Efficacy of Lumiracoxib Versus Diclofenac Sodium in Pain Control Following Extraction of Impacted Lower Third Molar

Eficacia de Lumiracoxib Frente a Diclofenaco de Sodio en el Control del Dolor Después de la Extracción de un Tercer Molar Inferior Impactado

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ABSTRACT: The aim of this paper was to compare the efficacy of two different anti-inflammatory agents, Diclofenac (Deltaflogin®) and Lumiracoxib (Prexige®) in the control of postoperative pain that results from surgical removal of impacted lower third molars. Twenty adult patients from the Oral and Maxillofacial Surgery Division of the Araraquara Dentistry School, UNESP who presented bilateral impacted lower third molars were included in the study. Removal of the impacted teeth was performed in each side in different operative moments in a split mouth design for the study. The anti-inflammatory drugs evaluated were randomly administered on the first and second surgical procedures. The pain level was recorded using an analogical visual scale at 6, 24, 48 and 72 hours after surgical intervention. Both lumiracoxib 400 mg and diclofenac 100 mg are efficient for acute pain control after surgical removal of impacted lower third molars. However, lumiracoxib offered better pain control.

KEY WORDS: pain; third molars; anti-inflammatory agents.

INTRODUCTION

The inflammatory process represents a defensive response against different types of physical, chemical or biological aggression. However, exacerbated inflammatory reactions can produce destructive phenomena increasing tissue damage. One example is excessive liberation of proteolytic enzymes and free radicals by neutrophils. Thus, modulation of inflammation is important to reduce pain and edema. It also facilitates healing and increases local vascular support (Vane, 1979).

Postoperative pain is usually treated with analgesic and non-steroidal anti-inflammatory drugs (NSAIDs), such as ibuprofen, paracetamol

(acetaminophen), nimesulide (De Menezes *et al.*, 2010; Bailey *et al.*, 2014), rofecoxib, celecoxib and lumiracoxib (Kellstein *et al.*, 2004). Traditional NSAIDs are non-selective and prevent prostaglandin synthesis via inhibition of both cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2). Otherwise, highly selective cox-2 inhibitors (coxibs) were introduced aiming to reduce or eliminate the risk of gastric complications associated to the use of traditional NSAIDs (Rafaniello *et al.*, 2016).

The role of traditional NSAIDs in managing postoperative pain after oral surgery have been widely studied, especially diclofenac (Tuzuner-Oncul *et al.*,

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2011; Akbulut *et al.*, 2014). On the other hand, regarding to coxibs group, most of papers have focused in rofecoxib and celecoxib use. In this context, we proposed to compare the analgesic efficacy and tolerability of lumiracoxib, which is structurally distinct from other COX-2 selective inhibitors (Mangold *et al.*, 2004), with diclofenac sodium after third molars surgery.

MATERIAL AND METHOD

The subjects were selected from a pool of patients referred to a Public Dentistry College between January and December 2007 for third molar evaluation. The Institutional Ethics Committee approved the present research and all subjects signed a free prior and informed consent (FPIC).

This study included twenty healthy, non-smoking patients without contraindications to oral surgery and not taking any medication that had indication for removal of bilateral impacted third molars with similar impaction and position. All patients were submitted to orthopantomographic radiograms and teeth were classified according to Winter's system (mesioangular, vertical, distoangular e horizontal positions) (Winter, 1926).

The patients were randomly assigned the following nonsteroidal anti-inflammatory drugs administered orally: Group 1: diclofenac sodium 100 mg (Deltaflogin®- Delta) tablets taken once per Day; Group 2: lumiracoxib 400 mg (Prexige® - Novartis) tablets taken once per day. Both drugs, kept in appropriate receptacles with a green or red label, so that neither the surgeon nor the patient knew what drug was taken at a given moment, constructing a double blind condition.

The study followed a split mouth design. Thus, the teeth were removed and the drugs were administered at two different moments. When the right impacted molar was removed, one of the drugs was used, while the other was given to the same patient when the left molar was removed. The minimum interval between the removal of the first and the second impacted lower third molar was 15 days.

Intraoral antisepsis was performed with 0.12 % chlorhexidine digluconate and extra-oral antisepsis with polyvinylpyrrolidone iodine. The nerve block of the inferior alveolar, lingual and buccal nerves was carried

out using 2 % mepivacaine with 1:100.000 adrenalin (Mepíadre, DFL Industria e Comércio S.A., Rio de Janeiro, RJ, Brazil).

The surgery to remove the lower third molar was made by the same surgeon and followed the standardized technique. Briefly, the same incision was used for both sides, and a mucoperiosteal flap was elevated. A 702 high-speed burr was used for ostectomy and sectioning the tooth under abundant irrigation with sterilized 0.9 % physiological solution. After extraction bone irregularities were removed and the surgical cavity was thoroughly cleansed. Interrupted 4-0 silk sutures (Ethicon, Sao Paulo, Brazil) were used for closure.

