Analgesic Efficacy of Etoricoxib on Acute Dental Pain due to Dental Extraction and Periodontal Surgery: Rapid Review

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Abstract:
Acute postoperative pain due to dental extraction and periodontal surgery is commonly associated with inflammation as a result of surgical tissue damage. Etoricoxib, a selective COX-2 inhibitor, has a long-duration analgesic activity and is expected to provide pain relief with reduced dosage requirements and enhanced convenience. The objective of this study is to comprehensively review the available evidence on the efficacy of etoricoxib in managing acute dental pain following dental extraction and periodontal surgery. A systematic search was conducted across electronic databases to identify double-blind, randomized, and controlled clinical trials comparing the analgesic effect of etoricoxib versus placebo or at least one active control group after dental extraction and periodontal surgery. Nine studies met the inclusion criteria. The data revealed that etoricoxib 120 mg was determined to be the minimum effective dose that had maximal efficacy in patients with moderate to severe acute pain following dental surgery. Etoricoxib at doses of 90 mg and 120 mg demonstrated comparable efficacy to 600 mg ibuprofen, 4 mg dexamethasone, and 600/670 mg naproxen sodium. Moreover, 120 mg etoricoxib exhibited superior efficacy compared to 50 mg diclofenac, 600 mg acetaminophen/60 mg codeine, and 10/650 mg oxycodone/acetaminophen. Etoricoxib is both effective and safe for managing early-stage acute pain after dental extraction and periodontal surgeries. No evidence of significant adverse effects associated with etoricoxib use was observed, thus making it a viable alternative treatment option.

Keywords: Analgesic, COX-2 inhibitors, etoricoxib, dental extraction, periodontal surgery.

Introduction
Acute post-operative pain is a manifestation of inflammation that occurs as a result of tissue damage from surgery (Clarke, Derry, & Moore, 2012). Dental extraction, especially surgical removal of the third mandibular, and periodontal surgery were widely oral surgery procedures associated with pain and swelling (Isola et al., 2019). The production of
inflammatory mediators such as prostaglandin following the surgery leads to an increase in vasodilatation and hypervascularization of the surgical site, causing peripheral edema (Isola et al., 2019).

Nonsteroidal anti-inflammatory drugs (NSAIDs) are the most commonly used drugs to inhibit the release of inflammatory mediators and relieve pain by inhibiting cyclooxygenases and thus the production of prostaglandins (Clarke, Derry, & Moore, 2012; Isola et al., 2019). Traditional NSAIDs inhibit both cyclooxygenase (COX) enzyme isoforms (COX-1 and COX-2). COX-1 is a constitutive enzyme. Its inhibition is associated with a lack of gastric protection. Despite, Selective COX-2 inhibitors were developed to address the problem, they primarily inhibit the action of COX-2, thereby avoiding the gastrointestinal adverse events associated with COX-1 inhibition (Isola et al., 2019; González-Barnadas et al., 2020).

Etoricoxib is a novel selective COX-2 NSAID, that rapidly absorbs, maximum plasmic levels reached after 1 hour, and elimination half-life is 25 hours (Steffens et al., 2010). Etoricoxib is a long-duration drug expected to cover postoperative pain and swelling after dental surgery or periodontal flap. The pain generally last for 2 to 3 days with greater intensity at first 3 to 5 hours. The swelling resolves between 5 to 7 days with the peak intensity at 12 to 48 hours after surgery (Sotto-Maior et al., 2011).

The purpose of this study is to evaluate the efficacy of etoricoxib on acute dental pain due to dental extraction and periodontal surgery. It is important to evaluate etoricoxib efficacy through its dose, onset, duration, and safety of analgesia.

Materials and Methods

The data synthesis protocol for a rapid review was conducted according to Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocol (PRISMA-P) guidance (Moher et al., 2015).

