Comparative Assessment of the Effect of Ibuprofen and Etodolac on Edema, Trismus, and Pain in Lower Third Molar Surgery: A Randomized Clinical Trial

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Purpose: To compare the efficacy of ibuprofen (IBU) and etodolac (ETO) for controlling pain, edema, and trismus after extraction of lower third molars.

Materials and Methods: Twenty adolescents and adults with 2 impacted mandibular-third molars (in similar positions) were selected for the study. Patients were randomly assigned either to the IBU group (600 mg of IBU 3 times a day for 3 days) or to the ETO group (300 mg of ETO 3 times a day for 3 days). Drugs were administered immediately after dental extraction.

Results: During the first 2 days after extraction, swelling was more pronounced in the IBU group than in the ETO group ($P = .033$). Seven days after surgery, there was no difference in the degree of edema between the groups. At the 2- and 7-day evaluation points, mouth opening was significantly more reduced in the IBU group than in the ETO group ($P < .05$). After the first 6 hours, the ETO group had more effective pain relief ($P < .05$), but after this time point, both groups reported similar degrees of relief. Compared with the IBU group, the ETO group had a lower need for administration of additional rescue analgesics.

Conclusions: After extraction of impacted lower third molars, we found that swelling, trismus, and pain were more effectively controlled with ETO than with IBU.

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Extraction of impacted third molars is the most common surgical procedure in dentistry.[1-5] This procedure often involves soft tissue flaps and removal of bone tissue, and postoperative inflammation is sometimes accompanied by severe pain, edema, and limited mouth opening.[6,7] The symptoms resulting from surgical trauma after removal of third molars are therefore an excellent clinical model for studying acute pain,[4,5,7-11] for which the efficacy of various commercially available therapeutic drugs[5,12] can be assessed.

Acute pain is often associated with physical signs originating from the sympathetic branch of the autonomic nervous system, which manifest as tachycardia, hypertension, sweating, mydriasis, and pallor.[8,13] In addition to analgesics, steroidal anti-inflammatory drugs and nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly prescribed for the rapid relief of moderate pain in inflammatory conditions and soft tissue trauma.[8,14,15] The mechanism of action of NSAIDs is the inhibition of the release of cyclooxygenase (COX), an enzyme that is

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responsible for the production of prostaglandins (PGs) and has 3 isoforms: COX-1, COX-2, and COX-3.[4,7,10]

Ibuprofen is an NSAID with analgesic and antipyretic properties, widely used in clinical practice because of its well-documented efficacy and safety compared with similar drugs.[1,16] It belongs to the class of derivatives of propionic acid, which reduce the biosynthesis of PGs and inhibit the migration of leukocytes, in addition to other functions.[15] Within the classification of anti-inflammatory drugs, ibuprofen belongs to the group of nonselective inhibitors of COX-1, an enzyme that confers protection to the gastric mucosa and renal tissues, and COX-2, an enzyme that contributes to the inflammatory process.[6,7]

On the other hand, the properties of etodolac appear to differ from those of other NSAIDs because it is more selective to the inducible COX-2 isoenzyme than to the constitutive COX-1.[17-19] This characteristic may explain its low incidence of side effects and gastrointestinal ulcerations.[20] The use of etodolac has been indicated for the treatment of osteoarthritis, rheumatoid arthritis, tendinitis, bursitis, sports injuries with acute pain, gout pain, orthopedic disorders, dysmenorrhea, postoperative pain (from general and dental surgical procedures), and pain associated with non-rheumatic inflammatory conditions or headaches.[14,18,21]

Drug delivery before the onset of pain allows prior absorption of the drug into the bloodstream, which leads to an onset of action at the time of discomfort.[9,22] Orally administered corticosteroids such as dexamethasone reduce swelling and pain after surgical procedures.[17] These drugs act early in the inflammation cascade by inhibiting phospholipase A2 and thus blocking the release of arachidonic acid, a precursor of PGs and leukotrienes.[22] Therefore, corticosteroids used in pre-emptive analgesia are effective in delaying and preventing postoperative sequelae.[9,23]

Although many studies have evaluated the postoperative action of ibuprofen and etodolac alone or in comparison with other types of drugs,[1,5,6,12,14-18,21,22,24-27] there have not yet been any studies evaluating the clinical pain control and anti-inflammatory postoperative benefits of ibuprofen and etodolac when used with pre-emptive analgesia with dexamethasone.

