Int. J. Oral Maxillofac. Surg. 2017; 46: 621–627
http://dx.doi.org/10.1016/j.ijom.2017.01.008, available online at http://www.sciencedirect.com

International Journal of Oral & Maxillofacial Surgery

Clinical Paper
Oral Surgery

Efficacy of oral diclofenac with or without codeine for pain control after invasive bilateral third molar extractions

P. Zupelari-Goncalves, G. M. Weckwerth, A. M. Calvo, L. F. Simoneti, T. J. Dionisio, D. T. Brozoski, E. A. Torres, J. R. P. Lauris, F. A. C. Faria, C. F. Santos

Bauru School of Dentistry, University of São Paulo, Bauru, São Paulo, Brazil

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Abstract. Postoperative pain and inflammation after oral surgery is mostly managed using non-steroidal anti-inflammatory drugs (NSAIDs). However, opioids combined with NSAIDs may improve pain management in patients, especially after traumatic oral surgery. Few studies have compared NSAIDs with and without opioid use after oral and maxillofacial surgery. This randomized, double-blind, cross-over study compared the clinical efficacy of either diclofenac (50 mg) and codeine (50 mg) or diclofenac alone (50 mg) for the management of postoperative pain after invasive third molar surgery. Volunteers ($n = 46$) who were scheduled to undergo the removal of symmetrically positioned lower third molars in two separate appointments were included. They reported significantly less postoperative pain at various time points within 24 h after surgery and also consumed significantly less rescue medication (paracetamol (acetaminophen)) throughout the study when they took diclofenac combined with codeine than when they took only diclofenac. In conclusion, oral diclofenac with codeine was more effective for managing postoperative pain than diclofenac without codeine. It was expected that patients taking two pain medications after surgery would generally have less pain than when taking only one of the two medications. The prospective cross-over design of the present work makes this study distinct from many others.

Key words: oral surgery; third molar; pain; diclofenac; codeine; NSAIDs; opioids.

Accepted for publication 9 January 2017
Available online 1 February 2017

Third molar surgery is the most common surgical procedure in dentistry. The third molars are often extracted prophylactically to avoid possible future complications and also for acute or chronic pericoronitis, cysts or tumours, periodontal problems, proximal carious lesions with the second molars, and root resorption of adjacent teeth.[1–3] One of the most widely accepted drug protocols involves the use of non-steroidal anti-inflammatory drugs (NSAIDs), which are the agents most

often used for the management of postoperative pain.[1,3–7] This class of drugs controls both pain and inflammation.[4,6–8] NSAIDs are easily accessed without a written prescription and are usually well tolerated physiologically. Furthermore, there is no real stigma attached to the use of NSAIDs, unlike other medications such as narcotics.

NSAIDs exert their therapeutic effects through the inhibition of cyclooxygenase (COX), which results in the inhibition of prostaglandin production.[9,10] Traditional anti-inflammatory drugs such as diclofenac, ibuprofen, and piroxicam significantly decrease cyclooxygenase 1 (COX-1) and cyclooxygenase 2 (COX-2). Consequently, these inhibitors produce analgesic, anti-inflammatory, and antipyretic effects.[11–13]

For the vast majority of surgical procedures performed, NSAIDs manage pain and inflammation satisfactorily and adequately. However, when dealing with more invasive oral surgeries that produce significant surgical trauma, a considerable degree of discomfort is commonly reported by patients taking NSAIDs, making it often necessary to use other medications to relieve the postoperative pain.[14] One alternative used for invasive surgeries is the combination of an NSAID and an opioid, with the NSAID managing pain and inflammation peripherally and the opioid acting centrally to manage the pain.[15] Of note, recent studies have indicated that opioids might also act peripherally.[8]

Briefly, opioid receptors are distributed widely in the brain and spinal cord and opioids are highly effective analgesics operating on a large number of nuclei in the insular cortex, amygdala, hypothalamus, periaqueductal grey area, rostroventral medulla, and the dorsal horn of the spinal cord. Activation of these nuclei stimulates the descending pathways of pain leading to powerful analgesic effects.[16] Thus, the use of opioids and NSAIDs combined can reduce peripheral pain by inhibiting COX via NSAIDs and activating the descending inhibitory pathways in the central nervous system (CNS) via opioids.[14,15]

Despite the extensive literature on each of these pain medications, few studies have investigated the combination of NSAID and opioid versus only NSAID for postoperative pain after invasive oral surgeries with major trauma. Thus, the aim of this study was to compare the clinical efficacy of 50 mg of diclofenac (NSAID) plus 50 mg of codeine (opioid) with the clinical efficacy 50 mg of diclofenac alone through an investigation of pain levels, inflammation, possible side effects, and the amount of rescue medication (paracetamol (acetaminophen)) consumed following lower third molar surgery using a randomized, double-blind, cross-over design.