Study selection Criteria

The focused question was formulated following the PICO (Leonardo, 2018):

- Population: Subject following dental extraction or periodontal surgery procedure
- Interventions: Administration of etoricoxib as oral analgesic for relief of postoperative pain
- Control: Placebo or other analgetic drugs for relief of postoperative pain
- Outcomes: Analgesic intake, pain intensity evaluation using any pain assessment

- The inclusion criteria for considering studies were RCTs, case-control, cohort studies, case series, case reports.

Literature search strategy

To identify studies a systematic search of the literature was conducted using PubMed and Science Direct database using Boolean operators and keywords ((etoricoxib) AND (acute dental pain or dental pain or pain or acute pain)) AND (extraction or dental extraction or odontectomy or third mandibular extraction or periodontal surgery). Inclusion criteria were articles published in 2003-2023, available in full text, and published in English.

A total of 23 scientific articles were identified from the three databases used were screened using the PRISMA method according to the established criteria. The final number of articles that entered the qualitative data synthesis stage was 9 articles. The selected articles were then extracted, and qualitative analysis was carried out using a narrative approach. The research procedure is briefly shown in Figure 1.

Results

The article selection (23 articles) were selected from Pubmed and Google Scholar. After reviewing titles and abstracts, 10 articles were excluded as they were not related to the review topic. 9 Articles were selected as they were related with the topic (Table 1 – Appendix 1).
Discussion

Surgical removal of impacted third molars is one of the most frequently performed procedures in oral and maxillofacial surgery and can lead to immediate and postoperative discomfort. The extent of swelling, trismus, and the severity of pain are the chief indicators of a patient's morbidity during the postoperative period after third-molar removal (Sotto-Maior et al., 2011). Therefore, pain evaluation following third-molar extraction is often used as a well-validated surgical model for analgetic medication efficacy in moderate to severe pain (González-Barnadas et al., 2020; Brown et al., 2013).

Figure 1. Flowchart of article search based on the PRISMA method
Source: Moher et al., 2015.

Acetaminophen, opioids, and nonsteroidal anti-inflammatory drugs (NSAIDs) are the standard treatment for postsurgical acute pain including analgesics (Daniels et al., 2011). Considering either benefits and harms, high doses of acetaminophen that are required for the adequate treatment of acute pain can lead to liver toxicities, taking over 4000 mg acetaminophen per day may cause liver failure. So it used must be limited or combined with opioids as multimodal analgesia (Daniels et al., 2011). However, opioid medication and medication combination are not better than NSAIDs. Furthermore, opioids present limiting tolerability factors, such as respiratory depression, impaired gastrointestinal motility, patient tolerability, and the risk of addiction (Daniels et al., 2011; Moore et al., 2018). NSAIDs appear to have more effective at relieving pain (Moore et al., 2018). ADA recommends it as first-line therapy for acute pain management.

Postoperative pain after dental surgery or periodontal flap, which generally lasts for 24 to 72 hours with greater intensity at 6 to 8 hours (Steffens et al., 2010; Isiordia-Espinoza et al., 2023). Some research shows that patients continue to require analgesia up to 3 days after multiple third molar extractions (Brown et al., 2013). Etoricoxib as COX-2—the selective drug has a long-duration analgetic activity. It is expected to cover the pain for 24 hours so that reduced the need for doses and is more
convenient (González-Barnadas et al., 2020; Brown et al., 2013). Onset of analgesia at 60 mg Etoricoxib is 30 minutes while 120,180 and 240 mg Etoricoxib provide faster onset of analgesia at 24 minutes (Malmstrom et al., 2004).

The analgesic efficacy of NSAIDs is linked with their activity in the inhibition of prostaglandin synthesis, specifically their action on the cyclooxygenase-2 enzyme. This inhibition of prostaglandin synthesis diminishes inflammation and pain. In general, higher inflammatory conditions require higher doses of NSAID for the adequate treatment of pain (Daniels et al., 2011). Malmstrom et al. stated that 120 mg etoricoxib is superior to 60 mg etoricoxib and has similar efficacy with 180 and 240 mg etoricoxib. 120 mg Etoricoxib was the minimum dose providing maximal analgesic effect for pain after dental impaction surgery (Malmstrom et al., 2004).