The objective of this double-blind, randomized, paired crossover study was to compare the anti-inflammatory effects of ibuprofen, 600 mg, with those of etodolac, 300 mg, both used with dexamethasone, 4 mg, given preoperatively, on pain, edema, and mouth-opening limitation in adolescent and adult patients undergoing surgery for bilateral removal of lower third molars at the Aracatuba Dental School, Universidade Estadual Paulista–UNESP.

Materials and Methods

ETHICAL CONSIDERATIONS AND PATIENT SELECTION

This study was approved by the local institutional ethical committee of human experimentation (No. 818.680). It was designed in concordance with the CONSORT (Consolidated Standards of Reporting Trials) guidelines (www.consort-statement.org) and ethical principles for medical research involving human subjects from the Declaration of Helsinki. Twenty healthy male and female patients aged 16 to 35 years were selected from among clinical surgery patients treated at Aracatuba Dental School, Universidade Estadual Paulista–UNESP.

All participants met the following inclusion criteria as determined by medical, clinical, and radiographic history[3,12,13,15,28]: *1)* good systemic and local health; *2)* aged 16 to 35 years; and *3)* orthodontic indication for bilateral removal of impacted third molars, both in a similar position according to the Pell and Gregory classification (class II B) and Winter classification (mesio-angulated) and with at least two thirds of the root formed, according to radiographic evaluation.

The exclusion criteria also were evaluated by history, clinical, and radiographic assessment[6-9,17,27,29]: *1)* lack of bilaterally symmetric anatomic position of the mandibular-third molars; *2)* presence of any local events in the area of interest that would contraindicate the surgical procedure, such as periodontitis, odontogenic cysts or tumors (associated or not associated with the third molar), trauma to the region, or any symptoms of infection; *3)* presence of systemic disease of any organ system, such as diabetes, hypertension, hyperthyroidism, osteoporosis, or gastrointestinal diseases, that might compromise the outcome of surgery or contraindicate the administration of the research drugs; *4)* use of any drug or medication in the 30 days before the surgical procedure; *5)* history of hypersensitivity to ibuprofen, etodolac, or dexamethasone; *6)* intolerance to other materials used in the research, such as 0.5% chlorhexidine, 0.12% chlorhexidine gluconate, or 4% articaine hydrochloride with epinephrine 1:100,000; and *7)* menstruation, pregnancy, or lactation at the time of surgery.

RESEARCH AND PHARMACOLOGIC PROCEDURES

The sample size was obtained by a power test performed on the website www.lee.dante.br/pesquisa/amostragem/amostra, which indicated a sample size of 9 patients per group to achieve a power of 0.8. After patient selection, 2 surgical procedures were performed by the same surgeon, as described later. The side to first undergo extraction and the drug to be used were randomly chosen using the website www.randomization.com, according to the CONSORT

flow diagram (Fig 1). The surgical procedures were as follows:

For the first treatment, 1 hour before the procedure, the patient ingested 1 tablet of dexamethasone, 4 mg. The patient then underwent extraction of the right or left lower third molar, randomly chosen by the research assistant. The patient received 9 tablets of ibuprofen, 600 mg (Brainfarma, Anápolis, Brazil), or etodolac, 300 mg (Flancox; Apsen, Santo Amaro, Brazil), to be administered orally, starting immediately after surgery and repeating doses every 8 hours for 3 days.

For the second treatment, after a minimum of 21 days, the same patient ingested 1 tablet of dexamethasone, 4 mg, 1 hour before the procedure and then underwent extraction of the other lower third molar. The operated side was contralateral to that of the first intervention. After surgery, the patient received 9 tablets of etodolac, 300 mg, or ibuprofen, 600 mg (whichever drug was not used in the first treatment) and was instructed to start taking the drug immediately after surgery, repeating doses every 8 hours for 3 days.

