-benefit ratio. Although cardiovascular events associated with the use of etoricoxib have been reported, studies show that these events are comparable to those of other NSAIDs, but further studies are still needed to evaluate long-term safety (Kim, et al. [10]). It was decided to compare etoricoxib against placebo to estimate the absolute effect on reducing postoperative pain after third molar extraction, since comparing it to placebo allows for separating the true treatment effect from the placebo effect. Similarly, it reduces the heterogeneity introduced by other NSAIDs, doses, and regimens.

Without this comparison, there is a risk of obtaining false negative or positive results due to non-specific treatment responses (Gomeni, et al. [11]). To date, three studies evaluating the effectiveness of etoricoxib as a preventative analgesic have been published in the Medline database: a review of systematic reviews on the management of postoperative pain, edema, and trismus in oral surgery (Pimenta, et al. [12]); a systematic review with meta-analysis on third molar surgery (Costa, et al. [13]); and a retrospective observational study evaluating the intramuscular injection of etoricoxib for acute pain in multiple surgeries in the Indian population (Shetty, et al. [3]). There are several lines of research on etoricoxib that cover aspects such as efficacy, safety, quality of life, clinical parameters, and the need for rescue analgesia in numerous areas of medicine, including the effectiveness of its use as a preventative analgesic. However, an up-to-date systematic review of clinical trials on this topic is not available, and there is controversy surrounding the published results. According to a 2015 study, preventive analgesia did not show a significant benefit in reducing postoperative pain after the extraction of impacted lower third molars (Costa, et al. [13]). However, in September of the same year, the same author determined that preventive administration of etoricoxib significantly reduced the intensity of postoperative pain and the need for rescue medication, but did not reduce inflammation or trismus (FWG Costa et al. [14]).

Due to the discrepancy in the findings, an updated systematic review of the results published to date is needed to reach a more concise conclusion that answers the question: Is the use of etoricoxib effective? Etoricoxib as a preventive analgesic, compared with a placebo, in reducing postoperative pain in patients undergoing third molar extractions?

- **General Objective:** To determine the effectiveness of Etoricoxib used as preventive analgesia in reducing postoperative pain after third molar extraction.
- **Specific Objectives:** Select relevant clinical studies, meeting the inclusion and exclusion criteria, in which the use of Etoricoxib as a preventive analgesic in third molar extraction has been evaluated, to obtain an adequate evidence base.

To analyze and compare postoperative pain levels in patients who received Etoricoxib, versus those who received placebo, previously reported in randomized clinical trials, using the visual analog scale (VAS), numerical rating scale (NRS) or verbal rating scale (VRS). To perform a qualitative analysis of the results obtained in the selected studies, in order to determine the impact of the use of Etoricoxib as preventive analgesia in the reduction of postoperative pain in patients undergoing third molar extraction.

Materials and Methods

A systematic review was designed based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 (PRISMA) guidelines. The inclusion criteria are randomized controlled trials (RCTs) that include adult patients, 18 years of age or older, undergoing third molar extraction under local anesthesia. These RCTs must

compare pain measured on the VAS, NSR, or RSV scales with etoricoxib as preemptive analgesia versus placebo, and the drug must be administered orally. RCTs must be double- or triple-blind with parallel arms and conducted in English and Spanish. Randomized controlled trials in which additional doses of analgesics are administered before third molar extraction or in which patients undergo any combination of analgesics were excluded. RCTs in which the extraction is performed under general anesthesia or conscious sedation were also excluded. Furthermore, RCTs in which patients have psychiatric disorders that make them dependent on others for decision-making or have a history of allergy to etoricoxib were excluded. RCTs comparing the preemptive analgesia of etoricoxib with any other medication besides placebo were also excluded. The participants in this study are adult patients ≥ 18 years old who require extraction of maxillary and/or mandibular third molars under local anesthesia, with no history of psychiatric disorders, no history of allergy to Etoricoxib, and who are not undergoing the administration of any combination of analgesics. The independent variable corresponds to the administration of Etoricoxib in milligrams as preventive analgesia, on the other hand, the dependent variable corresponds to the level of postoperative pain, measured through standardized pain scales.