Based on the results, approximately 83% of patients underwent surgical extraction of ≥2 third molars and impacted mandibular molar reporting a good response after receiving 120 mg etoricoxib during the 8 hours and >60% during the 24 hours. This is consistent with etoricoxib’s long-duration analgesic effect which has an elimination half-life of 25-27 hour (Malmstrom et al., 2004). Isola et al. (2019) reported that post-operative administration of 120 mg etoricoxib has a significant decrease at 2, 24, and 28 hours after surgery in the postoperative pain compared with 50 mg diclofenac and a placebo. The result show that 120 mg etoricoxib superior to a 50 mg diclofenac.

On Days 2 and 3, after the third molar extraction. The majority of patients given 90 mg etoricoxib and 120 mg etoricoxib gave positive outcomes, equal to the patient who receive 600 mg ibuprofen (Brown et al., 2013).

Daniels et al. (2011), report that both 90 mg and 120 mg etoricoxib showed efficacy in postoperative dental pain similar to 2400 mg ibuprofen, a rapid onset time, and a 24-hour duration of effect with single dosing. It’s also reported that etoricoxib was significantly better than 2400/240mg acetaminophen/codeine. Pain intensity evaluation which is used by the 4-point categorical scale may not perform as well as other scales, such as the 0 to 10 VAS or Likert scales, which may have been more sensitive.

The follow-up studies confirmed that 120 mg etoricoxib provided equivalent efficacy to 600 mg ibuprofen, 500/550 mg naproxen, and 100 mg diclofenac potassium. Slightly better efficacy than 400 mg celecoxib. Much better efficacy than ibuprofen 400 mg, aspirin 1000 mg and paracetamol 1000 mg, 600mg/60 mg paracetamol/codeine (Clarke, Derry, & Moore, 2012; González-Barnadas et al., 2020).

Steffen et al. (2010) stated that 120 mg of etoricoxib is effective for pain control after periodontal surgery. It has a similar efficacy with 8 mg dexamethasone to prevent pain and discomfort after periodontal surgery. Meanwhile, Sotto-maior et al. (2011) reported 120 mg etoricoxib has similar efficacy to 0 mg dexamethasone in the prevention of postoperative pain, swelling, and trismus after third molar surgery. Corticosteroids such as dexamethasone and methylprednisolone have been used extensively in dentoalveolar surgery for oral surgery, despite having no standard dosing regimen. The dose of corticosteroid must be equal or exceed the physiologic amount released by the body, suggesting a dose equivalent to 300 mg cortisol for maximum anti-inflammatory effect, which is equivalent to 9 mg dexamethasone (Sotto-Maior et al., 2011).

Long-term use of NSAIDs can be accompanied by adverse effects. Because of COX-1 inhibition cause nausea, vomiting, heartburn, abdominal pain, and bleeding. Patients who receive traditional NSAIDs following third molar surgery presented adverse events such as gastric lesions (8%) (Isola et al., 2019). Etoricoxib as COX-2–selective drug has advantages over traditional NSAIDs in preventing gastrointestinal complications. It also has the absence of platelet-aggregation inhibition, which may cause perioperative bleeding complications (Steffens et al., 2010). Furthermore, selective COX-2 inhibitors could be a suitable alternative in asthma patients with aspirin-exacerbated respiratory disease (AERD) (González-Barnadas et al., 2020).
The cardiovascular safety of commonly used NSAIDs is still a concern, especially for patients with cardiovascular disease (González-Barnadas et al., 2020; Schjerning, McGgettigan, & Gislason, 2020). Commonly for ibuprofen, diclofenac, and selective COX-2 inhibitors (González-Barnadas et al., 2020). Recent studies have revealed that daily doses exceeding 100 mg for diclofenac, 1200 mg for ibuprofen, and 200 mg for celecoxib are associated with an elevated risk of heart failure and mortality (Schjerning, McGgettigan, & Gislason, 2020).