The choice of right or left side for the initial operation was determined using the website www.randomization.com, and neither the surgeon nor the patient was aware which drug was administered for the chosen side. An assistant was responsible for collecting data regarding the operation sides and drug treatments.

After surgery, all patients received tablets of acetaminophen, 500 mg, and were instructed to take 1 tablet when there was pain, with a minimum interval of 6 hours between analgesic administrations. Patients were instructed to note the time and number of rescue analgesics used. This acetaminophen ingestion at 6-hour intervals was intended to control pain in cases in which the treatment used had minimal analgesic effect. Taking note of analgesic ingestions allowed us to assess whether any of the treatments provided insufficient analgesia.

SURGICAL PHASE

All surgical procedures were performed by the same operator, with a minimum interval of 21 days between operations. All patients underwent intraoral antisepsis by vigorous rinsing with aqueous 0.12% chlorhexidine gluconate for 1 minute and extraoral antisepsis with an alcoholic solution of 0.5% chlorhexidine.

The anesthetic technique was a truncal block of the inferior alveolar, buccal, and lingual nerves through application of 4% articaine with epinephrine

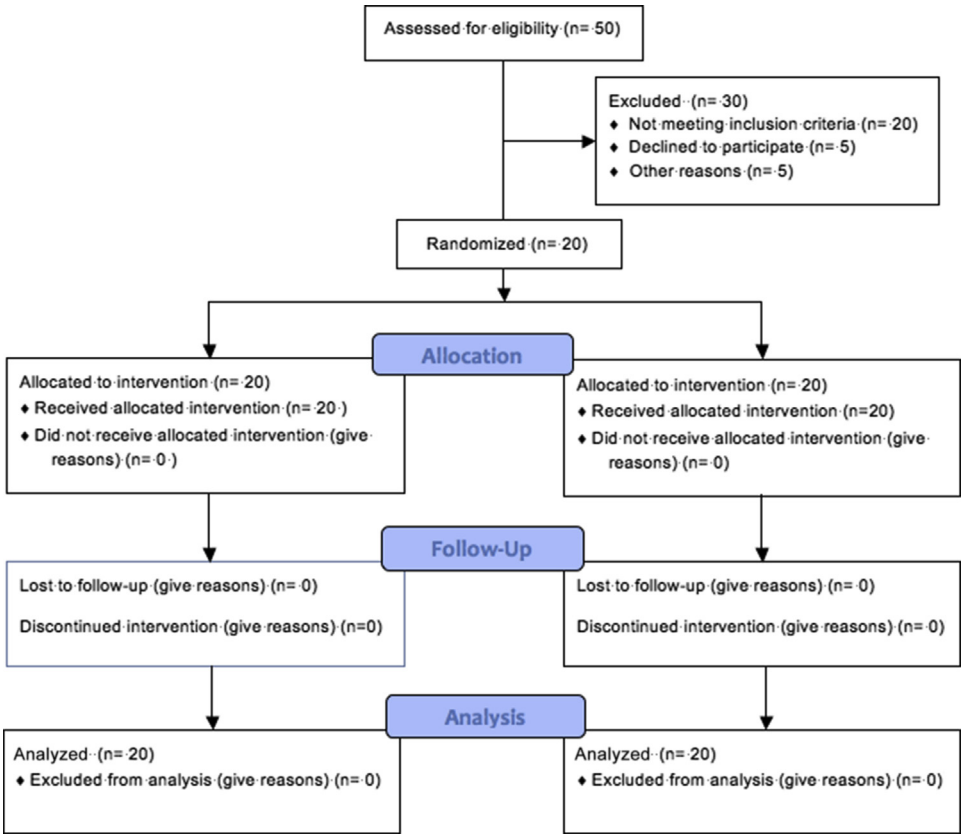

FIGURE 1. CONSORT (Consolidated Standards of Reporting Trials) flow diagram of patients allocation by randomization using www.randomization.com site.

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1:100,000 (DFL, Rio de Janeiro, Brazil) using a cartridge syringe with reflux (Duflex, Rio de Janeiro, Brazil) affixed with a long 27-gauge gingival needle (Unoject; DFL, Rio de Janeiro, Brazil), with a maximum of 4.5 mL applied (equivalent to the amount contained in 2.5 tubes).

