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Analgesic and anti-inflammatory dose–response relationship of 7.5 and 15 mg meloxicam after lower third molar removal: a double-blind, randomized, crossover study

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Abstract. Fifty patients were scheduled to undergo removal of symmetrically positioned lower third molars in two separate appointments. Meloxicam 7.5 or 15 mg was once daily administered in a double-blind, randomized and crossover manner after the surgery for 4 days. Objective and subjective parameters were recorded for comparison of postoperative courses. Patients treated with 7.5 mg meloxicam who underwent osteotomy reported higher pain scores at 1.5, 3, 4, 10, 12 and 16 h ($P < 0.05$) and ingested a greater amount of rescue analgesic medication ($P < 0.05$) than those who did not require osteotomy. A higher percentage of patients who underwent osteotomy medicated with 7.5 mg meloxicam needed rescue medication as compared to those who did not require osteotomy ($P < 0.05$). There was a similar mouth opening at suture removal compared with preoperative values for both doses ($P > 0.05$). There were no significant differences concerning swelling observed on the 2nd or 7th postoperative days in comparison with baseline ($P > 0.05$) between the two doses. Pain, trismus and swelling after lower third molar removal not requiring osteotomy can be successfully controlled by a dose regimen of 7.5 mg meloxicam once daily. For more aggressive extractions 15 mg meloxicam is advisable.

Key words: acute postoperative pain; cyclooxygenase inhibitors; lower third molar; non-steroidal anti-inflammatory drugs; meloxicam.

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Pain as a consequence of lower third molar surgery has been extensively studied and has become a model to evaluate the efficacy of many pharmacological therapeutic approaches. Frequently, this is a short-lasting and moderate pain, reaching its maximum intensity in a short period of time after the end of surgery, and in most of the cases patients require some kind of analgesic to treat it²⁴. Besides pain, swelling and mouth-opening limitation associated with the inflammatory response, there are undesirable consequences for patients who undergo surgical interventions in the oral cavity^{8,13,31}.

For pain, trismus and swelling control after lower third molar surgery, several non-steroidal anti-inflammatory drugs (NSAIDs) have been used^{3,8,30,31}. These medications have their therapeutic effect by means of the inhibition of cyclooxygenase (COX), which determines an inhibition of prostaglandin production^{15,18,23}. Three isoforms of COX are known: COX-1, a constitutive form expressed in almost all tissues, COX-2, predominantly induced and constitutively expressed in a limited number of tissues (renal medulla, prostate, brain and endothelium)^{15,18,20,23,27}, and COX-3, a COX-1-derived protein, most abundant in the cerebral cortex and heart^{5,11}. It is believed that COX-2 is the main isoenzyme for pro-inflammatory prostaglandin production^{8,31,15,23}, and that the inhibition of COX-3 could represent a primary central mechanism by which NSAIDs like acetaminophen and dipyron decrease pain and possibly fever^{5,11}.

According to their relative inhibition of COX isoenzymes, NSAIDs can be classified as non-selective, COX-2 preferential or COX-2 selective^{10,26}. Meloxicam is a NSAID of the acidic enolic class that preferentially inhibits the inducible COX-2 and shows a weaker influence on constitutive COX-1^{10,16,17}; it is thus largely used for treatment of acute and chronic painful, inflammatory and degenerative disorders^{16,25,32}. In dentistry, there are few studies concerning the use of meloxicam^{1,4,6,9,10,25}, and none of them assessed pain control in dental surgeries with postoperative administration of this agent. Such an assessment is important because it is likely that both the composition of peripheral inflammatory mediators and the central and peripheral mechanisms of hyperalgesia are different in models of acute surgical pain compared to endodontic²⁵ and periodontal disease^{4,6,9,10} or chronic painful disorders^{16,25,32}.

The aim of this work was to compare the efficacy of two doses of meloxicam, 7.5 and 15 mg, administered once daily for 4

days, in pain, trismus and swelling control after lower third molar removal. The experimental model of surgical removal of symmetrically impacted lower third molars was used^{8,13}.