Etoricoxib was generally well tolerated, adverse effects related to the use of COX-2-selective drugs, such as kidney or cardiovascular problems in patients undergoing surgical procedures such as impacted third molar removal are rare. It was only observed with chronic use (at least 4 weeks) (González-Barnadas et al., 2020; Steffens et al., 2010). Recent research by Vecchis et al. (2014) found that etoricoxib didn’t increase the risk of serious vascular event such as myocardial infarction and stroke when compared with placebo and naproxen for 4-week duration treatment. Etoricoxib has a lower incidence of nausea, vomiting and dizziness than acetaminophen-codeine and acetaminophen/oxycodone (Daniels et al., 2011; Chang et al., 2004). Proportional to ibuprofen and naproxen (Daniels et al., 2011; Malmstrom et al., 2004). Etoricoxib is effective and safe for the management of early-stage acute pain after dental extraction and periodontal surgeries (Isola et al., 2019). There is no evidence of serious adverse effects with the use of etoricoxib, but caution is required for high-risk patients (Isiordia-Espinoza et al., 2023).

**Conclusion**

Etoricoxib is effective and safe for the management of early-stage acute pain after dental extraction and periodontal surgeries. There is no evidence of serious adverse effects with the use of etoricoxib but caution is required for high-risk patients.

**Conflict of interests**

No conflict of interest.

