Ketoprofen Is More Effective Than Diclofenac After Oral Surgery When Used as a Preemptive Analgesic: A Pilot Study

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Aim: To evaluate the preemptive analgesia of ketoprofen in comparison with diclofenac after mandibular third molar surgery. **Methods:** This study was a double-blind, randomized clinical trial. Forty patients were randomized into two treatment groups (each with 20 patients) by using a series of random numbers: group A received ketoprofen 100 mg and group B received diclofenac 75 mg, all intramuscularly. Surgery was done 30 minutes after analgesic treatments. The durations of analgesia, pain intensity, analgesic consumption, and side effects were evaluated. The statistical analysis was done using the chi-square, Student *t*, Mann-Whitney *U*, and Log-Rank tests. **Results:** The duration of analgesia was longer in the ketoprofen group when compared with the diclofenac group. The number of patients taking the first rescue analgesic at 6 hours was lower in the ketoprofen group in comparison with the diclofenac group. Patients who received ketoprofen had lower pain intensity compared with patients who received diclofenac. **Conclusion:** Intramuscular ketoprofen 100 mg is more effective than intramuscular diclofenac 75 mg after mandibular third molar extraction when used as a preemptive analgesic. *J Oral Facial Pain Headache 2014;28:153–158. doi: 10.11607/ofph.1200*

Key words: *dental pain, diclofenac, ketoprofen, third molar surgery*

Pain associated with surgical removal of mandibular third molars ranges between moderate and severe during the first 24 hours after surgery, with pain peaking between 6 and 8 hours when a conventional local anesthetic is used.[1] Dental pain is largely inflammatory, and evidence-based medicine has shown that nonsteroidal anti-inflammatory drugs (NSAIDs) are the best analgesics for dental pain.[2,3]

The analgesic, anti-inflammatory, and antipyretic effects of NSAIDs are a result of the ability of these agents to inhibit cyclo-oxygenase (COX) enzymes, which catalyze the conversion of arachidonic acid to prostaglandins, which are fatty acids involved in the generation of pain, fever, and inflammation.[4,5] Diclofenac is a proven and commonly prescribed NSAID with analgesic, anti-inflammatory, and antipyretic properties; it has been shown to be effective in treating a variety of acute and chronic pain and inflammatory conditions.[6] Diclofenac has been used widely in pain control and has good analgesic effectiveness after third molar surgery.[7,8] Diclofenac exerts its action via inhibition of prostaglandin synthesis by inhibiting COX-1 and COX-2 with relative equipotency.[9] Ketoprofen, another widely used NSAID, is effective and well-tolerated in the treatment of acute and chronic pain of both rheumatic and traumatic origin, as well as postoperative pain.[10,11] The main mechanism of analgesic action of ketoprofen is the inhibition of COX and, consequently, the decreased production of prostaglandin E2.[11]

The practice of treating pain only after it has become well entrenched is slowly being supplanted by preventive approaches that aim to block transmission of the injury-induced primary afferent barrage before, during, and after surgery, and to stop the neurochemical cascade that leads to chronic pain by postsynaptic receptor blockade (eg, via N-methyl-d-aspartate receptor antagonists) and neuroprotection of antinociceptive dorsal horn interneurons, by arresting glial reaction, and by preventing the phenotypic switch that causes some

interneurons to become pronociceptive.[12] The aim of this pilot study was to evaluate the preemptive analgesia of ketoprofen in comparison with diclofenac after mandibular third molar surgery.

Materials and Methods

Design

This pilot study was a double-blind, randomized, clinical trial conducted in accordance with the Declaration of Helsinki. The Ethics Committee of the Naval Medical Center "Cirujano Mayor Santiago Távara" approved this study. All subjects were informed of the possible risks of oral surgery and treatments used. Each patient accepted and signed an informed consent form.

Selection Criteria

Inclusion criteria were: age 18 to 30 years; either sex; physical status 1 according to the Classification System of the American Society of Anesthesiologists[13]; clinical and radiographic diagnosis of an impacted mandibular third molar in mesioangular position, Class II (the space between the second molar and the ramus of the mandible is less than the mesiodistal diameter of the third molar), and position C (the impacted tooth is below the cervical line of the second molar) according to the Pell and Gregory Classification[14]; and no pain associated with the subject's third molar up to the day of the surgery. Exclusion criteria included the use of analgesics 1 week before the procedure, gastritis, peptic ulcer, pregnancy or lactation, and known hypersensitivity to the medications used.

Randomization

Patients were assigned sequential numbers in order of enrollment and received their allocated treatment according to a computer-generated randomization schedule prepared before the start of the study.