Material and methods

The institutional Ethics Committee approved the protocol of this study (#68/2005). All patients provided written informed consent during the pre-treatment screening period. The study population comprised 50 patients aged 18 years or over, with the two lower third molars in a similar position as observed on panoramic radiography. Eligibility criteria included absence of systemic illness and inflammation or infection at the extraction sites. Exclusion criteria included any history of allergic reaction to local anaesthetic, gastrointestinal bleeding or ulceration, cardiovascular and kidney diseases, and allergy to aspirin, meloxicam or any other NSAID. Pregnant women were also excluded from the study. Instructions for not using antidepressants, diuretics or aspirin in the days previous to surgery were given to the patients, since these drugs could cause haemorrhage or other blood problems, and interfere with the results of this investigation^{8,13}.

This was a double-blind study; that is, neither the surgeon nor the patients were aware of the dose of meloxicam (7.5 or 15 mg) being prescribed postoperatively at the two different appointments. Each patient required surgical treatment with the same magnitude of trauma on opposite sides of the mandibular jaw, which was performed in two visits 1–2 months apart^{8,13}. For postoperative pain relief, at the first appointment the patients randomly received either 7.5 or 15 mg meloxicam. At the second appointment, the dose not used previously was then administered in a crossover manner. One surgeon performed all operations and postoperative controls. The patients received a regional anaesthetic blockade of buccal, lingual and inferior alveolar nerves with 1.8 mL of 4% articaine with 1:100,000 adrenaline¹³. When anaesthesia of the inferior lip was achieved, an additional 0.9 mL of the same anaesthetic was infiltrated into the mucosa to guarantee homeostasis and anaesthesia of the site. The removal of third molars followed a standard surgical technique. Upon completion, the surgical sites were thoroughly irrigated, suctioned and sutured^{8,13}. Patients remained in the clinic for the first postoperative hour.

The NSAID administration protocol was 7.5 or 15 mg meloxicam once daily

for 4 days. Rescue analgesic medication was available to any patient as needed throughout the study; for this purpose, 750 mg paracetamol was provided to all patients^{8,13}. Patients recorded the date and time at which rescue medication was taken. They were also instructed not to interrupt the use of meloxicam, even if they had taken rescue analgesic medication. When bone tissue removal was necessary, 500 mg amoxicillin was prescribed every 8 h (tid), for 7 days to prevent infection^{8,13}.

The following parameters were assessed:

- duration of the surgery after anesthetic administration (in minutes), which corresponded to the period between the first incision and the last suture^{8,13,31};
- subjective postoperative pain evaluation, with the aid of a 100-mm-long visual analogue scale (VAS), with 0 anchored by 'no pain' and 100 anchored by 'worst pain imaginable'^{8,13,14}; subjects recorded the intensity of postoperative pain at 15-min intervals for the first 60 postoperative minutes, and 1.5, 2, 3, 4, 5, 6, 7, 8, 10, 12, 16, 24^{12,14}, 48, 72 and 96 h after the end of the surgery;
- 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, 2nd postoperative day and at the moment of suture removal (7th postoperative day); the postoperative ability to open the mouth was expressed as a percentage of preoperative measure^{13,31};
- time to first rescue analgesic medication, total amount of rescue analgesic medication (in mg) ingested during the postoperative period and percentage of patients who needed rescue medication;
- facial swelling determined by tape measuring on the 2nd and 7th postoperative days³¹; this method takes into account the sum of the following measures: distance between lateral corner of the eye and angle of the mandible, distance between tragus and outer corner of the mouth, and distance between tragus and soft tissue pogonion; the preoperative sum of the 3 measurements was considered as the baseline for that side; the difference between each postoperative measurement and the baseline 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)¹⁴;

- systolic, diastolic and mean arterial pressure, heart rate and oxygen saturation before and during the surgery, and after suture. During the surgery, measurements were made right after the regional anaesthetic blockade, and every 3 min. All the measurements were automated and non-invasive, performed with the aid of an equipment for monitoring haemodynamic parameters (Monitoring System, DX2010 model, Dixtal Biomédica Ind. e Com. Ltda, Marília/SP, Brazil).

