Int. J. Oral Maxillofac. Surg. 2011; 40: 292–297
doi:10.1016/j.ijom.2010.10.026, available online at http://www.sciencedirect.com

International Journal of Oral & Maxillofacial Surgery

Clinical Paper

Therapeutics

Comparison of oral versus sublingual piroxicam during postoperative pain management after lower third molar extraction

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Abstract. In this study, 53 patients received piroxicam, administered orally or sublingually, after undergoing removal of symmetrically positioned lower third molars, during two separate appointments. This study used a randomized, blind, cross-over protocol. Objective and subjective parameters were recorded for comparison of postoperative results for 7 days after surgery. Patients treated with oral or sublingual piroxicam reported low postoperative pain scores. The patients who received piroxicam orally took a similar average amount of analgesic rescue medication compared with patients who received piroxicam sublingually ($p > 0.05$). Patients exhibited similar values for mouth opening measured just before surgery and immediately following suture removal 7 days later ($p > 0.05$), and showed no significant differences between routes of piroxicam administration for swelling control during the second or seventh postoperative days ($p > 0.05$). In summary, pain, trismus and swelling after lower third molar extraction, independent of surgical difficulty, could be controlled by piroxicam 20 mg administered orally or sublingually and no significant differences were observed between the route of delivery used in this study.

Keywords: acute postoperative pain; cyclooxygenase inhibitors; lower third molar; nonsteroidal anti-inflammatory drugs; piroxicam; oral route; sublingual route.

Accepted for publication 29 October 2010
Available online 8 December 2010

Pain resulting from the trauma of lower third molar surgery has been studied extensively and has become an established model to evaluate the efficacy of many pharmacological analgesics. Frequently, this pain is moderate and temporary. Pain from lower third molar extraction reaches its maximum intensity 2–4 h after the end of surgery, and, in most cases, patients require analgesic treatment[26]. Besides pain, swelling and the limited articulation of the temporomandibular joint associated with inflammation, there are further undesirable consequences for patients who undergo surgical interventions in the oral cavity[6,11,37]. Treatment for pain, trismus and swelling after lower third molar surgery includes non-steroidal anti-inflammatory drugs (NSAIDs)[1,6,36,37]. Most NSAIDs function by inhibiting cyclooxygenase (COX) and thus, among other

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actions, ultimately result in an inhibition of prostaglandin production[15,17,25].

Three isoforms of COX are known. COX-1 is a constitutive form expressed in almost all tissues. COX-2, also known as prostaglandin-endoperoxide synthase 2 (PTGS2), is predominantly induced and constitutively expressed in a limited number of tissues (renal medulla, prostate, brain and endothelium)[15,17,22,25,32]. The isoenzyme COX-2 stimulates the synthesis of pro-inflammatory prostaglandins[6,15,25,37]. COX-3, a COX-1-derived protein, is most abundant in the cerebral cortex and heart[1,4,32]. COX-3 inhibition may represent the primary central mechanism by which NSAIDs such as acetaminophen and dipyrone decrease pain and possibly fever[4,8]. In accordance with their relative inhibition of COX isoenzymes, NSAIDs can be classified as nonselective, COX-2 preferential or COX-2 selective[7,31].

Numerous studies have evaluated the efficacy of the more traditional NSAIDs, including 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. NSAIDs were administered orally in all of these studies[1,5,6,9,20,24,25].

NSAIDs have also been administered sublingually. Sublingual administration of a drug can relieve pain faster than oral administration because this route avoids the first passage of the drug in the liver where some of the drug is metabolized. Sublingual administration of NSAIDs[18] may relieve pain faster than oral administration because the drug is absorbed by the veins in the floor of the mouth, leading directly to the superior vena cava, thus resulting in faster distribution of the drug to all tissues through the bloodstream. Drugs administered orally circulate through the bloodstream via the inferior vena cava, which takes longer to distribute the drug to all tissues compared with sublingual administration. Orally administered NSAIDs must pass through the caustic environment of the gastrointestinal tract; sublingual administration avoids the gastrointestinal tract.

Little clinical research has investigated the efficacy of administering the nonselective COX-2 inhibitor NSAID, piroxicam, to control pain, trismus and swelling resulting from the trauma of lower third molar surgery. This surgical procedure is a well accepted model used to evaluate the clinical efficacy of anesthetics and anti-inflammatory drugs[1,3,5]. When patients receive no analgesic medication they report a pain score of 80 on a visual analog scale (VAS) from 0 to 100 cm with zero representing 'no pain' and 100 representing 'the worst pain imaginable'[3,28]. It is necessary to manage pain for this surgery and this study did not use a placebo as a negative control.

