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Sublingual ketorolac and sublingual piroxicam are equally effective for postoperative pain, trismus, and swelling management in lower third molar removal

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Objective. Lower third molar removal provides a clinical model for studying analgesic drugs. The present study's aim was to compare the clinical efficacy of sublingual ketorolac and sublingual piroxicam in managing pain, trismus and swelling after lower third molar extraction in adult volunteers.
Study Design. In this double-blinded, randomized, crossover investigation, 47 volunteers received for 4 days ketorolac sublingually (10 mg 4 times daily) and piroxicam sublingually (20 mg once daily) during 2 separate appointments after lower third molar extraction of symmetrically positioned lower third molars. A surgeon evaluated objective parameters (surgery duration, mouth opening, rescue analgesic medication, and facial swelling) and volunteers documented subjective parameters (postoperative pain and global evaluation), comparing postoperative results for a total of 7 days after surgery. The means of the objective and subjective parameters were compared for statistical significance ($P < .05$).
Results. Volunteers reported low pain scores during the postoperative period when treated with either sublingual ketorolac or piroxicam. Also, volunteers ingested similar amounts of analgesic rescue medication (paracetamol) when they received either drug sublingually ($P > .05$). Additionally, values for mouth openings measured just before surgery and immediately after suture removal 7 days later were similar among volunteers ($P > .05$), and the type of nonsteroidal antiinflammatory drug (NSAID) used in this study showed no significant differences between swellings on the second or seventh days after surgery ($P > .05$).
Conclusions. Pain, trismus, and swelling after lower third molar extraction, independent of surgical difficulty, were successfully controlled by sublingual ketorolac (10 mg 4 times daily) or sublingual piroxicam (20 mg once daily), and no significant differences were observed between the NSAIDs evaluated. (Oral Surg Oral Med Oral Pathol Oral Radiol 2012;114: 27-34)

Pain resulting from the trauma of lower third molar extraction is a clinical model commonly used to study acute pain. Additionally, many patients require lower third molar surgery making this procedure quite common. More specifically, the postoperative pain experienced by the patient is typically moderate to severe lasting for ≥24 hours.[1] That is, pain from lower third molar extraction reaches its maximum intensity shortly after the end of surgery (2-4 h), and, in most cases, patients require some type of pain management.[2] Besides pain, swelling, and limited articulation of the temporomandibular joint associated with inflammation, there are further undesirable consequences for these patients who undergo oral surgery, such as loss of work or dietary limitations.[3-5] In general, treatment for pain, trismus, and swelling after lower third molar surgery may include nonsteroidal antiinflammatory drugs (NSAIDs).[3,5-7]

Most NSAIDs function by inhibiting cyclooxygenase (COX) and therefore, among other actions, ultimately result in an inhibition of prostaglandin production.[8-10] Currently, 3 isoforms of COX are recognized. One isoform, COX-1, is a constitutive form expressed in almost all tissues. Another isoform, COX-2, also known as prostaglandin-endoperoxide synthase 2, is predominantly induced and constitutively expressed in a limited number of tissues (renal medulla, prostate, brain, and endothelium).[8-12] The isoenzyme COX-2 stimulates the synthesis of proinflammatory prostaglandins.[3,5,8,10] The third isoform of COX, COX-3, a COX-1–derived protein, is most abundant in the cerebral cortex and heart.[12,13] COX-3 inhibition may represent the primary central mechanism by which NSAIDs such as acetaminophen and dipyrone decrease pain and possibly fever.[13,14] Finally, in accordance to their relative

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inhibition of COX isoenzymes, NSAIDs can be classified as nonselective, COX-2 preferential, or COX-2 selective.[15,16] Both ketorolac and piroxicam are nonselective COX inhibitors and both NSAIDs competitively block COX, thereby inhibiting prostaglandin synthesis.