Interventions

Forty patients were randomized into two treatment groups (each with 20 patients) by using a series of random numbers: group A, ketoprofen 100 mg; and group B, diclofenac 75 mg. These doses of ketoprofen and diclofenac were based on their use in several published studies about pain following oral surgery.[15–27] Drugs were prepared in an identical syringe by an independent investigator and were administered by the intramuscular route. The oral route was not used in order to avoid gastrointestinal irritation produced by these drugs as well as to avoid loss of drug through its metabolic breakdown in the liver during its absorption. Surgery was done 30 minutes after the administration of the drug.

All surgical procedures were carried out by the same surgeon in the Department of Oral and Maxillofacial Surgery of the Naval Medical Center "Cirujano Mayor Santiago Távara," and evaluations were done by an independent investigator. Anesthesia was obtained by nerve block of the lingual, buccal, and inferior alveolar nerves by using two 1.8-mL cartridges of 2% lidocaine containing 1:80,000 epinephrine. Additional local anesthesia (one or two cartridges of lidocaine) was used when patients had pain during surgery. The number of cartridges of lidocaine was recorded. Once local anesthesia was obtained, surgery was started. A mucoperiosteal flap was prepared by making an incision distal to the mandibular second molar along the anterior edge of the ascending ramus of the mandible. This flap was used to close the surgical wound. Suturing was done with 3-0 silk. In all cases, the duration of the operation (from incision to final suture) was recorded. In each patient, a full bony impacted mandibular third molar was extracted.

Assessments

The duration of analgesia of the administered drugs before surgery was evaluated as the time from the end of the surgery until the intake of the first rescue analgesic medication became necessary for the patient.

A 100-mm visual analog scale (VAS) was used to assess pain. The VAS consisted of an interval scale ranging from 0, representing no pain or discomfort, to 100, representing maximum pain or discomfort. Clinical assessments were done with the VAS at 10 minutes, 3 hours, and 6 hours after surgery. After that, patients were evaluated using an auto-recording at home at 9 hours and 12 hours. Patients returned the next day for a last clinical assessment (24 hours after completion of surgery).

Patients were given lysine clonixinate (125 mg) pills and were instructed to take one pill for rescue medication at least 6 hours apart, according to their requirements. At the end of the evaluation period (7 days), patients returned the unused lysine clonixinate. Pills were counted to determine the number of consumed pills. Total analgesic consumption of lysine clonixinate was evaluated. Intra- and postoperative complications and adverse events were recorded.

Blinding

Both patients and the independent evaluator were blinded regarding the administered drug.

Statistical Methods

Data are expressed as mean and standard deviation (SD), median and ranges, or frequency. For numeric variables with normal distribution, the Student *t*

Table 1 Demographic and Surgical Variables

Variable	Ketoprofen (n = 20)	Diclofenac (n = 20)	*P* value
Age (y)	23.6 ± 5.87	23.9 ± 4.95	.48
Sex (female:male)	11:9	13:7	.74
Weight (kg)	60.8 ± 9.72	58.41 ± 7.98	.40
Local Anesthesia (mL)	4.34 ± 0.57	4.45 ± 0.77	.60
Duration of surgery (min)	25 ± 3.00	23 ± 3.62	.93

Table 2 Indicators of Analgesic Effectiveness

Variable	Ketoprofen (n = 20)	Diclofenac (n = 20)	*P* value
Time to first rescue analgesic medication			
Mean ± SD	5.97 ± 2.29	3.92 ± 2.18	.006
Median / ranges	6.20/1.16–9.58	3.33/1.91–10.66	.004
Patients taking the first analgesic medication			
10 min	0	0	.99
3 h	2	7	.13
6 h	9	18	.007
9 h	18	19	.99
12 h	20	20	.99
24 h	20	20	.99
Global evaluation of pain intensity (VAS)	17.16 ± 6.81	22.16 ± 8.97	.48
Pain by the AUC of the VAS	98.75 ± 17.41	114.5 ± 9.9	.43
Total analgesic consumption (tablets)	7.75 ± 3.91	7.90 ± 5.74	.92
Adverse events	0	0	.99

test was used. For numeric variables without normal distribution and ordinal variables, the Mann-Whitney *U* test was used. For categorical variables, the chi-square test was employed. Time-event curves were carried out to evaluate the time of first analgesic medication and were compared using the Log-Rank test. The area under the curve (AUC) of the VAS was used to evaluate the overall assessment of pain. A *P* value less than .05 was considered a significant statistical difference.

Results

A total of 40 patients were enrolled in the study, and all patients were included in the statistical analysis. Both treatment groups were comparable in their sociodemographic characteristics. Data describing the difficulty of surgery were similar among the groups. There were no statistically significant differences with respect to any demographic or surgical variables among the two treatment groups (Table 1).