The same surgical procedure was performed on both sides of the jaw on two separate occasions in the same patient, then each side of the jaw was compared with the other to avoid individual variations[12,21]. In this way each patient served as his or her own control. This study compared the clinical efficacy of piroxicam orally or sublingually in managing pain after lower third molar removal.

Materials and methods

The Institutional Ethics Committee approved the protocol of this study (#108/2007). All 53 study patients provided written informed consent during the pre-treatment screening period. Eligibility criteria included patients aged 18 years or older who had two lower third molars in a similar position as observed using panoramic radiography. Exclusion criteria included: systemic illness and inflammation or infection at the extraction sites; any history of allergic reaction to local anesthetic; gastrointestinal bleeding or ulceration; cardiovascular and hepatic diseases; and allergy to aspirin, piroxicam or any other NSAID. Pregnant women were excluded from the study. Instructions for not using antidepressants, diuretics, aspirin or antibiotics 7 days prior to surgery were given to the patients, avoiding possible hemorrhage or other possible unwanted interactions with the drugs used in this investigation[3,5,6,11,19,34].

This research was a randomized, blind, cross-over study. Only one side of the mandibular jaw was operated on at a time. The surgery was performed over the course of two visits separated by 1–2 months[3,5,6,11,19,34]. During each patient's first appointment he or she randomly received either piroxicam orally or sublingually for postoperative pain relief (a coin was flipped to determined the route of delivery). During the patient's second appointment, the route of administration not used previously was administered in a crossover manner. Each patient remained unaware of how piroxicam would be administered until after their first surgery was completed. The surgeon was blinded to the delivery route of piroxicam. The entire dataset was analyzed by a third researcher naive to how pain was managed for each molar extraction.

One surgeon performed all operations and postoperative controls. All patients received local anesthetic blockade of buccal, lingual and inferior alveolar nerves via 1.8 ml of 4% articaine with 1:200,000 adrenaline[34]. When anesthesia of the inferior lip was achieved, an additional 0.9 ml of the same anesthetic was injected into the mucosa to guarantee hemostasis and anesthesia of the site. The removal of every third molar followed a standard surgical protocol[34]. Immediately following the extraction, each surgical site was thoroughly irrigated, suctioned, sutured[6,11] and the patient was given piroxicam orally or sublingually by a second dentist. Patients remained in the clinic for the first postoperative hour. During this time the local anesthetic blockade was still present. The aim of this study was to investigate and compare the efficacy of piroxicam administered orally or 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 piroxicam administered orally or sublingually.

Each patient experienced approximately the same magnitude of surgical trauma on each side of the mandibular jaw. The surgical trauma varied, however, with some patients requiring osteotomy during both surgeries. The study patients were subdivided into those who received osteotomy and those who did not.

The NSAID administration protocol was one 20 mg capsule of piroxicam taken orally or one 20 mg tablet of fast-dissolving dosage form piroxicam taken sublingually once daily for 4 days. Previous studies have shown that 20 mg of piroxicam effectively manages postoperative pain with few or no side effects[3,14,18,29,30,33,35]; whereas piroxicam doses less than 20 mg (e.g. 5 mg or 10 mg) were ineffective in managing postoperative pain[14]. Oral rescue analgesic medication was available to any patient as needed throughout the study; for this purpose, 750 mg tablets of paracetamol were provided to all patients[3,5,6,11,19,34]. Patients recorded the date and time at which rescue medication was consumed. They were instructed not to interrupt the use of the principal medication, even if they had consumed rescue analgesic medication.

Duration of surgery (min) after anesthetic administration, specifically, the period between the first incision and the last suture was recorded[6,11,37]. Subjective postoperative pain evaluations were documented, with the aid of a 100 mm VAS[6,11,13]. The intensity of postoperative pain was chronicled at 15-min intervals for