**References**


## Appendix 1

### Table 1. Summary of the Results from Selected Article

<table>
<thead>
<tr>
<th>No</th>
<th>Author</th>
<th>Study design</th>
<th>Treatment</th>
<th>Detail of patient, procedure, and evaluation</th>
<th>Important Result (conclusions)</th>
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<tbody>
<tr>
<td>1</td>
<td>Malstorm et al., 2004</td>
<td>Post operative analgesia</td>
<td>randomized, double-blind, parallel-group, single-dose</td>
<td>Group 1 = 60 mg etoricoxib Group 2 = 120 mg etoricoxib Group 3 = 180 mg etoricoxib Group 4 = 240 mg etoricoxib Group 5 = 400 mg Ibuprofen Group 6 = placebo Drugs were administered orally rescue medication acetaminophen/hydrocodone 500 mg/5 mg</td>
<td>Patients aged ≥ 16 years were included. The patient underwent surgical extraction of ≥2 third molars, of which ≥1 was an impacted mandibular molar. Local anesthesia was carried out with 2% lidocaine and 1:100,000 epinephrine. or mebohexital sodium Pain intensity was evaluated by TOTPAR, 4 point scale. etoricoxib 120 mg was determined to be the minimum dose that had maximal efficacy in patients with moderate to severe acute pain associated with dental surgery. Both etoricoxib and ibuprofen were generally well tolerated</td>
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<td>2</td>
<td>Steffens et al., 2010</td>
<td>Preemptive analgesia</td>
<td>randomized, double-blind, parallel-group, single-dose.</td>
<td>group 1 = placebo, group 2 = 8 mg dexamethasone group 3 = 120 mg etoricoxib. Drugs were given by oral route 1 h before surgery. Rescue medication (750 mg acetaminophen) was</td>
<td>Patients aged 20-56 years were included. The patient underwent third molar open-flap debridement surgeries. Local anesthesia was carried out with 2% mepivacaine and 1:100,000 epinephrine. Pain intensity and discomfort were evaluated by a 101-point numeric rate scale and a four-point verbal rate scale. etoricoxib and dexamethasone are effective for pain and discomfort prevention after periodontal surgeries</td>
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<td>3</td>
<td>Steffens et al., 2011</td>
<td>Preemptive analgesia</td>
<td>randomized, double-blind, parallel-group, multiple-dose.</td>
<td>group 1 = 200 mg celecoxib every 12 h group 2 = 120 mg etoricoxib every 24 h, group 3 = placebo Drugs were given by oral route 1 h before surgery. Rescue medication (750 mg acetaminophen)</td>
<td>Patients aged 18-56 years were included. The patient underwent third molar open-flap debridement surgeries Local anesthesia was carried out with 2% mepivacaine and 1:100,000 epinephrine. Pain intensity and discomfort were evaluated by a visual analog scale and a four-point verbal rate scale. etoricoxib and celecoxib have the similar efficacy</td>
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<td>4</td>
<td>Sotto-Maior et al., 2011</td>
<td>Preemptive analgesia</td>
<td>randomized, crossover, single-dose.</td>
<td>Group 1 = 120 mg etoricoxib Group 2 = 4 mg dexamethasone Drugs were given by oral route 1 h before surgery.</td>
<td>Patients aged 18-29 years were included. The patient underwent third molar surgery. The subjects were submitted to 1 surgical procedure for each side with an interval of 3 etoricoxib and dexamethasone have similar efficacy. for pain (vas 6 and 5), swelling, and trismus.</td>
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<tr>
<td>Study</td>
<td>Design</td>
<td>Group 1</td>
<td>Group 2</td>
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<td>Group 4</td>
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<tr>
<td>Isola et al., 2019</td>
<td>randomized, double-blind, parallel-group, single-dose</td>
<td>Group 1 = placebo</td>
<td>Group 2 = 50 mg diclofenac</td>
<td>Group 3 = 120 mg etoricoxib</td>
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<td>Brown et al., 2013</td>
<td>randomized, double-blind, parallel group</td>
<td>Group 1 = placebo</td>
<td>Group 2 = 120 mg etoricoxib every 24 h</td>
<td>Group 3 = 90 mg etoricoxib every 24 h</td>
<td>Group 4 = 600 mg ibuprofen every 6 h</td>
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<td>Daniels et al., 2011</td>
<td>randomized, double-blind, parallel group</td>
<td>Group 1 = 120 mg etoricoxib every 24 h</td>
<td>Group 2 = 90 mg etoricoxib every 24 h</td>
<td>Group 3 = 600 mg ibuprofen every 6 h</td>
<td>Group 4 = 600 mg acetaminophen/60 mg codeine</td>
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<td>Study</td>
<td>Design</td>
<td>Pain Medication</td>
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<td>8</td>
<td>Malmstrom et al., 2004</td>
<td>randomized, double-blind, parallel-group, single-dose</td>
<td>Rescue medication Hydrocodone bitartrate 5 mg/acetaminophen 500mg</td>
<td>Every 6 h Group 5 = placebo Rescue medication Hydrocodone bitartrate 5 mg/acetaminophen 500mg</td>
<td>Group 1 = placebo Group 2 = 120 mg etoricoxib Group 3 = 550 mg naproxen sodium Group 4 = 600 mg acetaminophen/60 mg codeine Drugs were administered orally. Patients aged ≥16 years were included. The patient underwent surgical extraction of ≥2 third molars, of which ≥1 was an impacted mandibular molar. Local anesthesia was carried out with 2% lidocaine and 1:100,000 epinephrine. or methohexital sodium rescue medication acetaminophen/hydrocodone 500 mg/5 mg Pain intensity was evaluated by TOTPAR etoricoxib 120 mg was similar to naproxen sodium 600/670 mg and superior to 600 mg acetaminophen/60 mg codeine.</td>
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<td>9</td>
<td>Chang et al., 2005</td>
<td>randomized, double-blind, parallel-group, single-dose</td>
<td>Rescue medication Hydrocodone bitartrate 5 mg/acetaminophen 500mg</td>
<td>Group 1 = 120 mg etoricoxib Group 2 = 650 mg acetaminophen/10 mg oxycodone Group 3 = placebo Drugs were administered orally. Patients aged ≥16 years were included. The patient underwent surgical extraction of ≥2 third molars, of which ≥1 was an embedded mandibular molar. rescue medication acetaminophen/hydrocodone 500 mg/5 mg Pain intensity was evaluated by TOTPAR etoricoxib 120 mg superior to oxycodone/acetaminophen 10/650 mg</td>
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