Paired *t*-test was used to compare duration of surgeries. Non-parametric Wilcoxon test was employed to assess the parameters 'rescue analgesic medication' and 'postoperative pain'. Data regarding 'mouth opening', 'facial swelling' and 'haemodynamic parameters' were submitted to statistical analysis using

ANOVA followed by Tukey test for multiple comparisons. Statistical significance was established at 5%. The results were presented as the mean ± standard error of mean (SEM).

Results

Initially, 50 patients were operated on. One patient was excluded from the study because he underwent 2 surgical procedures of different degrees of difficulty (with and without osteotomy), despite the fact that both lower third molars were radiographically in a similar position. The final assessment was thus restricted to the data of 49 patients (11 males and 38 females, mean age 22.8 years), who were divided into two categories: surgeries requiring osteotomy (29 patients), and surgeries not requiring osteotomy (20 patients).

The surgeries requiring osteotomy lasted 20.75 ± 1.83 min and 19.52 ± 1.36 min for patients taking 7.5 and 15 mg meloxicam, respectively.

Those not requiring osteotomy lasted 11.48 ± 0.62 min and 10.81 ± 0.69 min for patients taking 7.5 and 15 mg meloxicam, respectively. No statistically significant difference in the mean duration of the two surgeries in each patient was observed (*P* > 0.05). There was a statistically significant difference in the mean duration of operations performed with and without bone removal (*P* < 0.05), indicating that those involving osteotomy were more aggressive.

According to the patients' evaluation on VAS, the reported pain scores were low. Meloxicam 7.5 and 15 mg provided a sustained level of analgesia after lower third molar removal without bone removal (*P* > 0.05). The analgesic efficacy of 7.5 mg meloxicam was dependent on the magnitude of the surgical trauma; patients who underwent bone removal reported higher scores of pain at 1.5, 3, 4, 10, 12 and 16 postoperative hours (*P* < 0.05) than those whose surgeries did not require