All subjects were instructed to eat only soft food, and to abstain from mouth washing during the first 24 h and from brushing and flossing around the surgical area until suture removal (14 days post surgery). Furthermore, patients received orientation about local hemostatic measures, 24 hour limited activity and oral hygiene. Mouth rinses with 0.12 % chlorhexidine digluconate were used until suture removal.

Postoperative pain was assessed by means of an analogical visual scale during four days after third molar surgery (6, 24, 48 and 72 hours), always after 6 hours from the drug intake (Huskisson, 1983). The scale consists of a 100 mm straight line, which allows quantification of the postoperative pain.

Data referring to pain levels were analyzed using the Friedman test. In the case of statistical significance the Fisher LSD test for multiple comparisons was used. To compare pain levels described after ingestion of the different drugs the Wilcoxon test was used. The significance level considered was 5 %. Calculations were performed using the SPSS statistical software package (SPSS Inc., Chicago, IL, USA).

RESULTS

No accidents or complications were recorded with surgical procedures and the extraction socket healed uneventfully. Furthermore, all subjects complied with the research protocol, performed the follow-up measures and no drug side effect was reported.

Age of the patients ranged from 18 to 32 years old (24.4 ± 3.2), 18 were women. Operating time was

Table I. Pain intensity scores over the study period for the diclofenac sodium group.

	Period			
	6 hours	24 hours	48 hours	72 hours
Scores sum	72.50	54.00	42.50	31.00
Median	1.00	0.50	0.10	0.00
Medium score	3.62	2.70	2.12	1.55
Fr	28.18			
p	0.0001			
Multiple comparisons	Difference	p		
6h X 24h	18.50	>0.05		
6h X 48h	30.00	<0.05		
6h X 72h	41.50	<0.05		
24h X 48h	11.50	>0.05		
24h X 72h	23.00	<0.05		
48h X 72h	11.50	>0.05		

Table II. Pain intensity scores over the study period for the lumiracoxib group.

	Period			
	6 hours	24 hours	48 hours	72 hours
Scores sum	64.50	53.00	42.50	40.00
Median	0.50	0.10	0.00	0.00
Medium score	3.22	2.65	2.12	2.00
Fr	11.26			
p	0.0104			
Multiple comparisons	Difference	p		
6h X 24h	11.50	>0.05		
6h X 48h	22.00	<0.05		
6h X 72h	24.50	<0.05		
24h X 48h	10.50	>0.05		
24h X 72h	13.00	>0.05		
48h X 72h	2.50	>0.05

Fig. 1. Pain intensity (VAS) over the study period.

15 to 90 minutes (42.8 ± 17.0) and all patients had the anesthesia resolved within 6 hours, before observation for pain started.

Concerning about the impaction profile, eight teeth were horizontal (40.0 %) and vertical (40.0 %) and four (20.0 %) were mesioangulated, for each side. There were no significant differences between groups in relation to the patient's age and sex, as well as to the teeth position to be extracted.

Regarding to the median for pain for each group, we observed higher pain levels for the diclofenac sodium compared to lumiracoxib group (Fig. 1), however, in both groups, it was reported a progressing pain reducing during time point's measures. Furthermore, in diclofenac sodium (Table I) and lumiracoxib (Table II) groups occurred a statistically significant reduction in postoperative pain levels comparing 6 hours with 48 and 72 hours after surgery. Of note, patients in diclofenac sodium group also reported a significant pain reduction comparing 24 with 72 hours (Table I). The comparison of pain levels between the two anti-inflammatory drugs showed statistically better outcomes for lumiracoxib for the periods of 6, 24 and 48 hours, but not for the 72 hour period (Table III).

Table III. Pain intensity scores comparison of both drugs over the study period.

Period	z	p
6 hours	-2.5353	0.0112*
24 hours	-2.3541	0.0186*
48 hours	-2.5103	0.0121*
72 hours	-1.4270	0.1536

* $p < 0.05$

DISCUSSION

The development of therapeutic protocols for managing postoperative pain is a relevant issue after third molars surgery, given the more intense pain and inflammatory reaction compared to extraction of erupted teeth. Furthermore, over 90 % of the patients need analgesia

in the first 12 hours postoperatively. In this context, several papers have been published addressing analgesic effects of NSAIDS, however only three papers investigated lumiracoxib effects in oral surgery settings (Zelenakas *et al.*, 2004; Fricke *et al.*, 2008) and, to the best of our knowledge, this is the first paper to compare this drug efficacy with diclofenac, which is largely utilized in Brazilian dental treatments.