Postoperative pain is a qualitative variable of an ordinal type. It is operationally defined as the intensity of pain experienced by the patient after tooth extraction, measured within the first 24 hours using various scales over a 24-hour period, such as the visual analog scale (VAS). This consists of a 10-centimeter horizontal line, at the ends of which are the extreme expressions of a symptom: absence or lowest intensity on the left and highest intensity on the right. The patient is asked to mark the point on the line that indicates their intensity, and this is measured with a millimeter ruler. The intensity is expressed in centimeters or millimeters. Alternatively, a numerical rating scale (NRS) can be used; this is a numbered scale from 1 to 10, where 0 is absence and 10 is the highest intensity. The patient selects the number that best represents their pain. It assesses the intensity of the symptom, and the verbal rating scale (VRS); made up of adjectives that represent the increasing intensity of the pain, such as absence of pain, mild pain, moderate pain and severe or intense pain, to facilitate its interpretation these adjectives are assigned a number; 0,1,2,3 respectively (Vicente Herrero, et al. [15]). The dose of Etoricoxib corresponds to a nominal qualitative variable. It is operationally defined as a selective COX-2 inhibitor NSAID, administered orally one hour before extraction to study participants at doses of 60 milligrams, 90 milligrams, or 120 milligrams as a preventive anti-inflammatory analgesic agent, in order to evaluate its effect on postoperative pain control.

A search was conducted in the Medline database, in addition to a manual search of the bibliographies of the selected articles. The search engines used were PubMed, Ovid, and Google Scholar. Table 1 shows the search strategy. The study selection process involved independent review of all titles and abstracts by two authors, followed by the removal of duplicates. The full text of included studies was reviewed to confirm their inclusion. Discrepancies were resolved through discussion. The data for the studies was collected by two reviewers who, through independent visual inspection, synthesized the information in an Excel spreadsheet, to select the articles based on the inclusion and exclusion criteria, during the first semester of 2025 at the Austral University of Chile, Valdivia campus. The selection of studies was carried out using the PRISMA 2020 flowchart shown in Figure 1. Each of the included studies is shown in Table 2. The authors extracted the data from each of the included studies and entered them into an Excel spreadsheet for analysis. Table 3 shows the demographic analysis of the participants. For the results, the following data were extracted: study name, main author and year of study, pain intensity according to time; according to the pain scale, Etoricoxib dose, placebo use. The Cochrane Risk of Bias 2 (RoB 2) tool was used to assess the included studies, where 5 domains were evaluated: bias in the randomization of allocation, bias due to deviations from the assigned intervention, bias due to incomplete outcome data, and bias in the measurement of outcomes, and bias in the selection of reported results.

Table 1: Search strategy.

Engine Search	Search strategy	Deadline search	Filters
PubMed	("third molar") AND (exodontia OR "tooth extraction" OR "third molar surgery") AND ("preventive analgesia" OR "preemptive" OR preemptive) AND ("anti-inflammatory agents nonsteroidal" OR NSAID OR etoricoxib)	February 20 - March 20 2025	Article type: randomized controlled trial
Google Academic	Etoricoxib + preventive analgesia + pain + third molar surgery OR tooth extraction OR extraction	February 20 - March 20 2025	

Ovid	(All Fields: etoricoxib) AND (All Fields: third molar) AND (All Fields: exodontia OR All Fields: tooth extraction) AND (All Fields: preventive analgesia" OR "pre-emptive" OR preemptive)	February 20 - March 20 2025	Article type: randomized controlled trial
Manual Search	Review the bibliographies of the articles found. Cross-reference the bibliographies of selected studies.	February 20 - March 20 2025	Article type: randomized controlled trial