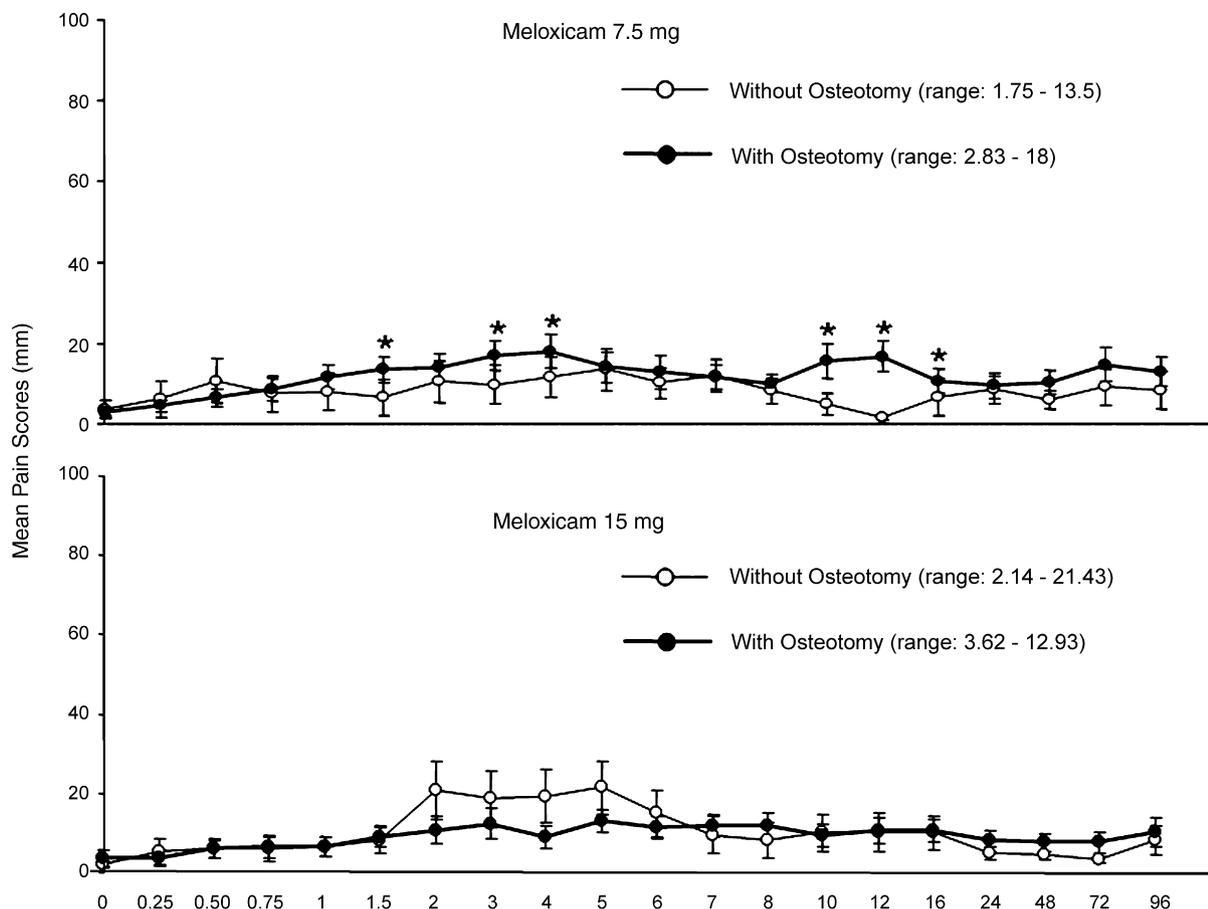


Fig. 1. Mean pain scores (in mm) recorded by patients (*n* = 49), with the aid of a 100-mm length VAS, at 0, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 10, 12, 16, 24, 48, 72 and 96 h after the end of the surgery for removal of lower third molar. Two doses of meloxicam, 7.5 or 15 mg, once daily for 4 postoperative days, were used in a double-blind, randomized and crossover manner. Data are the means ± SEM; (*) statistically significant difference (*P* < 0.05) between 7.5 and 15 mg meloxicam for the same postoperative period.

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

| | 7.5 mg meloxicam | | 15 mg meloxicam | |
|---|-------------------|-------------------|------------------|-------------------|
| | With osteotomy | Without osteotomy | With osteotomy | Without osteotomy |
| Patients taking rescue medication [n (%)] | 22 (75.86)* | 10 (50.00) | 16 (55.17) | 10 (50.00) |
| Time to first rescue medication (h) | 9.48 ± 4.22 | 5.23 ± 2.20 | 12.27 ± 6.38 | 11.14 ± 3.80 |
| Total amount of rescue medication (mg) | 1700.00 ± 300.00* | 825.00 ± 254.62 | 1137.93 ± 240.13 | 1285.71 ± 359.10 |

Data are mean ± SEM ($n = 49$).

*Statistically significant difference ($P < 0.05$) between 'with osteotomy' and 'without osteotomy' patients for 7.5 mg meloxicam.

osteotomy. In contrast, a sustained level of analgesia was provided by 15 mg meloxicam after all operations, regardless of the magnitude of trauma ($P > 0.05$) (Fig. 1).

The percentage of patients taking rescue analgesic medication was not the same in all groups. A higher percentage of patients who underwent osteotomy medicated with 7.5 mg meloxicam needed rescue analgesic medication than those who did not undergo osteotomy and were medicated with the same dose ($P < 0.05$, Table 1). There was no significant difference in the time to ingestion of the first rescue medication when patients were medicated either with 7.5 or 15 mg meloxicam ($P > 0.05$, Table 1). The total amount of rescue analgesic medication in the 7.5 mg meloxicam group was significantly lower for patients who underwent surgeries without osteotomy than for those whose surgeries were performed with osteotomy ($P < 0.05$, Table 1). This difference was not observed for patients treated with 15 mg meloxicam, irrespective of the necessity of bone removal ($P > 0.05$, Table 1).