Various studies have investigated the efficacy of the more traditional NSAIDs. These NSAIDs that have been examined include diclofenac, ibuprofen, meloxicam, piroxicam, and ketorolac, which are all nonselective for COX-2 inhibition, and valdecoxib, celecoxib, rofecoxib and etoricoxib, which are all selective for COX-2 inhibition. Furthermore, all of these studies administered NSAIDs orally.[3,6,10,17-20]

Besides oral administration, NSAIDs have been administered sublingually. There are certain advantages of administering analgesics sublingually compared with oral administration. In particular, sublingual administration of a drug can relieve pain faster than oral administration because the sublingual administration route avoids the gastrointestinal tract and also the first passage of the drug in the liver where some of the drug would be metabolized.[21] Also, some patients find taking medications sublingually to be more comfortable than taking medications orally. Finally, in some countries some drugs are available only in sublingual form. More precisely, ketorolac is available only in a fast-dissolving sublingual form in Brazil, whereas piroxicam is available in both sublingual and oral forms. Both ketorolac and piroxicam are currently the only 2 NSAIDs that are available in sublingual form in Brazil.

Currently, little clinical research has investigated the efficacy of sublingually administering the nonselective NSAIDs, piroxicam and ketorolac, to manage pain, trismus and swelling resulting from the trauma of lower third molar surgery. To the best of our knowledge, no one has compared the use of these 2 NSAIDs administered sublingually. Our laboratory recently published a study that investigated and compared the clinical efficacy of sublingual piroxicam and oral piroxicam after lower third molar extraction, and it was found that both sublingual piroxicam and oral piroxicam were able to successfully control postoperative pain, trismus, and swelling.[22] Moreover, some volunteers preferred taking the fast-dissolving sublingual administration compared with oral administration. The present study followed the previous study and investigated the clinical efficacy of sublingual piroxicam and sublingual ketorolac after lower third molar extraction in a completely separate patient group.

It was hypothesized that both ketorolac and piroxicam would have similar clinical efficacy when administered sublingually in volunteers after lower third molar surgery. The aim of this was to compare the clinical efficacy of sublingual ketorolac and sublingual piroxicam in managing pain, trismus, and swelling after lower third molar extraction in adult volunteers.

MATERIALS AND METHODS

This study used a double-blinded, randomized, crossover design. In brief, only 1 side of the mandibular jaw was operated on at a time, and these surgeries were performed over the course of 2 visits separated by 1-2 months.[3,4,20,23-25] During each volunteer's first appointment, the subject randomly received either ketorolac or piroxicam sublingually for postoperative pain relief. During the volunteer's second appointment, the drug not used previously was then administered in a crossover manner.

The Ethics Committee of the Bauru School of Dentistry, University of São Paulo, approved the protocol of this study (#105/2006). Each of the volunteers provided written informed consent during the pretreatment screening period. Eligibility criteria included volunteers aged ≥18 years who had 2 lower third molars in similar positions as observed using panoramic radiography, each requiring extraction.[26,27] Exclusion criteria included: systemic illness and inflammation or infection at the extraction sites; gastrointestinal bleeding or ulceration; cardiovascular and hepatic diseases; and any known allergies to the local anesthetic used, paracetamol, aspirin, ketorolac, piroxicam, or any other NSAID. Pregnant women also were excluded from the study. Instructions for not using antidepressants, diuretics, aspirin, or antibiotics 7 days before surgery were given to the volunteers, avoiding possible hemorrhage or other possible unwanted interactions with the drugs used in this investigation.[3,4,20,23-25]

One surgeon performed all surgical operations and postoperative controls. Before surgery, all volunteers received local anesthetic blockade of buccal, lingual, and inferior alveolar nerves via one 1.8-mL cartridge of 4% articaine with 1:200,000 epinephrine.[25] When anesthesia of the inferior lip was achieved, an additional 0.9 mL volume of the same anesthetic solution was injected into the mucosa to guarantee homeostasis and anesthesia of the site. Next, the extraction of every third molar followed a standard surgical protocol.[25] Immediately after the extraction, each surgical site was thoroughly irrigated, suctioned, and sutured.[3,4] A second dentist naive to the details of the surgery then instructed each patient how to take the fast-dissolving dosage form of ketorolac or piroxicam sublingually (randomly assigned by coin flip). During the next visit the patient was instructed how to take the second NSAID sublingually that was not administered in the first trial. At no time were volunteers given antibiotics.