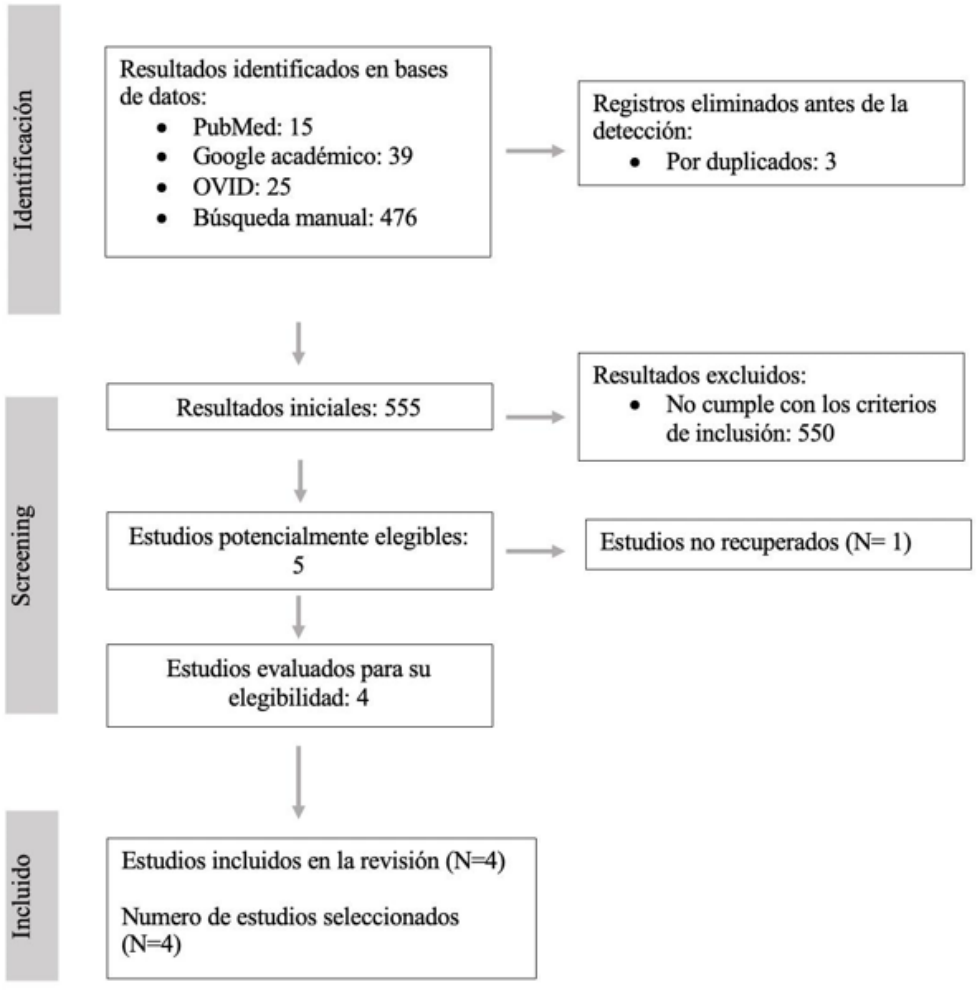

Figure 1: PRISMA 2020 flowchart.

Table 2: Characteristics of the included studies.

Study name, year, author, country	Characteristics of the sample	Surgical procedure	Dosage of Etoricoxib	Placebo	Type of effectiveness evaluation (EVA/ NRS/VRS)	Loss of tracking	Conclusión
Preemptive Oral Etoricoxib on Health-Related Quality of Life after Mandibular Third Molar Surgery: A Randomized, Double-Blind, Placebo-Controlled Clinical Trial. 2021a, Long Xie. Wuhan, China.	n: 60 participants. Group A: 30 participants assigned to receive Etoricoxib 60 mg (n=30). Group B: 30 participants assigned to receive placebo (n=30).	Extraction of an impacted third molar was performed under local anesthesia with 2% lidocaine to block the inferior alveolar, lingual, and buccal nerves. A triangular mucoperiosteal flap was created, followed by osteotomy and tooth sectioning using a high-speed handpiece. The tooth was extracted with an elevator, the alveolar tissue was curetted, and the area was irrigated with sterile saline solution. Sutures were placed with 4-0 silk.	Etoricoxib 60 mg tablets taken orally 30 minutes before surgery.	Placebo administered orally 30 minutes before surgery.	EVA	There were no tracking losses.	Preoperative administration of Etoricoxib can relieve pain and reduce the need for postoperative analgesics.
Does low dose of etoricoxib play pre-emptive analgesic effect in third molar surgery? A randomized clinical trial.	n: 56 participants. Group A: 28 participants assigned to receive 60 mg of Etoricoxib (n=28).	Extraction of impacted third molar, local anesthesia with 2% lidocaine to block the inferior alveolar and lingual nerves.	Etoricoxib 60 mg tablets orally 30 minutes before surgery.	Placebo administered orally 30 minutes before surgery.	EVA	There were no tracking losses.	The preventive oral administration of Etoricoxib is an effective strategy for pain management, compared to placebo, in third molar surgery.
2021b, Long Xie. Wuhan, China.	Group B: 28 participants assigned to receive placebo (n=28).	Local and buccal anesthesia was administered using 4% articaine with 1:100,000 epinephrine to reduce intraoperative bleeding. A mucoperiosteal flap was created, followed by osteotomy and tooth sectioning with a high-speed turbine. The tooth was extracted with an elevator, the alveolar tissue was curetted, irrigated with sterile saline solution, and sutured with 4-0 silk.					
A split-mouth, randomized, triple-blind, placebo-controlled study to analyze the pre-emptive effect of etoricoxib 120mg on inflammatory events following removal of unerupted mandibular third molars	n: 22 participants (44 surgical sites). Group A: 22 surgical sites assigned to receive Etoricoxib 12 mg (n=11). Group B: 22 surgical sites assigned to receive placebo (n=11).	Extraction of an unerupted mandibular third molar, using local anesthesia with 2% mepivacaine and epinephrine 1:200,000. A full-thickness flap was created, bone was removed with a bur cooled with distilled water, and the incision was sutured with 4-0 silk.	Etoricoxib 120 mg orally 1 hour before surgery.	Placebo via oral, 1 surgery.	EVA	Group A: 2 participants (4 surgical sites) did not return for evaluation. Group B: 2 participants (4 surgical sites); experienced postoperative infection and did not return for evaluation.	The administration of etoricoxib showed a superior postoperative analgesic effect compared to placebo after third molar extraction.