The time to first rescue analgesic medication was longer in those who received ketoprofen in comparison with patients treated with diclofenac (Table 2). The duration of analgesia (time for first analgesic medication after surgery) was evaluated with time-event curves and showed a longer time of analgesia in the ketoprofen group compared with the diclofenac group (Fig 1). The number of patients taking the first rescue analgesic medication at 6 hours after surgery was significantly lower in the ketoprofen group in comparison with the diclofenac group (Table 2).

Patients receiving ketoprofen showed lower pain intensity when compared with patients who received diclofenac after 3 hours of completion of surgery, according to the VAS scores. Interestingly, as Fig 2 shows, all VAS scores of ketoprofen group were lower throughout the period of evaluation in comparison with diclofenac group. However, pain intensity showed a statistical difference only after 3 hours. The global evaluation of pain intensity by using the VAS and overall assessment of pain (AUC of the VAS) was lower in the ketoprofen

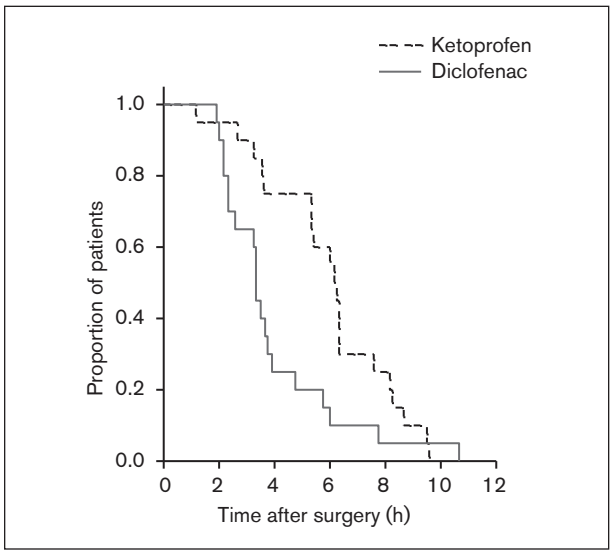

Fig 1 Time-event curves of time of first rescue analgesic medication ($P = .023$).

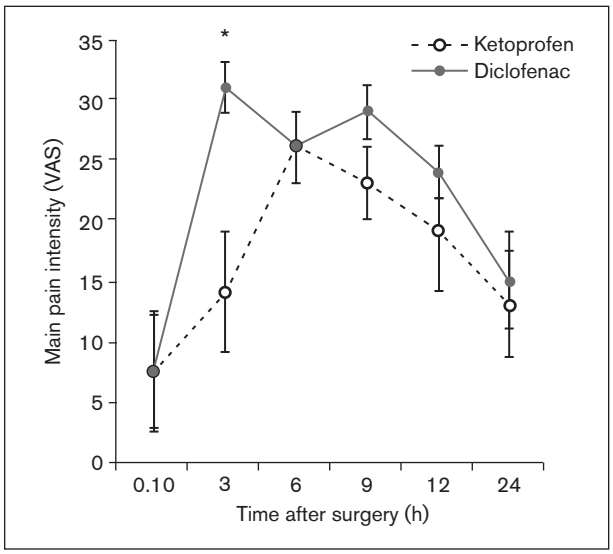

Fig 2 Pain intensity evaluated by the VAS after surgery (*$P = .001$).

group compared with diclofenac group but without any statistical difference. The analgesic consumption was lower in the ketoprofen group when compared with the diclofenac group, but this difference was also not statistically significant. There were no complications associated with the surgical procedure itself. No patients reported adverse events (see Table 2).

Discussion

This study shows that the preemptive administration of ketoprofen is more effective than diclofenac in the control of pain after third molar surgery. The mean duration of analgesia obtained by the preemptive administration was longer in patients who received ketoprofen compared with those who received diclofenac. This difference in the duration of analgesia was about 2 hours, which is clinically important. Furthermore, the number of patients requiring the first rescue analgesic at 6 hours was less in the ketoprofen group, thus showing the benefits of longer-duration analgesia. According to the VAS scores, pain intensity was also lower in the ketoprofen group in comparison with patients who received diclofenac. It is important to note that the ketoprofen group had lower pain intensities throughout the evaluation period.