After surgery, volunteers remained in the clinic for the first postoperative hour. During this time, the local

anesthetic blockade was still present. Above all, the aim of this study was to investigate and compare the efficacy of either ketorolac or piroxicam sublingually to guarantee a painless postoperative period. It was not the aim of this study to determine or compare the onset of pain management by ketorolac and piroxicam sublingually.

Briefly, for 4 consecutive days the NSAID administration protocol was 1 10-mg tablet of fast-dissolving dosage form of ketorolac taken sublingually 4 times daily (every 6 h) or 1 20-mg tablet of fast-dissolving dosage form of piroxicam taken once daily. Volunteers were aware that 2 different NSAIDs would be administered and that 1 drug would be taken once daily, whereas the other drug would be taken 4 times daily, yet each patient remained naive to what drugs were used.

Additionally, oral rescue analgesic medication was available to any volunteer as needed throughout this study; for this purpose, 750-mg tablets of paracetamol were provided to all volunteers.[3,4,20,23-25] In general, volunteers recorded the date and time at which rescue medication was consumed. They were also instructed not to interrupt the use of the principal medication (ketorolac or piroxicam), even if they consumed the rescue analgesic medication (paracetamol).

The following parameters were collected and assessed. Surgery duration (min) after anesthetic administration, specifically the period between the first incision and the last suture, was cataloged.[3-5] Subjective postoperative pain evaluations were documented with the aid of a 100-mm long visual analog scale (VAS), with 0 representing "no pain" and 100 representing "worst pain imaginable."[3,4,28] The intensity of postoperative pain was chronicled at 15-minute intervals for the first 60 postoperative minutes, and 1.5, 2, 3, 4, 5, 6, 7, 8, 10, 12, 16, 24, 48, 72, and 96 hours after the end of the surgery as evaluated by the volunteers.[4,20,23-25,29] Time (h) to first rescue analgesic medication and total amount (mg) of rescue analgesic medication ingested during the postoperative period was documented by each volunteer. Also, the surgeon measured and recorded the mouth opening distance (in mm) between the mesial-incisal corners of the upper and lower right central incisors at maximum opening of the jaws before the surgery, during the second postoperative day, and at the moment of suture removal (seventh postoperative day). The postoperative ability to open the mouth was expressed as a percentage of preoperative measurements.[4,5] The surgeon also measured and recorded facial swelling during the second and seventh postoperative days.[5] This method produced a single value for each volunteer, namely, the sum of the following measurements: the distance (mm) between the lateral corner of the eye and the angle of the mandible, the distance (mm) between the tragus and the outer corner of the mouth, and the distance (mm) between the tragus and the soft tissue pogonion. The preoperative sum of these 3 measurements was considered to be the baseline value. The difference between the sum of the postoperative measurements and the baseline value indicated the facial swelling for that day. Each volunteer documented incidence, type, and severity of adverse reactions (gastrointestinal irritation, nausea, vomiting, bleeding, allergy, headache, dizziness, sleepiness, and any other kind of reaction).[28] Each volunteer also rated his or her global evaluation of the postoperative period (seventh postoperative day) using a 5-level Likert scale. The format of the Likert items was "excellent," "very good," "good," "fair," or "poor."[30]

A statistician used paired t tests to compare the duration of the entire surgeries. The nonparametric Wilcoxon test was used to assess the parameters "postoperative pain" and "rescue analgesic medication." The statistician also tested the "mouth opening" and "facial swelling" parameters for normal distribution and these parameters were compared using an analysis of variance followed by the Tukey test for multiple comparisons. Statistical significance was set at $P < .05$. Data are represented as a mean ± SEM.

RESULTS

In this crossover study, a total of 47 volunteers, with 28 women and 19 men, were investigated. Their ages ranged from 18 to 37 years with an average age of 23 years. No significant differences were found between male and female volunteers, and no correlation was found between age and any variable tested (data not shown).

Each volunteer experienced approximately the same magnitude of surgical trauma on each side of the mandibular jaw (Table I). However, among the volunteers the surgical trauma varied, with some volunteers requiring osteotomy. More explicitly, the need for osteotomy was determined by radiographic analysis confirmed by visual inspection during surgery, and each patient that required osteotomy required bilateral osteotomies. Additionally, volunteers were randomly assigned ketorolac or piroxicam after their first surgery regardless of their need for osteotomy.