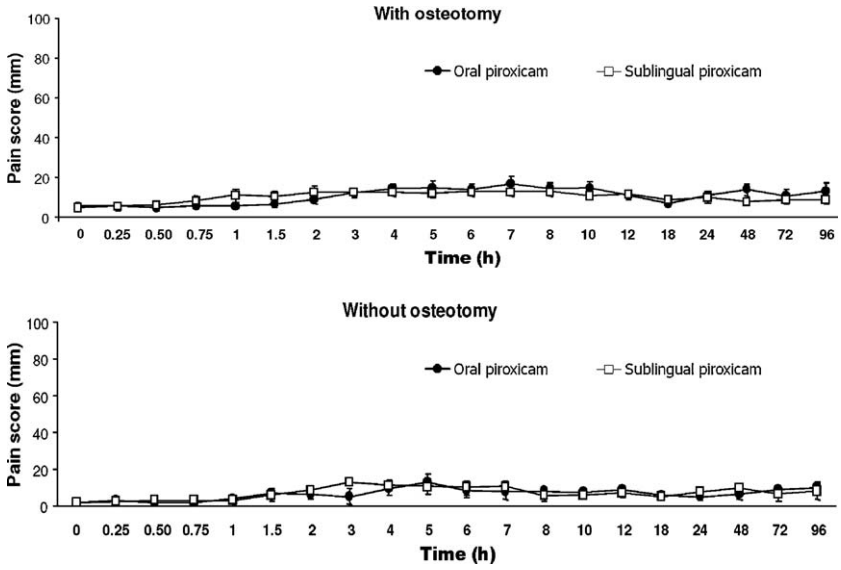

Fig. 1. Mean pain scores (in mm) recorded by patients ($n = 21$ without osteotomy and $n = 32$ with osteotomy), with the aid of a 100 mm VAS at 0.25, 0.50, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 10, 12, 16, 24, 48, 72 and 96 h after the end of surgery for lower third molar extraction. Two administration routes of 20 mg of piroxicam, oral or sublingual, for 4 postoperative days, were used in a randomized, blind, crossover manner. Data are represented as means ± 1 SEM.

the first 60 postoperative minutes, and 1.5, 2, 3, 4, 5, 6, 7, 8, 10, 12, 16, 24, 48, 72 and 96 h after the end of the surgery as evaluated by the patients[3,5,10,11,19,34]. Time (h) to first rescue analgesic medication and total amount (mg) of rescue analgesic medication ingested during the postoperative period were documented by each patient. Mouth opening (distance in mm) between the mesial–incisal corners of the upper and lower right central incisors at maximum opening of the jaws was measured and recorded before 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[11,37]. Facial swelling was measured and recorded during the second and seventh postoperative days[37]. This produced a single value for each patient, which is 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 three measurements was considered the baseline value. The difference between the sum of the postoperative measurements and the baseline value indicated the facial swelling for that day. Incidence, type and severity of adverse reactions (gastrointestinal irritation, nausea, vomiting, bleeding, allergy, headache, dizziness, sleepiness and any other kind of reaction) were documented by each patient[13]. Global evaluations of piroxicam's efficacy during the seventh postoperative day were rated using a five level Likert scale by volunteers who received sublingual and oral piroxicam (20 mg). The format of the Likert items was: excellent, very good, good, fair or poor[23].

Paired *t*-tests were used to compare the duration of the entire surgeries. The nonparametric Wilcoxon test was employed to assess the parameters 'postoperative pain' and 'rescue analgesic medication'. Data regarding 'mouth opening' and 'facial swelling' were tested and confirmed for normal distribution and the values were compared using an ANOVA followed by Tukey's test for multiple comparisons. Statistical significance was set at $p < 0.05$. Data are represented as a mean ± standard error of the mean.

Results

There were 53 volunteers (15 male and 38 female, mean age 22 years) in this study. The participants were also subdivided into two subgroups: 21 patients without osteotomy and 32 with osteotomy. Surgery requiring osteotomy lasted 20.61 ± 1.49 min and 17.41 ± 1.48 min for patients taking piroxicam orally and sublingually, respectively, and for patients not requiring osteotomy the surgery lasted 10.05 ± 0.39 min and 9.95 ± 0.29 min, for the same groups, respectively. No significant differences in the mean duration of the two surgeries in each patient were observed ($p > 0.05$). There was a significant difference in the mean duration of operations performed with and without bone removal ($p < 0.05$), indicating that surgery involving the more time consuming osteotomy was more aggressive. Overall the duration of surgery was short.

In the postoperative pain scores, documented by each patient, no significant differences were observed between the two routes of piroxicam administration ($p > 0.05$) (Fig. 1). All scores of pain recorded in both studies were small.

The amount of analgesic rescue medication taken by patients was small and no differences were observed between patients given piroxicam orally or sublingually, irrespective of the necessity for bone removal (Table 1). There was no significant difference in the time of ingestion of the first rescue medication when patients were medicated with piroxicam either orally or sublingually, in both subgroups ($p > 0.05$, Table 1).

