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Pre-emptive analgesic effect of lornoxicam in mandibular third molar surgery: a prospective, randomized, double-blind clinical trial

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Abstract. The aim of this study was to establish whether the pre-emptive use of lornoxicam (16 mg) in third molar surgery ensures successful postoperative analgesia and reduces rescue analgesic intake when compared to postoperative application, and in comparison with placebo. Ninety patients were split randomly into three groups: group A received lornoxicam 60 min before surgery and placebo 60 min after surgery; group B received placebo 60 min before surgery and lornoxicam 60 min after surgery; group C received placebo 60 min before surgery and placebo 60 min after surgery. Postoperative pain was recorded on a visual analogue scale and on a numerical rating scale at 1, 2, 4, 6, 8, 12, and 24 h after surgery. The patients recorded total dose of paracetamol intake during the 24 h after the procedure. The efficacy of postoperative analgesia was greater in lornoxicam groups when compared to the placebo group; there was no difference between the two lornoxicam groups (A and B). Patients in group C took their first rescue analgesic dose earlier after surgery than patients in the two lornoxicam groups. The average dose of paracetamol taken in group C was 1000 mg, while it was 500 mg in the lornoxicam groups.

Key words: third molar surgery; pain; analgesic; NSAID; lornoxicam..

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The extraction of third molars is one of the most common procedures performed by oral surgeons and represents a well understood model of pain in research aimed at establishing the efficacy of analgesic drugs in the treatment of acute pain.[1,2] The lower third molars are at least partially impacted. As a result, the procedure is considered to be surgically difficult and is associated with the risk of to pain, swelling, and trismus during the postoperative period.[3] In terms of perceived pain, the

first 12 h after the surgical extraction of an impacted lower third molar are considered the most unpleasant.[4] After this first 12-h period, the intensity of pain diminishes, and in the absence of postoperative complications the pain becomes minimal or is totally absent by the second postoperative day.[5] Pre-emptive analgesia in the preoperative period is a strategy used in the management of postoperative pain that may greatly impact the patient's perception of pain.[6,7]

The flow of nociceptive signals has a dual phase character during the perioperative period.[8–12] The first phase is directly related to the nociceptive stimulation that results from the injuries produced by the surgical procedure.[8–12] The second phase occurs during the postoperative period and is the direct result of the inflammatory responses associated with injury.[8–12] This second phase is also caused by changes in the nociceptive structures of the spinal cord that occur during the first phase.[8–12] The role of pre-emptive analgesia is to inhibit the first phase, while possibly protecting the central nervous system from the noxious stimulation occurring during the surgery itself.[8,10,12–14] The approach effectively leads to a limitation of the development of peripheral and central sensitization – the reasons for primary and secondary hyperalgesia.[8,10,12–14] Primary hyperalgesia refers to pain sensitivity in the surgical wound, while secondary hyperalgesia refers to pain sensitivity in the untouched surrounding tissues.[8,10,12–14] The clinical implication of pre-emptive analgesia in limiting the development of postoperative hypersensitivity may be a reduction in pain and need for rescue analgesics during the postoperative period.[10,13,15]

Different groups of medications are applied in clinical practice to induce a pre-emptive analgesia effect, among which are the non-steroidal anti-inflammatory drugs (NSAIDs). The main mechanism of action of the NSAIDs is the inhibition of cyclooxygenase activity and, as a result, the synthesis of prostaglandins, which have pro-pain and proinflammatory effects.[8,16]

Lornoxicam, one of the oxicam class of NSAIDs, has a beneficial pharmacodynamic profile ensuring safety for the patient that is strongly derived from its balanced effects on both cyclooxygenase 1 (COX-1) and cyclooxygenase 2 (COX-2).[17–20] Its other mechanism of action is through the inhibition of the production of interleukin 6, interleukin 1, tumour necrosis factor alpha, and induced nitric oxide synthase.[21,22] Research studies have concluded that a dose of 16 mg of lornoxicam in third molar surgery shows a comparable effect to 20 mg of morphine, as well as to 10 mg of ketorolac and 1000 mg of diflunisal.[23–25]