As a part of an *ad hoc* analysis, the 47 volunteers were subdivided into 2 groups: 25 volunteers without the necessity of osteotomy and 22 with the need for an osteotomy. The surgeries requiring osteotomy lasted an average 19.88 ± 1.29 minutes and 19.60 ± 1.86 minutes for volunteers taking ketorolac and piroxicam, respectively. Volunteers who required no osteotomy had surgeries lasting 10.20 ± 0.29 minutes and 10.14 ± 0.29 minutes for those who took

Table I. Study variables

Study variable	*Piroxicam*	*Ketorolac*	*P value*
Time of operation (min)	14.69 ± 1.60	14.73 ± 1.34	.432
Local anesthesia used during surgery (mL)*	2.74 ± 0.04	2.72 ± 0.03	.285
Mouth opening (mm)—preoperative period	48 ± 2	47 ± 2	.122
Facial contour (mm)—preoperative period	123 ± 3	125 ± 1	.158
Temperature (°C)—preoperative period	36.1 ± 0.1	36.1 ± 0.1	.412

*Local anesthesia: 1 cartridge contained 1.8 mL of 4% articaine with 1:200,000 epinephrine. No significant differences were found when each patient was treated with ketorolac or piroxicam administered sublingually ($P > .05$) during 2 surgeries separated by an interval of 1-2 months.

ketorolac and piroxicam, respectively. No significant differences between the mean durations of the 2 surgeries in each volunteer were observed ($P > .05$). However, there was a significant difference in the mean duration of operations performed with and without bone removal ($P < .05$), indicating that the surgeries involving the more time-consuming osteotomy were more aggressive (data not shown). Overall, the durations of all surgeries were brief.

In the postoperative pain scores documented by each volunteer, no significant difference between piroxicam and ketorolac existed ($P > .05$; Fig. 1). Furthermore, all scores of pain recorded were minimal when compared with the full 100-mm-length VAS.

Likewise, the average total amount of analgesic rescue medication consumed by volunteers was quite small, being on average <2 tablets per person in each group tested during the entire time period of the study. When volunteers received ketorolac, they showed a trend to consume more rescue medication compared with piroxicam, but the difference was not statistically significant ($P > .05$; Table II).

There was no significant difference in the time of ingestion of the first rescue medication when volunteers were medicated with either ketorolac or piroxicam ($P > .05$; Table II). When volunteers received piroxicam, they showed a trend to take their rescue medication earlier then when these volunteers received ketorolac, but this difference was not statistically significant ($P > .05$; Table II).

There was only a major limitation of the volunteers' mouth opening during the second day. During the seventh day after surgery, the values for mouth opening measurements returned to baseline values ($P > .05$; Table II). Similar mouth openings were recorded during the second and seventh postoperative days whether volunteers took sublingual ketorolac or sublingual piroxicam. Additionally, no significant differences in the mouth opening parameters were observed between the groups with and without osteotomy (data not shown).

A similar result was observed for the values taken for swelling during the second and seventh day after surgery. Volunteers showed no significant differences between the groups. Swelling tended to be increased during the second day, which returned to baseline measurements during the seventh day ($P > .05$; Table II), but this increase in swelling was not statistically significant and was the same regardless of the NSAID taken sublingually.

Additionally, 5 volunteers who received piroxicam documented adverse reactions, with 4 volunteers reporting drowsiness and 1 reporting mild bleeding at the site of surgery (Table II). Seven other volunteers noted adverse reactions when they received ketorolac (Table II). Specifically, these volunteers reported gastric discomfort (4 volunteers), nausea (1 volunteer), headache (1 volunteer), and chest pain (1 volunteer). None of the volunteers who reported adverse reaction for 1 drug reported adverse reactions with the other drug. There was no significant difference in the number of adverse side effects reported between the volunteers when using piroxicam or ketorolac ($P > .05$; Table II).

There were no significant differences observed between the volunteers' global evaluations for piroxicam and ketorolac (Fig. 2). According to the volunteers' global evaluations of their postoperative period, both NSAIDs were classified as "good," "very good," and "excellent" in general, and no volunteers, regardless of osteotomy, classified the postoperative period as "poor." When osteotomy was necessary, one volunteer who took piroxicam and another volunteer who took ketorolac classified the period as "fair."