2015b, FWG Costa. Fortaleza, Ceará, Brazil.							
Comparison of preemptive etoricoxib and dexamethasone in third molar surgery – a randomized controlled clinical trial of patient-reported and clinical outcomes	n: 90 participants. Group A: 30 participants received 90 mg of Etoricoxib (n=30). Group C: 30 participants received a placebo (n=30).	Extraction of impacted mandibular third molar. Regional nerve block of the inferior alveolar, lingual, and buccal nerves with 4% articaine and 1:100,000 epinephrine local anesthetic.	Etoricoxib 90 mg tablets taken orally 1 hour before surgery.	No pre-medication should be given 1 hour before surgery.	EVA	Group A: 2 participants with alveolitis. Group C: 2 participants with alveolitis and who were also taking another medication.	Etoricoxib administered as a preventive treatment is well tolerated and capable of reducing pain perception in patients.
2023, V. Mijailovic. Belgrado, Serbia.							
N: number of participants, EVA: visual analog scale, NRS: numerical rating scale, VRS: verbal rating scale.							

Table 3: Demographic analysis of participants by study.

Author, year	Administration	Men	Women	Age (years)
Long Xie, 2021a	Etoricoxib	18	12	29.5 ± 5.8
	Placebo	19	11	27.5±3.9
Long Xie, 2021b	Etoricoxib	13	15	29.4±5.0
	Placebo	10	18	28.1 ±5.0
FWG Costa, 2015b*	Etoricoxib y placebo	8	10	> 18 años
Iva Mijailovic, 2023	Etoricoxib	8	22	22.4±3.78
	Placebo	15	15	23.57 ± 4.05

Note: *Split-mouth study. The values are expressed as mean ± standard deviation.

For each included study, the risk of bias was assessed in each specific domain, and risks were classified as: low risk (green circle), high risk (red circle), and uncertain risk (yellow circle). Only studies with a moderate/uncertain and/or low risk were considered. Critical appraisal was performed by the authors and approved by the review team. In case of disagreement, a third reviewer was consulted. The risk of bias was assessed using the Cochrane RoB2 tool by two independent reviewers (CSBS and FEVM), who resolved any disagreements through discussions with a third author (DEBA). The risk of bias assessment for the study by author (FWG Costa, et al. [14]) was determined to be high risk in two domains. In domain 2, "bias due to deviations from assigned intervention," regarding the analysis to estimate the effect of intervention assignment, not all initially assigned participants were included; four participants were excluded due to loss to follow-up; and an intention-to-treat (ITT) analysis was not reported. This has a substantial impact on the outcome because clinically important events may have been missed, which could alter the result. In domain 5, "bias in the selection of reported outcomes," there is no evidence of a pre-specified analysis or a published protocol, and it is not mentioned that the analysis was defined before data access. In all other domains, the risk of bias was assessed as low. On the other hand, the studies by (Long Xie, et al. [16,17]), and the study by (Iva Mijailovic, et al. [18]) were determined to have a low risk of bias, as they satisfactorily met all the assessed domains.

These studies were considered to have been methodologically sound and their results demonstrate a real effect of the intervention, meaning they have high internal validity, which strengthens their applicability in clinical decision-making. Table 4 illustrates the summary of the risk of bias assessment for all included studies.

Table 4: Assessment of the risk of bias according to the Cochrane RoB 2 tool.

