UNIVERSIDADE FEDERAL DO CEARÁ

FACULDADE DE FARMÁCIA, ODONTOLOGIA E ENFERMAGEM

PROGRAMA DE PÓS-GRADUAÇÃO EM ODONTOLOGIA

AVALIAÇÃO COMPARATIVA DA ANALGESIA PREEMPTIVA DO IBUPROFENO E ETORICOXIBE EM CIRURGIA DE TERCEIROS MOLARES: UM ENSAIO CLÍNICO RANDOMIZADO, DUPLO-CEGO, PLACEBO-CONTROLADO, CRUZADO

FÁBIO WILDSON GURGEL COSTA

FORTALEZA

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Tese submetida ao Programa de Pós-Graduação em Odontologia, da Universidade Federal do Ceará, como requisito parcial para a obtenção do grau de Doutor em Odontologia

Área de Concentração: Clínica Odontológica
Orientador: Prof. Dr. Eduardo Costa Studart Soares
Co-orientadora: Profa. Dra. Cristiane Sá Roriz Fonteles

FORTALEZA
2013

Dados Internacionais de Catalogação na Publicação
Universidade Federal do Ceará
Biblioteca de Ciências da Saúde

C872a Costa, Fábio Wildson Gurgel.
Avaliação comparativa da analgesia preemptiva do Ibuprofeno e etoricoxibe em cirurgia de terceiros molares: um ensaio clínico randomizado, duplo-cego, placebo-controlado, cruzado. / Fábio Wildson Gurgel Costa. – 2013.
50 f. : il. color., enc. ; 30 cm.

Tese (doutorado) – Universidade Federal do Ceará; Centro de Ciências da Saúde; Faculdade
de Farmácia, Odontologia e Enfermagem; Departamento de Odontologia; Programa de Pós-Graduação em Odontologia; Doutorado em Odontologia, Fortaleza, 2013.
Área de Concentração: Clínica Odontológica.
Orientação: Prof. Dr. Eduardo Costa Studart Soares.
Co-Orientação: Profa. Dra. Cristiane Sá Roriz Fonteles.

1. Dente Serotino. 2. Ensaio Clínico. 3. Dor. 4. Edema. 5. Trismo. I. Título.

CDD 617.605

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Aprovada em: 20 de março 2013

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Dedico este trabalho à Deus e às três
grandes Marias da minha vida
(Rodrigues, Helena e Helane)

AGRADECIMENTOS

À Deus, "*Com Ele tudo.... Sem Ele nada*". Agradeço pelo dom da vida, pela capacidade de aprender e por mais esta oportunidade de crescimento e conquista.

Às minhas mães, Maria Helena Costa Nunes e Maria Rodrigues Martins, *in memorian*, por tudo que sou hoje, pelo grande exemplo de ética, dedicação, carinho, competência, responsabilidade, compromisso e perseverança. Agradeço pelo amor incondicional e por cada segundo que estiveram ao meu lado. Espero que estejam, ao lado de Deus, orgulhosas e muito felizes, e que continuem a guiar meus passos e me ajudar a superar os obstáculos da vida. Amo vocês.

Ao meu querido pai, Ulisses Gurgel Nunes, pelo apoio e participação na minha formação pessoal e profissional. À sua esposa, Patrícia, por suportar seus momentos hipocondríacos (brincadeira pai!).

Aos meus queridos irmãos, Ulisses Júnior, Maria Adelaide e Miguel Ângelo, pelo carinho, amizade e apoio que me deram em vários momentos.

À minha querida irmã, Maria Helane Costa Gurgel, por fazer parte da minha vida tanto nos momento bons (que foram muitos) e ruins (os quais nos tornaram fortes). Obrigado pelo carinho, zelo, amizade, exemplo de superação, e por ser o tio de duas crianças abençoadas, a Maria Eduarda e Laura. Agradeço, também, ao Eduardo Castelo, seu esposo, pela amizade e consideração que sempre transpareceu.

A todas as minhas tias, especialmente Fátima, Diá, Aparecida e Luiza, que foram fundamentais em muitos momentos da minha vida, e que sempre estiveram comigo em oração.

À minha amada namorada, e grande companheira, Thyciana Rodrigues Ribeiro por se fazer presente na minha vida em todos os momentos bons e difíceis (e espero que

se faça sempre!). Obrigado pelo cuidado e por me proporcionar o convívio com pessoas tão especiais, que são seu pai (Silvio), mãe (Lúcia) e kennedy.

Ao mestre, grande amigo e segundo pai, Dr. Eduardo Costa Studart Soares, pelo apoio e dedicação sempre incondicionais. Muito obrigado por esses mais de 10 anos de ensinamentos e por ter contribuído substancialmente na minha vida pessoal e profissional. Obrigado pelo exemplo de ser humano, idoneidade, competência, perseverança e determinação em tudo o que faz. Agradeço, também, à sua esposa Luciana, que sempre me recebeu de forma acolhedora, e a seus queridos filhos Carolina e Guilherme que sempre me encheram de alegria.

À estimada professora e amiga Dra. Cristiane Sá Roriz Fonteles, pelo apoio fundamental nos momentos que mais precisei durante minha trajetória na pós-graduação. Muito obrigado por tudo, especialmente seu exemplo de caráter, dedicação, preciosismo, competência e amizade.

Ao grande professor e amigo Dr. Henrique Clasen Scarparo, pelas suas valorosas e importantes sugestões na banca de pré-defesa, e por ser um exemplo de caráter e competência.