DISCUSSION

This study investigated the clinical efficacy of managing postoperative pain using 2 NSAIDs, ketorolac and piroxicam, which were administered sublingually after the lower third molar was extracted under local anesthesia. The degree of difficulty of the surgical procedure and the local trauma caused by the surgery varied among the volunteers, depending on whether it was necessary to remove bone tissue to extract the lower third molars. Surgical trauma on either side of the jaw in each volunteer was not significantly different. However, there was a difference in surgical trauma observed among those who received osteotomy and those who did not. However, after an *ad*

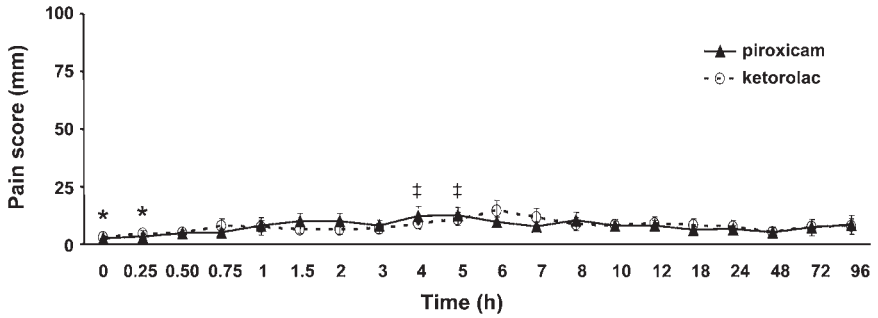

Fig. 1. Mean pain scores (mm) recorded by volunteers (n = 47) with the aid of a 100-mm-length visual analog scale at 0.25, 0.50, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 10, 12, 16, 24, 48, 72, and 96 hours after the end of the surgery for lower third molar extraction. Two drugs, ketorolac (10 mg 4 times daily) and piroxicam (20 mg once daily), were administered sublingually for 4 postoperative days and were used in a double-blind, randomized, crossover manner. During each time point studied, piroxicam and ketorolac were not significantly different from one another ($P > .05$; Tukey test); ‡ $P < .05$ piroxicam versus piroxicam at time 0 h; * $P > .05$ ketorolac versus ketorolac at time 6 h. Data are represented as mean ± SEM.

Table II. Outcome variables during the second and seventh days after lower third molar extraction

Outcome variable	*Piroxicam*	*Ketorolac*	*P value*
Mouth opening (%)*—2nd day	77.4 ± 2.6	77.6 ± 2.5	.310
Mouth opening (%)*—7th day	93.0 ± 2.6	88.8 ± 2.7	.056
Swelling (mm)†—2nd day	6.0 ± 2.2	3.2 ± 0.4	.182
Swelling (mm)†—7th day	0.6 ± 3.5	−1.8 ± 2.7	.399
Temperature (°C)—2nd day	36.1 ± 0.1	35.4 ± 0.9	.141
Temperature (°C)—7th day	36.1 ± 0.1	36.1 ± 0.2	.419
Total amount of rescue medication (mg)‡	1069 ± 180	1372 ± 243	.099
Time to first rescue medication (h)	13.17 ± 3.32	20.55 ± 5.50	.089
Reports of adverse reactions	5	7	.713

*Mouth opening and swelling are relative to preoperative values (Table I).
†Swelling values are the differences of the second or seventh postoperative days from the facial contour during the preoperative period (Table I).
‡Rescue medication provided was paracetamol (750-mg tablets).

hoc analysis of each parameter separated into 2 subdivisions (with or without osteotomy), no potential confounding variables were found. Because the treatment groups were randomly assigned, necessity for osteotomy was evenly distributed between treatment groups and there was no need to adjust for volunteers with osteotomy.

Lower third molar surgery is a well accepted and commonly used procedure to evaluate clinical efficacy of anesthetics and antiinflammatory drugs.[20,23] When patients receive no analgesic medication, they report a pain score of 8 on a VAS from 0 to 10 with 0 representing no pain and 10 representing worst pain imaginable.[1] Clearly, managing pain for these surgeries is necessary, and the present study did not use a placebo in a subset of volunteers as a negative control. Furthermore, in this study the same surgical procedure was performed on both sides of the jaw on 2 separate occasions in the same volunteer and then each side of the jaw was compared with the other, thus avoiding individual variations.[26,27] In this way each volunteer served as his or her own control.