By use of a No. 15 scalpel blade (Med Blade, Manaus, Brazil), a linear mucoperiosteal incision was made in the distal region of the second lower molar, with or without a vestibular relaxing incision in the mesial second molar region. After mucoperiosteal detachment with a No. 9 molt periosteal elevator (Quinelato, Rio Claro, Brazil), a Minnesota retractor (Quinelato) was applied to the operative field. When necessary, osteotomy and root resection were performed using a No. 702 carbide bur (Labor dental, São Paulo, Brazil) on a high-speed handpiece (Kavo, Joinville, Brazil) with abundant irrigation with 0.9% saline solution (Sanobiol, Pouso Alegre, Brazil). Dental removal was completed with curved and straight Seldin extractors (No. 2, 1R, or 1L; Quinelato), and close inspection was then performed to remove the dental follicle.

Bone edges were refined to remove the bone spurs with bone lime (Quinelato) and then irrigated with abundant sterile 0.9% saline solution (Sanobiol). Wounds were closed with interrupted No. 4-0 nylon surgical sutures (Ethicon; São Paulo, Brazil). Surgical procedures were performed in the morning and afternoon (between 8 AM and 6 PM) in an air-conditioned environment at the surgery department of Aracatuba Dental School.

POSTOPERATIVE PHASE

Immediately after the surgical procedure, patients were directed to maintain a liquid or soft and cold diet in the first 48 hours after surgery and to avoid physical exertion, sun exposure, and mouthwash use in the first 24 hours. Patients with the development of any postoperative complications, such as bleeding or dry or purulent alveolitis, were treated and therefore excluded from the research.

An appointment was scheduled from 48 hours to 168 hours (7 days) postoperatively to observe the patients and evaluate the extent of their edema and mouth-opening limitation. Sutures were removed 7 days postoperatively. All the trismus and edema measurements were performed by a third examiner who was not aware of the patient's group.

PAIN ASSESSMENT

Pain levels were assessed using an 11-point visual analog scale, the BS-11.[30] This scale used a line with 11 identical boxes whose extremes represented the limits of pain from absent to severe, on which patients were asked to note the presence and degree of pain during the 24 hours after surgery.

At 6, 12, and 24 hours after surgery, patients were instructed to mark an *X* in 1 box of the BS-11 scale to indicate their pain intensity. The scale consisted of 11 boxes with the words "no pain" (0) noted at the left edge and the words "worst possible pain" (10) at the opposite end. The BS-11 was adapted to include these terms to increase patient understanding of the scale. The pain assessment scale was provided to patients at the end of each surgical intervention so that they could record their pain severity and any necessary analgesic consumption.

EDEMA EVALUATION

Before surgery, the facial contour of each patient was evaluated by measuring the distance from the tip of the chin to the lower edge of the earlobe through the mandibular interincisal line (between dental elements 41 and 31) using a metric measuring tape.[31] These measures were registered, preoperatively and from 48 to 168 hours (7 days) postoperatively, in a document created for each patient.

All measurements were taken in maximum intercuspation with the lips in the resting position and were repeated 3 times by the same operator to increase accuracy and show reliability of the method.[32] Before measurement, the points at the lower edge of the earlobe and average interincisal line at the tip of the chin were marked with a skin tattoo pen (Henafix, Belo Horizonte, Brazil); these marks remained for about 10 days to standardize the preoperative and postoperative measurements.

MOUTH-OPENING ASSESSMENT

For evaluation of mouth-opening limitation, the maximum interincisal opening was measured with a digital caliper (Mitutoyo, Japan) between the incisal edge of the upper central incisors and the lower central incisors on the right side preoperatively and 48 and 168 hours (7 days) postoperatively. Mouth opening was measured 7 days after suture removal.