The efficacy of diclofenac as analgesic medication after third molars surgery is a well-established issue (Tuzuner Oncul *et al.*; Akbulut *et al.*), which also was confirmed in our paper. However, this drug was associated to worst outcomes compared to others NSAIDS, including aceclofenac (Kollu *et al.*, 2013) and ketoprofen (Velasquez *et al.*, 2014), but no statistically significant differences in analgesic efficacy was described between diclofenac sodium and ibuprofen (Esteller-Martínez *et al.*, 2004), Naproxen and Etodolac (Akbulut *et al.*). In the present study, diclofenac was chosen given its analgesic and anti-inflammatory properties, but also due to the low cost and widely distribution by the Brazilian public health system.

Regarding to specific COX-2 inhibitors, including lumiracoxib, the literature also confirms its application to third molar managing postoperative pain (Kellstein *et al.*; Zelenakas *et al.*; Fricke *et al.*), which was also observed in the present paper. The selection of lumiracoxib to this research was due to the lack of studies with this drug in oral surgery settings. Furthermore, this drug demonstrated some advantages compared to others specific COX-2 inhibitors, such as fastest onset of analgesia and the longest time to rescue medication use than celecoxib (Kellstein *et al.*; Zelenakas *et al.*; Fricke *et al.*) and better outcomes on the summed (time-weighted) pain intensity difference over the first 8 h post dose compared to rofecoxib 50 mg (Kellstein *et al.*)

Comparing non-selective COX inhibitors with specific COX-2 blockers, different outcomes have been reported. Similar effects were observed between celecoxib and loxoprofen (Yamashita *et al.*, 2014). On the other hand, Zelenakas *et al.*, reported that Lumiracoxib 400 mg produced onset of analgesia in a shorter time than shown by ibuprofen 400 mg. In our study, we also observed that Lumiracoxib was more efficient in pain control than diclofenac. The onset occurs in about 37 minutes and persists for up to 24 hours. The difference in effectiveness between the studied drugs decreases with time and is equivalent

after 4 days. This is to be expected because the peak in pain occurs between 3 and 12 hours postoperatively (Hyrkas *et al.*, 1994).

Regarding to impaction profile of third molars, differences have been pointed in literature. Some authors stated that the most frequent position of impaction is the mesioangular (Carter, 2015; Mahdey *et al.*, 2015), which is in discordance with our study, since this position corresponds to only 20 % of the teeth that were removed. However, other studies reported that vertical position is the most common observed (Kumar-Pillai *et al.*, 2014; Yilmaz *et al.*, 2015), as we observed in our paper, differing just by the high prevalence of horizontal impaction, which is not commonly reported. These differences in the impaction profile could be due to the race discrepancies, patient selection criteria and study population.

The chronic oral administration of non-selective NSAIDs are linked with many gastrointestinal complications like ulceration, bleeding and perforation (Rafaniello *et al.*), while highly selective COX-2 inhibitors (coxibs) are associated with an increased risk of adverse cardiovascular events (Patrino, 2016). However, in our study, it was not observed any side effects of NSAIDs, which can be reasonably explained by the absence of previous systemic disease in patients, the short-term drug intake and no other age-related factors.

The study model for dental pain arising from extraction of impacted third molars has been shown to provide a reliable model for determining the short-term efficacy of new drugs (Cooper & Beaver, 1976). Furthermore, important drug manufacturers have applied it for evaluation of their products (May *et al.*, 2001). However, it is relevant to be stated that standardization is difficult due to several variables, such as experience of the surgeon and pain threshold for the individual patient. Measuring pain is challenging because of the subjectivity, complexity and multiple dimensions involved in the pain experience.

CONCLUSION

This study demonstrated that both lumiracoxib 400 mg and diclofenac sodium 100 mg are an effective and well-tolerated analgesic for post-operative dental pain after third molars surgery. However, lumiracoxib was associated with better outcomes in pain relief on time-points 6, 24 e 48 hours after surgery when compared to diclofenac sodium 100 mg.

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RESUMEN: El objetivo de este trabajo fue comparar la eficacia de dos agentes antiinflamatorios distintos, Diclofenaco (Deltaflogin®) y Lumiracoxib (Prexige®) en el control del dolor postoperatorio resultante de la extracción quirúrgica de terceros molares inferiores impactados. Fueron incluidos, veinte pacientes adultos de la División de Cirugía Oral y Maxilofacial de la Escuela de Odontología de Araraquara, UNESP que presentaron terceros molares inferiores impactados. La extracción de los dientes impactados se realizó en distintos tiempos operatorios a cada lado en un diseño de estudio de boca dividida. Los antiinflamatorios evaluados fueron administrados de forma aleatoria en el primer y segundo procedimiento quirúrgico. El nivel de dolor se registró utilizando una escala visual análoga a las 6, 24, 48 y 72 horas después de la intervención. Ambos; lumiracoxib 400 mg y diclofenaco 100 mg son eficientes para el control del dolor agudo, después de la extracción quirúrgica de terceros molares inferiores impactados. Sin embargo, lumiracoxib ofreció mejor control del dolor.

PALABRAS CLAVE: dolor, terceros molares, agentes antiinflamatorios.

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