The method used in this study to measure swelling is widely accepted in the literature.[5,21] The benefits of this method lie in its simplicity. It is noninvasive, cost-effective, and timesaving and provides numeric data for determination of soft tissue contour changes. The results of this protocol showed changes in facial soft tissue contours on the second and seventh postoperative days, corroborating the results observed by Calvo et al.[20] (meloxicam) and Graziani et al.[21] (piroxicam). On the seventh postoperative day, for both groups, the magnitude of swelling was far less than that observed on the second postoperative day, with measures close to the baseline (preoperative) values.

Closely related to swelling, mouth opening in the 2 postoperative periods was the same among all groups. These data are in agreement with other studies that used other NSAIDs,[3,4,20,21] which showed the effectiveness of NSAIDs in controlling pain, swelling, and trismus after lower third molar extraction.

In the present study, the length of time that each NSAID needed to completely relieve pain was not investigated. Rather, the aim of this study was to in-

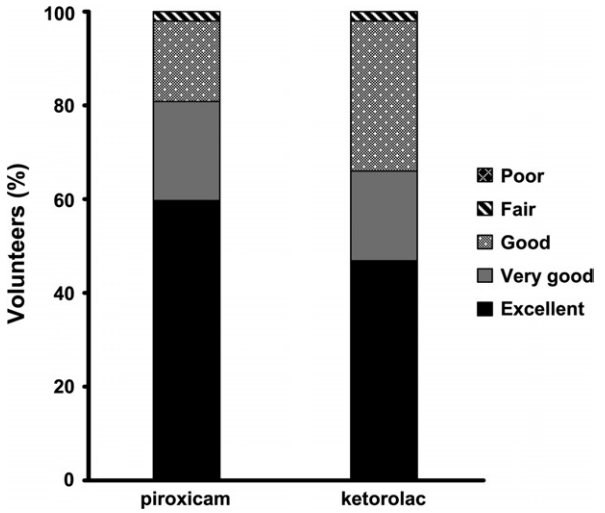

Fig. 2. Global evaluations of ketorolac's and piroxicam's efficacy during the seventh postoperative day was rated with the use of a 5-level Likert scale by volunteers (n = 47) who received sublingual ketorolac (10 mg 4 times daily) and sublingual piroxicam (20 mg once daily). The format of the Likert items was "excellent," "very good," "good," "fair," or "poor". The volunteers' ratings of each drug's efficacy during this postoperative period after lower third molar extraction were collated and represented by 2 bar charts, with or without osteotomy. Sublingual ketorolac and sublingual piroxicam were depicted as 2 separate datasets, and no significant differences were detected (Kruskal-Wallis 1-way analysis of variance: $P > .05$).

vestigate and compare the efficacy of either ketorolac or piroxicam sublingually to guarantee a painless postoperative period. Treating installed pain is markedly different from preventing the onset of pain. By preventing the onset of pain, one avoids the central sensitization of the involved pain pathways. An entirely different experimental protocol would be necessary to compare the onset of pain relief by ketorolac and piroxicam, because volunteers were still under the effects of local anesthesia from the surgery. As stated earlier, in the present study, volunteers were given ketorolac and piroxicam immediately after the end of surgery.[25] It was observed, however, that both NSAIDs were able to relieve pain before the effects of the local anesthetic dissipated.

Although various studies have investigated the efficacy of the more traditional NSAIDs administered orally, little clinical research has investigated the efficacy of NSAIDs administered sublingually. One goal of the present clinical study was to provide practitioners with information regarding another option for pain management. Although the protocol of this study did not allow the investigation of the onset of pain relief, the sublingual administration of a drug can relieve pain faster than orally administered pain medication. Additionally, from a practical standpoint, if a patient is experiencing nausea, a sublingual drug will not be regurgitated and rendered ineffective, unlike standard oral pain medication.