STATISTICAL ANALYSIS

Values were imported into the SigmaPlot software program (version 13.0; Systat Software, San Jose, CA) to perform descriptive statistics and association tests for comparisons between ibuprofen and etodolac. The Shapiro-Wilk test was used to evaluate the normality of data distribution, followed by the application of parametric or nonparametric tests as appropriate. The Kruskal-Wallis test was used for preoperative edema measurements. One-way analysis of variance was used for edema measurements at 2 and 7 days postoperatively and for trismus

measurements before surgery and at 2 and 7 days postoperatively. Two-way analysis of variance was applied to pain scale data. Statistical significance was set at $P < .05$.

Results

Removal of the third molars was performed in 20 patients (9 male and 11 female patients). All patients underwent close follow-up during the postoperative period to obtain measurements of trismus and edema. There were no cases of postoperative complications or adverse reactions to the study drugs.

With both ibuprofen and etodolac, edema peaked at 48 hours postoperatively, with facial contours returning closer to normal on the seventh day (Fig 2). Statistically significant differences between protocols were found at 48 hours postoperatively; etodolac-treated patients had less edema after surgery. Before surgery, the mean facial measurement of both groups was 13 ± 1.48 cm. Forty-eight hours postoperatively, the mean facial measurements of the ibuprofen group and the etodolac group were 15.1 ± 1.61 cm and 14 ± 1.52 cm, respectively ($P = .033$). On the seventh postoperative day, a regression of edema was observed and there was no statistical difference between groups; the mean values for the ibuprofen group and the etodolac group were 14.05 ± 1.25 cm and 13.5 ± 1.73 cm, respectively.

A reduction in mouth opening occurred in all postoperative periods, regardless of the drug used (Fig 3). However, this reduction was more pronounced in the ibuprofen group. The difference between drug groups was statistically significant ($P = .02$) at the 48-hour evaluation, with the etodolac group having a mean mouth-opening limitation of 14.2 ± 9.67 mm compared with 22.25 ± 8.56 mm in the ibuprofen group. Residual trismus after 1 week was still significantly different between groups; the etodolac group had residual trismus of 4.6 ± 6.1 mm, as compared with 10.45 ± 9.15 mm in the ibuprofen group.

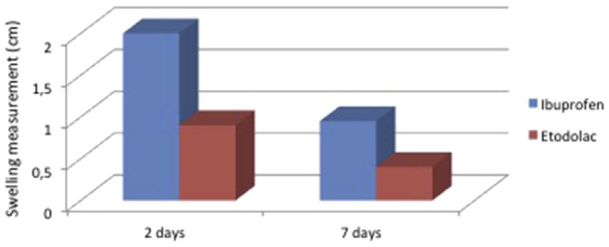

FIGURE 2. Swelling measurement (in centimeters) at 2 and 7 days postoperatively with anti-inflammatory drugs (ibuprofen and etodolac).

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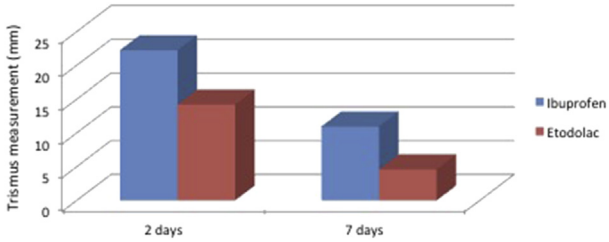

FIGURE 3. Trismus measurement (in millimeters) at 2 and 7 days postoperatively with anti-inflammatory drugs (ibuprofen and etodolac).

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There were no statistically significant differences regarding postoperative pain after 12 hours between protocols ($P > .05$, Tukey test). However, patients indicated lower postoperative pain scores at all evaluation times with the use of etodolac compared with ibuprofen (Fig 4). The ibuprofen group used more than twice as many rescue analgesics as the etodolac group (34 tablets vs 15 tablets).