	D1	D2	D3	D4	D5	Overall
Long Xie, 2021a	+	+	+	+	+	+
Long Xie, 2021b	+	+	+	+	+	+
FWG Costa, 2015b	+	-	+	+	-	-
Iva Mijailovic, 2023	+	+	+	+	+	+
	Randomisation process	Deviations from the intended intervention	Missing outcome data	Measurement of the outcome	Selection of the reported result	

Note: +: Low Risk, !: Some concerns, -: High risk.

Results

Main Result

Pain intensity was measured as the primary outcome in all included studies using the visual analog scale (VAS). The collected data are shown in Table 5. In the (Long Xie, et al. [16]), although no baseline measurements were reported, a progressive decrease in pain intensity was observed in the etoricoxib group compared to the placebo group starting at 24 hours. In the (Long Xie, et al. [17]), at 12 hours, the etoricoxib-treated group showed a value of (1.1 ± 1.5), compared to (2.3 ± 2.2) in the placebo group. At 24 hours, this difference remained, with (0.9 ± 1.3) in the treated group and (1.5 ± 1.5) in the placebo group. In the study by FWG Costa [14], pain intensity was assessed, with a greater decrease in pain observed at 6 hours. The group treated with Etoricoxib presented a value of (0.8 ± 1.5) compared to the placebo group (3.8 ± 2.1). Finally, the study by Iva Mijailovic (2023) reported more detailed results between 2 and 24 hours. At 2 hours, the values for the Etoricoxib group were (1.1 ± 2.8) versus (3.9 ± 3.2) in the placebo group, and at 12 hours, the values were (0.9 ± 1.5) and (2.7 ± 3.2), respectively.

Table 5: Pain intensity measured on a visual analog scale.

Time (hours)		0	2	4	6	8	10	12	24	48	72	96	120	144	168
Long Xie 2021a	Etoricoxib (60 mg)								2.9 f 2.2	1.9 ± 1.9	1.5 ± 1.7	0.8 ± 1.1	05 ± 0.8	0.4 ± 0.6	0.4 ± 07
	Placebo								5.6 ± 2.7	4.7 ± 3.0	3.7 ± 2.9	3.0 ± 2.7	2.3 ± 2.3	1.5 ± 1.8	1.0 ± 1.4
Long Xie 2021b	Etoricoxib (60 mg)		1.1 ± 1.4	2.1 ± 1.6	1.8 ± 1.4	1.5 ± 1.5		1.1 ± 1.5	0.9 ± 1.3						
	Placebo		2.9 ± 2.8	4.5 ± 2.5	3.8 ± 2.3	3.1 ± 2.5		2.3 ± 2.2							
FWG Costa 2015b	Etoricoxib (120 mg)	0.0 ± 0.0	0.2 ± 0.4	0.5 ± 0.7	0.8 ± 1.5	0.2 ± 0.1	0.4 ± 1.3	0.4 ± 1.3	0.4 ± 0.6	0.3 ± 1.0	0.7 ± 1.8		0.0 ± 0.0		0.0 ± 0.0
	Placebo	0.8 ± 0.6	2.9 ± 2.5	4.5 ± 1.7	3.8 ± 2.1	2.7 ± 1.6	1.8 ± 1.7	1.0 ± 1.3	2.0 ± 2.4	1.6 ± 2.4	1.2 ± 2.3		0.6 ± 1.6		0.0 ± 0.0
Iva Mijaiovic 2023	Etoricoxib (90 mg)		1.12 ± 2.8	1.56 ± 2.62	1.25 ± 2.34	0.23 ± 0.97	0.44 ± 1.41	0.93 ± 1.8	0.97 ± 1.53	1.1 ± 1.68	0.53 ± 1.48				0.22 ± 0.7
	Placebo		3.85 ± 3.22	3.28 ± 3.28	1.89 ± 2.96	1.63 ± 3.27	1.47 ± 2.41	2.7 ± 3.22	1.67 ± 1.54	1.32 ± 1.67	2.26 ± 2.6				0.5 ± 0.85

Note: The values are expressed as mean ± standard deviation.