NSAIDs, including ketorolac and piroxicam, are not completely free from adverse effects. Some individuals, for example, exhibit allergic reactions to NSAIDs and the use of ketorolac and piroxicam as well as other NSAIDs is not recommended. Additionally, volunteers with an increased risk for hepatic failure,[31,32] peptic ulcers,[32] and gastrointestinal inflammation[32] should avoid using NSAIDs, including ketorolac and piroxicam. Ketorolac tromethamine has been reported to have a significant risk of adverse side effects. In a worldwide evaluation of ketorolac from 1990 to 1993, 97 deaths were associated with the use of ketorolac.[33] According to one datasheet for piroxicam "approximately 30% of all patients receiving daily doses of 20 mg of piroxicam experience[d] [adverse] side effects" and in some of these remote cases these side effects were severe enough to cause death.[32] Consequently, volunteers were excluded from this study if they had any history of allergic reactions to any drugs, including NSAIDs, gastrointestinal bleeding or ulcerations, or cardiovascular or hepatic diseases. In particular, the volunteers in this study experienced few adverse side effects with either sublingual ketorolac or sublingual piroxicam.

Previously, Trindade et al. found that both sublingual and oral piroxicam were able to successfully control postoperative pain prevention, trismus, and swelling.[22] In that study, 53 volunteers received piroxicam administered orally or sublingually immediately after lower third molar extraction, whereas in the present study 47 volunteers received ketorolac or piroxicam sublingually. Ketorolac sublingually and piroxicam orally or sublingually have similar clinical efficacy to control pain, trismus, and swelling after lower third molar surgery. In both studies, volunteers exhibited similar values for mouth opening measured just before surgery and immediately after suture removal 7 days later ($P > .05$). Also, the type of NSAID used or the route of administration used in the previous study[22] showed no significant differences between swellings on the second or seventh postoperative days ($P > .05$). In sum, pain, trismus, and swelling after lower third molar extraction, independent of surgical difficulty, could be successfully controlled by ketorolac administered sublingually (10 mg 4 times daily), piroxicam administered sublingually (20 mg once daily), or piroxicam administered orally (20 mg once daily), and no differences were observed between the route of delivery used in the previous study[22] and the type of NSAID used in the present study.

It was necessary to obtain consenting adults requiring bilateral third molar extraction meeting the eligibility criteria set forth in the protocol. With this aside, the subjects enrolled were a random sampling of visitors to our institution, which hopefully characterizes the population at large. As in most clinical studies, it was necessary to balance the available resources, such as volunteers, time, and cost, with obtaining a sample size big enough to both represent the population at large and have enough statistical power to detect a clinically significant difference. Therefore, the sample size used in this study was determined by similar previously published clinical studies and a balance of the available resources for this study.[3,4,20,22-25]

Additionally, a *post hoc* power analysis was performed investigating the likelihood that the lack of observed differences between ketorolac and piroxicam treatments was based on an actual parity rather than simply being underpowered. In particular, patients experiencing postoperative pain or chronic pain scoring <44 mm on a 100-mm VAS tend to describe pain as "mild" or report minimal impact of their pain on daily activities.[34] Therefore, it seems reasonable to assume an increase of 30 mm to be clinically significant, because this increase would approximately place one of the treatments above a pain scoring of 44 mm. A *post hoc* 2-tailed power analysis (G-Power 3.1.2), given an error probability of 0.05% with a sample size of 47 using a clinical difference in pain scores of 30 mm with an α level of 0.05 yields a power ($1 - \beta$) of 0.9794.[35] Also it should be noted that in the present study the use of multiple comparisons should also decrease the probability of a type II error.

This study confirmed the hypothesis that ketorolac and piroxicam would effectively control inflammation and postoperative pain after lower third molar extraction. The quantification of pain scores by VAS, the amount of rescue medication taken by volunteers, and the global evaluation of the drugs by the volunteers remained the same regardless of the NSAID used. In every parameter tested, when either ketorolac and piroxicam were administered sublingually no significant differences were observed.

CONCLUSION

The data from this study demonstrate that postoperative pain, trismus, and swelling in volunteers subjected to lower third molar extraction can be successfully controlled by either ketorolac or piroxicam, both administered sublingually. Additionally, in this study, volunteers experienced few adverse side effects with either sublingual ketorolac or sublingual piroxicam.

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