There was similar mouth opening on the 2nd and 7th postoperative days compared with the preoperative measures for patients taking 7.5 or 15 mg meloxicam in both categories ($P > 0.05$, Table 2). There were no significant differences concerning the swelling observed on the 2nd and 7th postoperative days in comparison with baseline measures for patients treated with both doses of meloxicam when surgeries were performed with or without osteotomy ($P > 0.05$, Table 2). No adverse reactions to both doses of the NSAID were observed. Regarding haemodynamic parameters, there was no statis-

tically significant difference in blood pressure, heart rate and oxygen saturation before and during the surgery, and also after suture (data not shown).

Discussion

This study evaluated the clinical efficacy of oral 7.5 or 15 mg meloxicam in patients after lower third molar removal under local anaesthesia. To the best of the authors' knowledge, it is the first study focusing on analgesic and anti-inflammatory efficacy of meloxicam administered postoperatively in this model, so that comparison with other reports may be difficult.

The degree of difficulty of the surgical procedure and the trauma locally caused varied among the patients depending on whether it was necessary to remove bone tissue to extract the lower third molars. The establishment of two categories (with or without osteotomy) guaranteed that the sole variable in each category would be the dose of anti-inflammatory agent used after surgery (7.5 or 15 mg meloxicam). This allowed the comparison of the efficacy of the two doses for postoperative pain, trismus and swelling control.

According to the VAS, 7.5 mg meloxicam proved statistically less effective than 15 mg meloxicam for pain control during the first postoperative hours (Fig. 1). It should be noted that using a VAS for pain evaluation alone may not have significant clinical relevance, since pain scores for both postoperative periods, whether the patient was subjected to osteotomy or not, were very low (less than 30 mm on a 100-mm VAS). Although the ideal goal remains to eliminate pain completely, postoperative pain scores that are

rated as less than 40 (on a 100-mm VAS) are likely to be considered satisfactory by the majority of individuals²¹. Patients experiencing postoperative or chronic pain scoring less than 44 mm on a 100-mm VAS tend to describe their pain as 'mild' or report minimal impact of their pain on daily activities²¹.

The amount of rescue analgesic medication used may reflect, at least in part, a relative dissatisfaction with the study medication²¹. The higher percentage of patients taking rescue analgesic medication and the greater total amount of rescue medication taken by patients who underwent surgery with osteotomy medicated with 7.5 mg meloxicam corroborates the lack of efficacy of this dose in more aggressive procedures when compared to 15 mg meloxicam. In contrast, DREISER et al.¹⁶ found no difference in mean daily paracetamol consumption and in the number of patients who took paracetamol as rescue medication when they were treated with 7.5 and 15 mg meloxicam for acute sciatica.

With regard to mouth opening in the two preoperative periods, the results showed that there was no statistically significant difference, which demonstrates that all patients recovered totally after the first surgery, irrespective of the dose of meloxicam employed (data not shown). Additionally, there was no statistically significant difference regarding mouth-opening limitation at the moment of suture removal (Table 2). These results are in agreement with those of other studies on other NSAIDs^{8,13} or steroids³¹.

Various methods have been used to measure facial swelling. The method employed in our study is non-invasive,

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

| | 7.5 mg meloxicam | | 15 mg meloxicam | |
|------------------------------------|------------------|-------------------|-----------------|-------------------|
| | With osteotomy | Without osteotomy | With osteotomy | Without osteotomy |
| Mouth opening (%; 2nd postop. day) | 67.27 ± 3.48 | 66.30 ± 3.88 | 69.38 ± 3.37 | 67.83 ± 5.25 |
| Mouth opening (%; 7th postop. day) | 89.11 ± 3.70 | 92.41 ± 3.76 | 93.04 ± 2.99 | 93.03 ± 3.96 |
| Swelling (mm; 2nd postop. day) | 6.94 ± 2.91 | 3.30 ± 3.91 | 6.46 ± 3.00 | 6.48 ± 4.29 |
| Swelling (mm; 7th postop. day) | -0.60 ± 0.23 | -0.10 ± 3.86 | -0.54 ± 3.14 | -1.46 ± 3.66 |