Secondary Outcome

Additionally, the included studies analyzed the use of rescue analgesics after etoricoxib administration. These studies showed that the etoricoxib-treated group experienced a significant reduction in the need for and total consumption of rescue analgesics compared to the placebo group, both in the first 24 hours and in the following 7 days. In (Long Xie, et al. [16]), only 46.7% of patients receiving etoricoxib required the first analgesic compared to 90% in the placebo group, and total consumption was lower (1.3 ± 2.0 vs. 4.2 ± 4.2). Similarly, (Long Xie, et al. [17]) reported that 71.4% of the etoricoxib group did not require analgesia compared to 25% in the placebo group, with lower consumption (0.4 ± 0.9 vs. 1.1±0.9). In the study by (FWG Costa, et al. [14]), although most patients required analgesia, the amount was significantly lower with etoricoxib (1.6 ± 1.3) vs. (4.0 ± 2.5). Finally, (Iva Mijailovic, et al. [18]) demonstrated a substantial reduction in the total dose (2300 ± 2548.16 mg) vs. (5233.33 ± 4018.78 mg). These findings are shown in Table 6.

Table 6: Comparison of rescue analgesia consumption in the included studies.

Author Year	Evaluation Period	Variable	Etoricoxib Group	Placebo Group	p-value
Long Xie 2021a	7 days	Patients who took the first rescue analgesic.	14 (467%)	27 (90%)	<0001
		Patients who did not require rescue analgesia.	16 (533%)	3 (10%)	<0001
		Total consumption of rescue analgesics	13 ± 20	42 ± 42	2
Long Xie 2021b	24 hours	Patients who took the first rescue analgesic.	8 (286%)	21 (75%)	1
		Patients who did not require rescue analgesia.	20 (714%)	7 (25%)	1
		Total consumption of rescue analgesics	04 ± 09	11 ± 09	4
FWG Costa 2015b	7 days	Patients who took rescue pain medication.	14 (777%)	18 (100%)	104
		Patients who did not require rescue analgesia.	4 (222%)	0 (0%)	104
		Total consumption of rescue analgesics.	16 ± 13	40 ± 25	<0001
Iva Mijailovic 2023	7 days	Total consumption of rescue analgesics (mg).	2300 ± 254816	523333 ± 401878	0000*

Note: Values are expressed as n (%) and mean ± standard deviation.

*Statistically significant difference ($p<0.05$).

Summary of Results

Table 7 shows the qualitative synthesis of the results from the low risk of bias studies.

Certainty of the Evidence: The GRADE PRO system was used to assess the quality of the evidence generated. The assessment was based on the primary outcome. Only one study raised concerns about risk of bias and impression. No concerns were raised in the remaining studies. Therefore, the synthesis of results was narrowed down to studies with a low risk of bias and a high level of certainty, as shown in Table 7. The GRADE assessment is summarized in Table 8. This systematic review is based on a qualitative synthesis of the included studies; therefore, no further analyses, such as meta-analysis, are contemplated due to the heterogeneity of the data and the qualitative nature of the evidence.

Table 7: Summary of results.

Author year	Study design	Intervention/Comparison	Outcome evaluated	Outcome measurement	Results	Results and Conclusion of the authors	Level of certainty	Risk of bias
Long Xie 2021a	Randomized clinical trial	Etoricoxib 60 mg/ Placebo	Effect of preventive oral administration of Etoricoxib on postoperative pain and quality of life.	Health-related quality of life questionnaire (UK-OHRQOL) and visual analogue scale.	The mean EVA pain score in the Etoricoxib group was lower than in the control group at all time intervals.	Postoperative pain scores in the etoricoxib group were significantly lower than in the control group on each day of postoperative observation.	High	Low
Long Xie 2021b	Randomized clinical trial	Etoricoxib 60 mg/ Placebo	Reduction of post-operative pain.	Visual analog scale, Kaplan-Meier curves, and log-rank analysis.	Postoperative pain scores in the etoricoxib group were significantly lower than those in the placebo group during the first 12 hours. The number of patients requiring no rescue analgesia and the average amount of rescue medication used were significantly lower in the etoricoxib group than in the placebo group.	The low dose of Etoricoxib has a preventive analgesic effect, resulting in a reduction in the use of painkillers after third molar extraction.	High	Low
Iva Mijailovic 2023	Randomized clinical trial	Etoricoxib 90 mg/ Placebo	Impact of etoricoxib premedication during IMTM surgery on PSP, ROM, and inflammation. Secondary outcomes included the incidence of adverse events, assessment of postoperative pain perception, and trismus.	using the Likert scale and visual analogue scale.	Significantly lower VAS scores were observed in the pre-mediation groups.	The preventive administration of Etoricoxib is well tolerated and capable of reducing the perception of postoperative pain.	High	Low

Note: VAS: visual analog scale, IMTM: impacted mandibular third molar, PSP: postoperative patient satisfaction, RM: rescue medication, AE: adverse events.

Table 8: GRADE evaluation of the included studies.