Discussion

This study investigated the clinical efficacy of managing postoperative pain using the NSAIDs ibuprofen and etodolac after lower third molar surgery, via a well-accepted and commonly used procedure for evaluating anesthetics and anti-inflammatory drugs.[4,5,7-9] When patients receive no analgesic medication, they report a pain score of 8 on a visual analog scale from 0 to 10, with 0 representing no pain and 10 representing the worst pain imaginable.[33] Clearly, managing pain for these surgical procedures is necessary; thus, our study did not use a placebo group as a negative control. However, the same surgical procedure was performed on both sides of the jaw on 2 separate occasions in the same volunteer, and each side of the jaw was compared with the other to avoid

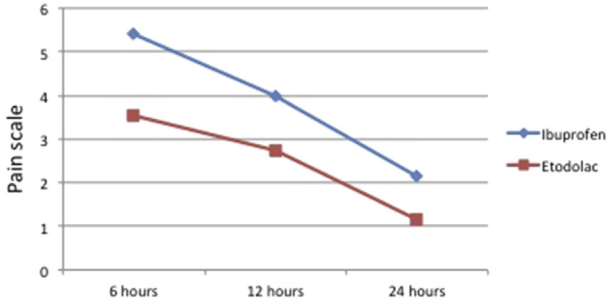

FIGURE 4. Pain scale assessed by visual analog scale at 6, 12, and 24 hours postoperatively with anti-inflammatory drugs (ibuprofen and etodolac).

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individual variations. In this way, each volunteer served as his or her own control. Akbulut et al[34] found similar results for pain and trismus comparing naproxen, etodolac, and diclofenac after third molar removal and better edema control with diclofenac. The NSAID used in our study showed different behavior with better inflammation suppression with the use of etodolac. To our knowledge, this is the first randomized clinical study to compare the effect of etodolac and ibuprofen on trismus, edema, and pain after third molar removal surgery.

Facial edema occurs gradually in response to tissue trauma in the third molar region, with peak swelling 48 hours after surgery.[35] There are various methods for evaluating edema after oral surgical procedures, including the visual analog scale, measurement with silk suture, or measurement with the aid of plethysmography.[36] The method chosen in our study consisted of a linear measurement from the earlobe to the midline of the chin. Ibuprofen improves patient recovery by limiting edema when administered both preoperatively and postoperatively.[35] In our study, etodolac was more effective in controlling edema at the 48-hour measurement that represents the peak of inflammation. One week after surgery, both groups presented edema resolution and re-establishment of the facial contour.

Limited mouth opening is another unwanted effect commonly reported after oral surgical procedures. In investigations, inter-incisor distance measurements performed before and after the operation are commonly used to evaluate trismus.[29,35,36] In this study, reduced trismus was observed with the administration of etodolac compared with ibuprofen. This difference was observed at both 2 and 7 days postoperatively. Trismus impedes eating and talking and reduces the quality of life of patients; in this sense, decreased trismus means decreased discomfort and increased quality of life. Therefore, etodolac may be preferred over ibuprofen to promote a faster return of oral function.

The etodolac group had slighter pain and ingested fewer analgesics compared with the ibuprofen group. This fact clearly indicates that the NSAIDs used in this research, alone, were not able to prevent postoperative pain and additional analgesics should be prescribed in association with them to prevent discomfort after oral surgery.

PGs are produced from oxidation of arachidonic acid by COX-1 or COX-2. COX-1 is responsible for baseline levels of PGs, whereas COX-2 produces PGs after stimulation. Selective inhibition of COX-2 has been considered to reduce levels of inducible PGs in inflammation, but to have no effect on constitutive PGs. Etodolac selectively inhibits COX-2, which is involved in PG synthesis and metabolism in inflammation. The maximum daily dose is 1,200 mg for etodolac and 3,200 mg for ibuprofen. In our study the etodolac group ingested 75% of the maximum daily dose limit, and the ibuprofen group ingested 56%. The choice of medication dose was based on the commonly used dosage in similar studies. When the anti-inflammatory effect of multiple doses of ibuprofen was compared, minimum improvement was noted when doses were increased from 400 to 600 mg.[37]

In conclusion, the results of this study indicate that etodolac was more effective in diminishing edema 2 days after surgery and trismus 2 and 7 days after surgery. Etodolac gave better pain relief 6 hours after surgery; beyond this time, ibuprofen and etodolac had the same behavior. In light of these data, we conclude that etodolac may be a better alternative than ibuprofen for preventing inflammatory effects associated with extraction of impacted third molar teeth.

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