Research on the efficacy of lornoxicam in the area of third molar surgery is particularly scarce in the literature.[23–31] Additionally, the diverse and inconsistent methodologies of such research conducted in the field of oral surgery make it difficult to determine the impact of the drug on the nociception process in the perioperative period; thus it has not been possible to draw unambiguous conclusions on the subject of the efficacy of pre-emptive analgesia in oral surgery.[32–35]

In the face of this wide diversity in research on the efficacy of pre-emptive analgesia and because of the scarcity of studies on this subject in the oral surgery literature, further research on this subject is required.

The aim of this study was to determine whether it is more beneficial to use lornoxicam 16 mg oral in a pre-surgical approach (inhibition of the first phase of nociception) or in a post-surgical approach (inhibition of the second phase). It was sought to establish whether the pre-emptive use of lornoxicam ensures more successful postoperative analgesia and a reduction in total analgesic intake when compared to postoperative application, and in comparison with placebo.

Materials and methods

This prospective clinical study was conducted on a group of 90 patients referred to the department of oral surgery of the study institution for the surgical extraction of an impacted lower third molar for orthodontic indications. The necessary ethical approval was obtained prior to commencement of this study. Strict inclusion criteria based on clinical and radiological examinations were applied in this research. Patients undergoing the surgical extraction of a partially or totally impacted lower third molar (Pell and Gregory classification IIB or IIIB), with no associated inflammation of the tissue in its vicinity, were included. For selection, the patient had to be aged 18–50 years old and in general good health. Exclusion criteria were the following: hypersensitivity to paracetamol, lornoxicam, acetylsalicylic acid, or any other NSAID, lactose intolerance (placebo), pregnancy, lactation, and any analgesic intake in the 24 h immediately prior to the surgery.

Patients who met the study criteria were split randomly into three equal groups (30 patients in each): group A patients received an oral dose of 16 mg lornoxicam 60 min before surgery and an oral dose of placebo 60 min after surgery; group B patients received an oral dose of placebo 60 min before surgery and an oral dose of 16 mg lornoxicam 60 min after surgery; group C patients received an oral dose of placebo 60 min before surgery and an oral dose of placebo 60 min after surgery.

A sample size of 22 patients per group was calculated to be necessary to detect a strong effect using Cohen's approach[36]; an error of 0.05 and power of 80% was defined to calculate this sample size. Thirty patients were enrolled per group to take into account the possibility of any drop-outs.

Before entering the study, all patients received written consent forms outlining the subject matter and aims of the research. Neither the patient nor the oral surgeon was informed of the group assignment throughout the entire study process. To ensure allocation concealment, 90 identical non-transparent sequentially numbered envelopes were used; each contained a group number assigned previously using a random number generator. Identical unmarked capsules containing either 16 mg of lornoxicam or the same weight of placebo were administered. All capsules were prepared in a pharmaceutical laboratory and were placed in smaller envelopes with codes determining the sequencing of administration. Thus, each of the sequentially numbered envelopes contained two smaller envelopes as stated above.

Sixty minutes after the application of the pre-surgical randomly assigned drug, the patient underwent truncal block of the lingual and inferior alveolar nerves and buccal infiltrative anaesthesia with a total of 3.6 ml of 4% articaine hydrochloride with epinephrine (1:200,000). Fifteen minutes after the anaesthesia procedure, a triangular incision was performed and a mucoperiosteal flap was elevated on the buccal side. The bone covering the impacted tooth was removed with the use of a hand-piece and round bur, under copious water irrigation. After the impacted tooth had been extracted, the surgical wound was rinsed with sterile saline solution. Sutures were placed once proper haemostasis had been assured.

Sixty minutes after the completion of surgery, the patient received the post-surgical assigned drug and completed the study pain scales under the direction of an oral surgeon. In addition, each of the patients received four pills (500 mg of paracetamol each) as rescue analgesic. None of the patients was prescribed an antibiotic. The determination of pain was