Author year	Study design	Risk of bias	Inconsistency	Indirect Evidence	Vagueness	Other considerations	Etoricoxib	Placebo	Certainty	Importance
Long Xie 2021a	randomized trials	it's not serious	it's not serious	it's not serious	it's not serious	none	30	30	⊕⊕⊕⊕ High	IMPORTANT
Long Xie 2021b	randomized trials	it's not serious	it's not serious	it's not serious	it's not serious	none	28	28	⊕⊕⊕⊕ High	IMPORTANT
FWG Costa 2015b	randomized trials	very serious to	serious	it's not serious	scribble	none	20	20	⊕00O Very low a,b,c	IMPORTANT
Iva Mijailovic 2023	randomized trials	it's not serious	it's not serious	it's not serious	it's not serious	none	28	28	⊕⊕⊕⊕ High	IMPORTANT

Note: CI: Confidence Interval

a. The risk of bias assessment in the study by author FWG, Costa was determined to be high in 2 domains. In domain 2, "bias due to deviations from the intended intervention," regarding the analysis to estimate the effect of the intervention assignment, not all participants who were initially assigned were included; 4 participants were excluded due to loss to follow-up, and an intention-to-treat (ITT) analysis was not reported. This has a substantial impact on the outcome because clinically important events may have been missed, which could alter the result. In domain 5, "bias in the selection of the reported results," there is no evidence of a prespecified analysis or a published protocol, and it is not mentioned that the analysis was defined before accessing the data. In all other domains, the risk of bias was assessed as low.

b. Domain 2 (Deviations from the intended intervention): High risk because not all initially assigned participants were included (4 losses to follow-up) and an intention-to-treat (ITT) analysis was not performed. Consequence: Possible loss of clinically important events → bias that may alter the estimated effect. Domain 5 (Selection of reported results): High risk because there is no evidence of a prespecified protocol or analysis defined before accessing the data. Consequence: Risk of selective reporting, inconsistency, and lack of transparency.

c. The results are not precise because: The study has limited statistical power. It does not report 95% confidence intervals. There is high variability in some outcomes.

Discussion

The objective of this Systematic Review was to evaluate the effectiveness of etoricoxib as a preventive analgesic in third molar extractions. The studies included in the review have demonstrated that preoperative administration of etoricoxib is associated with a decrease in the intensity of postoperative pain compared to placebo, especially in the first 24 hours after extraction, which corresponds to the period of greatest pain intensity. Previous studies have shown that etoricoxib is a safe and effective alternative in the management of postoperative pain, edema, and trismus in patients undergoing oral surgery (Pimenta, et al. [12]). Currently, this study represents the first systematic review to evaluate preventive analgesia with etoricoxib. Previous studies, such as a meta-analysis evaluating postoperative analgesia with this drug, have demonstrated its greater analgesic efficacy compared to ibuprofen and diclofenac, as well as significantly reducing the number of patients requiring rescue analgesia after third molar surgery, compared to other NSAIDs. Furthermore, this study observed that preventive analgesia with etoricoxib resulted in lower VAS scores compared to placebo throughout the entire follow-up period (Vicente Herrero, et al. [15]). These findings support the results obtained, indicating that etoricoxib not only reduces pain intensity early and sustainably, but also decreases the need for rescue analgesia. In this context, preoperative analgesia with etoricoxib is a more effective and predictable alternative to other traditional NSAIDs such as ibuprofen, whose preoperative administration has been questioned by a systematic review that concluded there is no evidence to support its use due to inconsistencies in its results, requiring further research on the effects of preoperative analgesia in surgical pain management (Gately, et al. [8]).

This positions etoricoxib as a more reliable alternative for surgical pain management, reducing variability in analgesic response and achieving better clinical outcomes. Etoricoxib is a selective COX-2 inhibitor NSAID characterized by its rapid absorption and prolonged half-life of up to 24 hours. It exhibits marked tissue distribution and is 92% bound to plasma proteins. Reaching its maximum concentration in 1-2 hours. Its elimination half-life is approximately 22 hours (Xie L,

et al. [16]), allowing for stable analgesic control. In addition, there is a lower gastrointestinal and renal risk compared to traditional NSAIDs; however, potential cardiovascular effects have been reported (Biase, et al. [1-4]). In third molar extractions, due to the position of these teeth and the surgical complexity of their extraction, the postoperative pain experienced is usually significant and can affect the quality of life of patients, so preventive analgesia seeks to avoid peripheral and central sensitization, offering better pain control (Barbalho, et al. [5-8]). The subjective nature and the various factors that can influence the experience of pain make it very difficult to measure quantitatively (Gately, et al. [8]). The use of the VAS to measure pain intensity appears to be the simplest and most widely used method. The demand for a comfortable postoperative recovery and a rapid return to daily activities has increased the importance of controlling postoperative inflammation, especially pain and swelling.