Materials and methods

This randomized, double-blind, cross-over study was approved by the Ethics Committee on Human Research of the University of Sao Paulo, Bauru School of Dentistry (FOB/USP) and was registered at ClinicalTrials.gov (NCT02547896).

The following eligibility criteria were used to select volunteers: age $\geq$18 years; two lower third molars in symmetrical positions included and/or impacted,[3] requiring invasive oral surgery; lack of inflammation or infection at the extraction sites; absence of systemic diseases that could possibly interfere with the study. Exclusion criteria included the following: history of allergy to local anaesthetics or any contraindication to receiving articaine; history of bleeding or gastrointestinal ulcers, kidney disease, asthma, or allergic sensitivity to any NSAIDs; patients who were pregnant or breast-feeding; use of antidepressants within 1 year before the research; use of anticoagulants, diuretics, and/or antibiotics within 2 months before surgery; use of any illicit drug at any time; patients undergoing any treatment for alcohol or drug addiction; hepatic, kidney, intestinal, cardiac, pulmonary, circulatory, and/or brain dysfunction.

Briefly, the volunteers selected for this study required invasive surgeries for two symmetrically positioned lower third molars with the following classifications: Pell and Gregory class IIB, IIC, IIIA, IIIB, and IIIC and/or Winter horizontal, distal, inverted, and transalveolar.[3] The Pell and Gregory classification is based on the relationship between the impacted lower third molar and (1) the ramus of the mandible (class I–III) and (2) the second molar (class A–C). In class A, the occlusal plane of the impacted tooth is at the same level as the occlusal plane of the second molar; in class B, the top of the crown of the third molar is between the occlusal plane and the cervical line of the second molar; in class C, the third molar is under the cervical line of the second molar. Classes I–III are related to the distance of the impacted tooth to the anterior border of the mandible: in class I, there is available space; in class II, the distal portion of the impacted third molar is covered by bone; in class III, all of the crown of the third molar is covered by bone.

Initially, 50 patients who met all of the necessary criteria were screened and referred for inclusion in the study. Four of these 50 patients were excluded: two patients had postoperative complications and the other two patients dropped out of the study. In total, 92 third molars were extracted (two for each of the 46 patients).

All surgeries were performed by the same maxillofacial surgeon (PZG). Briefly, 4% articaine with 1:200,000 epinephrine was used for all subjects.[5–7,17,18] Local anaesthesia was performed through a block of the inferior alveolar, oral, and lingual nerves, using a single 1.8-ml cartridge of anaesthetic. If after 5 min the subject did not feel anaesthesia of the lower lip, they were given additional anaesthetic until the lower lip was numb, without exceeding the maximum amount of anaesthetic allowed for each subject. To reduce bleeding and ensure mucosal anaesthesia, an additional 0.9 ml of anaesthetic (half of a cartridge) was administered using the terminal infiltration technique, which was applied directly to the gingival tissue around the third molar.

The steps of the surgery were as follows: after complete anaesthesia of the patient, an incision was made on the top of the alveolar bone above the impacted third molar and at the buccal–distal aspect of the second molar in a vertical descending direction, thus creating a triangular incision in this region. This triangle-shaped flap was folded down, allowing a direct view of the surgical field. Using a number 702 bur under constant irrigation with distilled water, an osteotomy was performed to remove the bone around the impacted tooth. Finally, using the same drill and irrigation, crown sectioning was performed, if necessary. The tooth was removed completely and the surgical cavity was cleaned, with the removal of bone spicules and with alveolar curettage. Abundant irrigation with 0.9% sterile saline was carried out. Suturing was performed using a 4–0 nylon suture, with three simple stitches over the flap. Postoperative care included a 48-h rest period, the application of ice packs, routine cleaning and brushing of the oral cavity, and the consumption of soft and frozen foods.

Immediately after the first surgery, the volunteers randomly consumed either one tablet of diclofenac (50 mg) every 8 h for 4 days, or one tablet of codeine (50 mg) and diclofenac (50 mg) every 8 h for 4 days. The medication was provided to all patients by the same researcher (EAT), who had previously prepared the tablets and placed them into two different envelopes: brown envelopes for diclofenac and