There was only a major limitation of the patients' mouth opening during the second day. During the seventh day following surgery, the values for mouth opening measurements returned to baseline values ($p > 0.05$, Table 2). Similar mouth openings were recorded during the second and

Table 1. Consumption of rescue analgesic medication (paracetamol) recorded for comparison of postoperative courses after removal of lower third molars.

	Total amount of rescue medication (mg)		Time to first rescue medication (h)	
	With osteotomy	Without osteotomy	With osteotomy	Without osteotomy
Oral piroxicam	1,928.57 ± 355.61	892.86 ± 270.20	12.08 ± 6.03	3.34 ± 1.67
Sublingual piroxicam	1,750.00 ± 312.71	607.14 ± 179.42	12.85 ± 3.83	9.78 ± 4.90

No significant differences were found between piroxicam administered orally and sublingually ($p > 0.05$).

Table 2. Mouth opening and swelling recorded for comparison of postoperative courses after lower third molar extraction.

	Mouth opening (%, 2nd postoperative day)		Mouth opening (%, 7th postoperative day)		Swelling (mm, 2nd postoperative day)		Swelling (mm, 7th postoperative day)	
	With osteotomy	Without osteotomy	With osteotomy	Without osteotomy	With osteotomy	Without osteotomy	With osteotomy	Without osteotomy
Oral piroxicam	74.17 ± 4.58	79.92 ± 4.44	91.53 ± 4.39	96.90 ± 2.22	33.86 ± 5.93	16.19 ± 5.86	6.24 ± 4.34	−3.62 ± 9.05
Sublingual piroxicam	74.57 ± 4.17	79.93 ± 4.22	92.34 ± 2.70	96.89 ± 2.33	30.24 ± 8.45	21.00 ± 8.24	7.05 ± 7.21	−2.52 ± 5.24

No significant differences were found between piroxicam administered orally and sublingually ($p > 0.05$).

seventh postoperative days between the preoperative measurements for patients taking either oral piroxicam or sublingual piroxicam. No significant differences in the mouth opening parameters were observed between the groups with and without osteotomy.

A similar result was observed for the values taken for swelling during the second and seventh day after surgery. Patients showed no significant differences between the groups. Swelling tended to be increased during the second day, but returned to baseline measurements during the seventh day ($p > 0.05$, Table 2); this increase in swelling was not statistically significant and was the same regardless of the drug delivery route.

Six patients had gastric discomfort when oral piroxicam was used and one patient had gastric discomfort with sublingual piroxicam. Two patients noted sleepiness with oral piroxicam and two with sublingual piroxicam.

According to the patients' global evaluations of their postoperative period piroxicam administered by either route was classified as good, very good and excellent for most patients. Four patients who took oral piroxicam and two patients who took piroxicam sublingually classified the period as fair when osteotomy was necessary and one patient, in the same subgroup, who took oral piroxicam, classified the period as poor (Fig. 2).

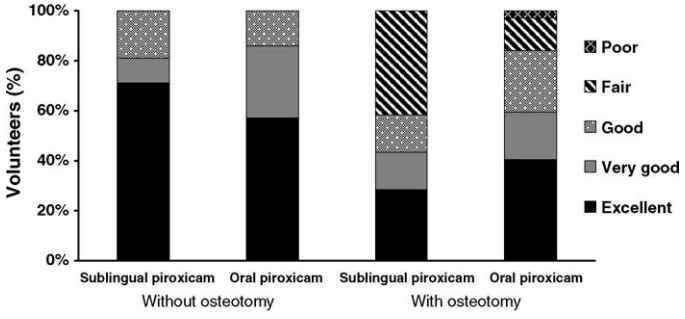

Fig. 2. Global evaluations of piroxicam's efficacy during the seventh postoperative day were rated using a five level Likert scale by volunteers ($n = 53$) who received sublingual and oral piroxicam (20 mg). The format of the Likert items was: excellent, very good, good, fair or poor. The patients' ratings of piroxicam's efficacy during this postoperative period after lower third molar extraction were collated and represented by two bar charts, with and without osteotomy. Sublingual piroxicam and oral piroxicam were depicted as two separate datasets.

Discussion

This study investigated the clinical efficacy of the NSAID, piroxicam, which was administered either orally or 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 patients, and depended 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 patient was not significantly different but there was a difference between those who received osteotomy and those who did not. The establishment of two subgroups (with or without osteotomy) assured that the sole variable in this study would be the route of drug delivery. This allowed the comparison of the efficacy of each delivery route for managing postoperative pain, trismus and swelling.