This is why the importance of preventive analgesia lies in controlling pain before it occurs to minimize postoperative pain by interrupting afferent signals. The most effective agents for reducing central sensitization are analgesics, which act on the pain caused by incisions and the inflammation that occurs during third molar extraction (Kissin [19]). The use of preventive analgesia such as Etoricoxib has a positive effect on the physical aspects of patients' quality of life, including enjoyment of food, appearance, speech, general health, comfort, and breath odor (Xie L, et al. [16]). The interpretation of the results of this review suggests that preemptive analgesia with etoricoxib is effective because it prevents peripheral and central sensitization that occurs after surgical trauma and other inflammatory reactions. This drug is able to reach the surgical site at an effective concentration and reduce PGE2, which is highly expressed in peripheral tissue and the central nervous system during and after surgery. This process produces a complete blockade of PGE2 production in the surgical wound, thereby relieving pain and reducing the need for postoperative analgesics (Xie L, et al. [16]). Preventative etoricoxib produces a significant reduction in the concentration of tumor necrosis factor. α, which results in significantly reduced clinical parameters of pain, trismus and edema compared to the placebo group (Albuquerque, et al. [20]). According to a recent meta-analysis, the use of preventive analgesia decreases postoperative pain scores and the amount of rescue medication needed after third molar extraction by suppressing afferent nerve impulses at the time of surgery and in the initial postoperative period, with the aim of preventing central hyperalgesia and, consequently, reducing postoperative pain (Kissin, et al. [19-22]).

This systematic review has several limitations that should be considered when interpreting the results. First, there is a limited number of clinical trials available on the use of etoricoxib in the evaluated context, which limits the robustness of the conclusions. Furthermore, considerable methodological heterogeneity was observed among the included studies, such as in treatment protocols, administered doses, and the timing of pain measurements using the VAS (Visual Analogue Scale). This variability made it difficult to compare studies, and therefore a meta-analysis was not possible; instead, a qualitative synthesis of the findings was performed. Furthermore, during the assessment of the risk of bias, methodological deficiencies were identified in the study by author (FWG Costa [14]), which presented a high risk of bias in two domains, which compromises the internal validity of its results and, therefore, influences the overall interpretation of the evidence. Another relevant limitation was the exclusion of databases in other languages, which may have restricted the identification of relevant studies and thus introduced publication bias. Despite these limitations, it is worth noting that the included studies had adequate follow-up, which lends a degree of confidence to the observed results. However, it is recommended that the findings be interpreted with caution and that future research with more homogeneous methodological designs and broader coverage of bibliographic sources be considered.

Despite the limitations of our review, current evidence supports the use of etoricoxib as a prophylactic analgesic for reducing postoperative pain following third molar extractions. According to the summarized evidence, prophylactic analgesia in third molar extractions. Molars reduced postoperative pain scores and also reduced the use of rescue analgesics. Furthermore, its safety profile makes it a recommended alternative for patients with a history of gastric ulcers or allergies to traditional NSAIDs, excluding patients with cardiovascular risk.

Conclusion

Based on a review of clinical trials that met the eligibility criteria and considering the limitations of this study, etoricoxib has been shown to be effective as a preoperative analgesic in third molar extractions. Available results indicate that its preoperative administration can significantly reduce the intensity of postoperative pain and decrease the need for rescue analgesia. However, it is important to interpret these findings with caution.

The qualitative analysis of the included studies supports the effectiveness of etoricoxib in this clinical context; however, methodological heterogeneity—in terms of dosage, timing of administration, and follow-up time—limits the possibility of conducting a robust quantitative analysis and drawing definitive conclusions. Therefore, although these results are promising, further randomized clinical trials with standardized methodologies are recommended. This will confirm the use of etoricoxib as a preventive analgesic in third molar surgery and allow for comparison of studies in future research. We suggest that future studies in this area adopt homogeneous criteria regarding dosage, timing of administration, and pain measurement scales to generate stronger evidence that will contribute to establishing clear clinical recommendations.

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Catalina Soledad Barrientos Soto. Biomed J Sci & Tech Res