Data are mean ± SEM ($n = 49$).

simple, cost effective and timesaving, and provides numeric data for determination of soft-tissue contour changes. The measurements of facial swelling taken in the study by ÜSTÜN et al.³¹, who prescribed two different doses of a corticosteroid for swelling control, are very similar to the present data on the 2nd postoperative day (around 7 mm). Corticosteroids are well known as potent and widely used drugs to decrease the swelling related to third molar surgery³¹. GRAZIANI et al.¹⁹ also found very similar results on the 2nd postoperative day when patients were medicated with another NSAID (piroxicam). On the 7th postoperative day, for both groups the magnitude of swelling was far less than that observed on the 2nd 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.

Some consideration of the use of antibiotics in this work is necessary. The literature contains arguments for and against the use of routine antibiotic prophylaxis in third molar surgery and the main source of controversy is the lack of reliable and sensitive clinical criteria for identifying postoperative infection in these patients⁷. PETERSON'S criterion for antibiotic use is that the surgical procedure should have a significant risk of infection²⁸. Undoubtedly, amoxicillin, like every other antibiotic, has no direct influence on the control of pain, swelling or postoperative trismus, but it seems that preventing postoperative infection may have an indirect influence on these parameters. Operative field infection in this area may lead to transmission of the infection to the submandibular space leading to the inflammatory infiltration of an attachment of the masseter and the medial pterygoid, which leads to trismus. Similarly, perimandibular inflammatory infiltration associated with bacterial infection during surgery may also contribute to the appearance of swelling. It could be argued that using antibiotic in one group and not using it in the second one, and then comparing the parameters of these groups may have led to some adulteration of the results. There have also been reports published that specific postoperative oral prophylactic antibiotic treatment after the removal of lower third molars does not contribute to better wound healing, less pain or increased mouth opening^{2,7,22,29,33}. This

is supportive of the present results regarding pain, swelling and trismus not being affected by the prescription of amoxicillin to those patients who underwent bone removal. Another point that needs to be addressed is the regimen used of antibiotic medication for 7 days in this and a previous study¹³. This is at odds with the application of preoperative antibiotic therapy as a single dose²² and longer than other regimens of antibiotic use for 4^{2,7} or 5²⁹ postoperative days. In future studies, account will be taken of all the above facts, since there is no justification for routine use of antibiotics after removal of uninfected lower third molars^{2,7,22,29,33}.

Considering that meloxicam is classified as a COX-2 preferential drug, it is often well tolerated for acute or chronic use by patients with complaint pain^{25,32}, despite the loss of its COX-1-sparing effect with increasing doses^{20,26}. Meloxicam doses > 15 mg/day have been associated with significantly more adverse events than doses of ≤15 mg/day without enough improvement in efficacy to justify the higher dose¹⁸. Besides, a decreased incidence of gastrointestinal adverse events, perforations, ulcerations and bleeding was observed for 7.5 and 15 mg meloxicam as compared with non-selective NSAIDs¹⁸. In the present study, no clinically significant adverse reaction could be observed for either dose of meloxicam. Although this NSAID was used for a short period of time, the absence of adverse reactions even for 15 mg meloxicam is in agreement with the findings of YOCUM et al.³², who reported that this drug did not demonstrate any dose-dependent increase in total adverse events when patients with osteoarthritis were chronically treated with 3.75, 7.5 and 15 mg/day.

In conclusion, postoperative pain, trismus and swelling in patients subjected to lower third molar removal not requiring osteotomy can be successfully controlled by a dose regimen of 7.5 mg meloxicam once daily. For more aggressive third molar extractions due to osteotomy, 15 mg meloxicam is advisable.

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