The method employed in this study to measure swelling is widely accepted in the literature[18,37]. The benefits of this method lie in its simplicity. It is non-invasive, cost effective, timesaving, and provides numeric data for the determination of soft-tissue contour changes. The results of this protocol showed changes in facial soft-tissue contours during the second and seventh postoperative days corroborating the results observed by Calvo et al.[5] (meloxicam) and Graziani et al.[18] (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 lower than baseline values. These findings could be because patients lost weight during the postoperative period, causing changes in facial soft-tissue contours, or due to the fact that the method employed is not as accurate as a computed tomography scan or magnetic resonance imaging for precise measurement of facial soft volume.

Mouth opening (closely related to swelling) in the two postoperative periods was the same among all groups. These data are in agreement with other studies that used other NSAIDs[5,6,11,18], which showed the effectiveness of NSAIDs in controlling pain, swelling and trismus after lower third molar extraction.

In this study, the route of NSAID delivery was not related to the efficacy of piroxicam on the management of postoperative pain, trismus and swelling when the lower third molar was extracted. In theory, sublingual administration should have had a significantly faster onset of action compared with oral administration. In a different experimental protocol this could improve pain relief in the postoperative period, yet in the present study it was not possible, nor was it the aim, to compare the onset of pain relief by piroxicam since patients were still under the effects of local anesthesia from the surgery. Patients were given piroxicam immediately following the end of surgery[34]. Both delivery methods used in this study relieved pain before the effects of the local anesthetic dissipated.

NSAIDs including piroxicam are not completely free of adverse effects. Some individuals exhibit allergic reactions to NSAIDs. Patients with an increased risk for hepatic failure[16,27], peptic ulcers[16], and gastrointestinal inflammation[16] should

avoid using NSAIDs, including piroxicam. According to one datasheet for piroxicam 'approximately 30% of all patients receiving daily doses of 20 mg of piroxicam experience[d] [adverse] side effects', the most common side effects were typically mild including: abdominal discomfort (6%), flatulence (5%), nausea (5%), abdominal pain (5%), epigastric distress (5%), constipation (4%), and diarrhea (3%)[16]. Some of the more rare side effects such as gastrointestinal bleeding (0.1%) and peptic ulceration (2%) are more dangerous, and in some of these remote cases these side effects were severe enough to cause death[16]. Consequently, patients were excluded from this study if they had a history of: allergic reactions to any analgesic drugs including NSAIDs; gastrointestinal bleeding or ulcerations; or cardiovascular or hepatic diseases.

There are conflicting statements about the adverse side effects of 20 mg of oral piroxicam. Barroso et al. reported a significant increase in the number of patients who reported adverse side effects when they received 20 mg of oral piroxicam daily for 4 days compared with oral Rheumazin® (10 mg piroxicam, 1 mg dexamethasone, 35 mg orphenadrine citrate, 2.5 mg cyanocobalamin)[2]. In this case there were 10 reports of adverse side effects in the 41 patients tested with 20 mg of piroxicam. Ohnishi et al. reported few adverse side effects[30]. Specifically, when patients received 20 mg of oral piroxicam daily for 5 days only 4 of 84 patients experienced adverse side effects and none were 'serious or unusual'[30]. Desjardins[14] evaluated the incidence of the adverse effects of piroxicam in 798 patients from 5 studies and concluded that 'a wide range of piroxicam doses are safe when administered in single doses for the treatment of acute dental pain'.

This study confirmed the hypothesis that piroxicam administered orally or sublingually would effectively control inflammation and the onset of pain after lower third molar removal. The quantification of pain scores by VAS, the amount of rescue medication taken by patients and the global evaluation of the drug by the patients remained the same regardless of the route of delivery of piroxicam. In every parameter tested, when piroxicam was administered orally or sublingually no significant differences were observed.

In conclusion, postoperative pain, trismus and swelling in patients subjected to lower third molar extraction can be controlled successfully by 20 mg of piroxicam administered either orally or sublingually.

Funding

Sources of support: Paulo Alceu Kiemle Trindade, Adriana Maria Calvo, Débora Amgarten Ribeiro and Daniel Thomas Brozoski were supported by fellowships from FAPESP (2006/56215-1, 2005/53354-8, 2008/04357-2 and 2009/15372-5, respectively).

Competing interests

None declared.

Ethical approval

The Ethics Committee of the Bauru School of Dentistry, University of São Paulo approved the protocol of this study (#108/2007).

Acknowledgement. The authors would like to thank Vera Lúcia Rufino for her excellent secretarial assistance.

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