The present results are in agreement with a clinical study by Tai et al,[28] who compared ketoprofen 200 mg and diclofenac 100 mg in multiple doses for 4 days after third molar surgery. They used intravenous diazepam and nalbuphine, as well as methohexitone or propofol, for general anesthesia induction; paracetamol 500 mg was also used as the rescue analgesic. Moreover, the surgical difficulty was not evaluated. In the current study, ketoprofen 100 mg and diclofenac 75 mg were administered 30 minutes before surgery, and local anesthesia was used. These clinical differences are very important because the present study allowed for evaluating the analgesic effectiveness of both NSAID drugs in a clearer manner. In addition, lysine clonixinate was used as the rescue analgesic, and surgical difficulty was evaluated according to the Winter and Pell and Gregory Classification. Despite these differences, the present findings about pain were similar to those observed by Tai et al.[28] On the other hand, Niemi et al[29] have reported that administering diclofenac 1 mg/kg 30 minutes before and 4 hours after maxillofacial surgery is more effective than ketoprofen 1.35 mg/kg administered in the same manner. This study was performed using general anesthesia, and oxycodone was used as the rescue medication; a lower requirement of oxycodone was demonstrated in the diclofenac group in comparison with the ketoprofen and saline groups.

Ketoprofen and diclofenac have also been previously compared with other NSAIDs after third molar surgery. A study by Seymour et al[30] showed that ketoprofen 25 mg is more effective for pain control than acetaminophen 500 and 1,000 mg for postoperative pain in third molar surgery. Another study by Seymour et al[31] demonstrated that buffered ketoprofen 12.5 mg was superior to ibuprofen 200 mg for both reducing pain intensity and providing an earlier onset of pain relief. A study by Sunshine et al[32] also showed that ketoprofen 12.5 and 25 mg provided significantly

greater pain relief with a faster onset and shorter duration of effect than ibuprofen 200 mg. The results of these studies are clinically important because both acetaminophen as well as ibuprofen are the NSAIDs most often used in the treatment of the postoperative dental pain after mandibular third molar surgery.[7,33] Nevertheless, Olmedo et al[34] showed that ketorolac 10 mg and 20 mg produced better analgesic efficacy than ketoprofen 50 mg and placebo after third molar surgery. Patients receiving ketorolac required less rescue analgesic and had better pain relief than did patients receiving ketoprofen or placebo. On the other hand, diclofenac (50 or 75 mg) has been reported to have a similar degree of pain relief to paracetamol 1 g, ibuprofen 600 mg, and ketorolac 30 mg after third molar removal.[19,35–37] However, meloxicam 15 mg, tenoxicam 40 mg, lornoxicam 8 mg, and aceclofenac 100 mg have shown better analgesic efficacy than diclofenac (50 or 75 mg) after third molar surgery.[19,22,38,39]

In addition to its effects on COX, ketoprofen is characterized by other pharmacologic effects that may be relevant to its anti-inflammatory and analgesic activities. Ketoprofen also inhibits the lipoxygenase pathway of the arachidonic acid cascade, leading to a decrease in the synthesis of leukotrienes.[11] It is a powerful inhibitor of bradykinin (an important chemical mediator in pain and inflammation); it stabilizes the lysosomal membranes against osmotic damage, and it prevents the release of lysosomal enzymes that mediate tissue destruction in inflammatory reactions.[40] Interestingly, it has been shown that ketoprofen, like other NSAIDs, has both peripheral and central sites of action through the inhibition of central prostaglandin biosynthesis; both brain COX and nitric oxide synthase are inhibited. Ketoprofen is rapidly and readily distributed into the central nervous system and passes through the blood brain barrier within 15 minutes, due to its high level of liposolubility. It has been recently demonstrated that, besides the inhibition of prostaglandin synthesis in the central nervous system, ketoprofen also interacts with the serotonergic system.[11] All these mechanisms of ketoprofen may explain its higher efficacy versus other NSAIDs.[11]

The use of NSAIDs after surgery may increase the risk of bleeding by their antiplatelet effects; however, the evidence of increased bleeding is conflicting. NSAIDs inhibit COX and also decrease the production of thromboxane A2, a potent platelet-aggregating agent, thus increasing the risk of postoperative bleeding. However, there are no epidemiologic studies of serious adverse events in the dental surgical model, although there is a theoretical risk of serious adverse events that could occur with the use of NSAIDs in this model.[41] The antiplatelet effects of NSAIDs do not appear to significantly alter postoperative coagulation and may be protective for myocardial infarct and thromboembolism.[42] Naclério-Homem et al[43] demonstrated that preoperative and postoperative administration of ketoprofen 50 mg and diclofenac 25 mg is safe for removal of third molars; the results of pre- and postoperative blood coagulation tests of all patients ranged within normal values. For this reason, preoperative medication of these drugs seems to be safe for oral surgery. In the present study, no patient reported bleeding or hemorrhage.

An important limitation of this study was the lack of a control or placebo group. Placebo analgesia no doubt contributed to the pain relief in both treatment groups, but this does not detract from the variables predicting analgesia or the results of the statistical analysis of this study.

In conclusion, intramuscular ketoprofen 100 mg is more effective than intramuscular diclofenac 75 mg after mandibular third molar extraction when used as a preemptive analgesic.

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