Aos estimados professores Dr. Fabrício Bitu e Dra. Ana Paula Negreiros Nunes Alves, pelo exemplo de competência, generosa acolhida, atenção e apoio sempre dispensados.

Às professoras Karuza Alves, Delane Gondim e Hellíada Vasconcelos por suas contribuições valorosas na banca de pré-defesa e, sobretudo, pela amizade.

À todos os professores, funcionários, alunos e grande amigos do curso de Odontologia da UFC Campus Sobral, por estes quatro anos de muitas alegrias e conquistas pessoais e profissionais.

À Universidade Federal do Ceará (UFC) e ao Programa de Pós-Graduação em Odontologia, pela oportunidade de ter realizado o curso de Mestrado e, agora, o de Doutorado.

À coordenadora do Programa de Pós-Graduação em Odontologia da UFC, Profa. Dra. Lidiany Rodrigues pelo exemplo de competência, apoio e compreensão necessários à conclusão deste trabalho, e em nome da qual agradeço a todos os professores e funcionários do Programa pelos ensinamentos e tempo de dedicação dispensados.

A todos os colegas de Doutorado pelo agradável convívio e oportunidade de tê-los conhecido.

Aos colegas e estimados amigos Tácio Pinheiro, Ivo Pita, Marcelo Ferraro, Rafael Linard, Rômulo Medeiros, Samuel Carvalho, Diego Esses, Ernest Pouchain, Carlos Diego, Bárbara Carneiro, Carlos Bruno, Saulo Ellery e Denise Moraes pela atenção, dedicação, empenho e companheirismo. Agradeço pelos momentos de alegria e de ensinamento.

Aos colegas Paulo Goberlânio e Marcelo Leite que pela grande ajuda na análise estatística e tradução dos capítulos da presente tese, respectivamente. Muito obrigado.

À professora Marivan Ferraro, pela realização da revisão gramatical, do presente trabalho, com tamanha paciência e dedicação.

Aos bibliotecários Norma de Carvalho, Rosane Maria, Raimundo Cézar, Rita de Cássia, Valder Cavalcante, Maria Dolores, Maria Josineide, e Flávio Pereira, da Biblioteca de Ciências da Saúde da UFC, pela atenção e correção das referências bibliográficas.

Enfim, àqueles que, injustamente, não foram citados, mas que certamente contribuíram muito para a realização deste trabalho.

RESUMO

A cirurgia de terceiros molares é um procedimento frequente em Odontologia relacionado a variados graus de dor pós-operatória. Nesse contexto, drogas anti-inflamatórias não-estereoidais têm sido comumente utilizadas em estudos que avaliaram a eficácia da analgesia preemptiva como uma estratégia para controle da dor. Portanto, o objetivo do presente estudo foi avaliar a eficácia da analgesia preemptiva e ação anti-inflamatória do ibuprofeno e etoricoxibe em cirurgia de terceiros molares mandibulares comparado a um placebo. Foi realizado um ensaio clínico randomizado, duplo-cego, placebo-controlado cruzado com pacientes submetidos a cirurgia para remoção de terceiros molares mandibulares, com padrões similares de inclusão óssea e dificuldade cirúrgica entre os lados direito e esquerdo, e que requeriam remoção óssea sob anestesia local. Dezoito pacientes elegíveis foram randomicamente alocados em três grupos para receber 1 hora preoperatoriamente dose única de ibuprofeno 400mg, etoricoxibe 120mg, ou placebo. Intensidade de dor, uso de medicação analgésica de resgate, edema e máxima abertura bucal foram avaliados. A mediana (mínimo - máximo) global dos escores de dor diferiu entre os grupos ($p < 0,0001$): ibuprofeno, 0,0 (0,0 – 5,5); etoricoxibe, 0,0 (0,0 – 3,5); placebo, 1,0 (0,0 – 7,0). Etoricoxibe reduziu os escores de dor significantemente em comparação ao ibuprofeno ($p < 0,05$). O pico de dor ocorreu 6 horas após a cirurgia entre os 3 grupos comparados ($p < 0,0001$). Medicação de resgate foi utilizada em 83,33%, 75% e 100% dos procedimentos cirúrgicos que receberam ibuprofeno, etoricoxibe e placebo, respectivamente ($p = 0,1967$). A média de medicação de resgate consumida diferiu entre os grupos ibuprofeno (1,7±2,0) e etoricoxibe (0,8±0,6) e placebo (1,0±2,7) durante todo o período de estudo ($p = 0,0052$), e foi significantemente menor no grupo do etoricoxibe em comparação com o grupo placebo ($p < 0,05$). Entre os períodos de avaliação do estudo, não existiu diferença estatisticamente significante dos grupos entre si em relação à mediana dos valores de edema facial ($p > 0,05$) e à média dos valores de máxima abertura bucal ($p > 0,05$). Em conclusão, ibuprofeno e etoricoxibe reduziram significantemente a intensidade de dor pós-operatória e a necessidade do uso de medicação de resgate comparado ao grupo placebo. Etoricoxibe mostrou melhor atividade analgésica preemptiva do que o ibuprofeno. Ambas as drogas não exerceram efeito anti-inflamatório significante capaz de reduzir edema e trismo em comparação ao grupo placebo.

Palavras-chave: dente serotino, ensaio clínico, dor, edema, trismo.

ABSTRACT

Third molar surgery is a frequent procedure in dentistry related to variable degrees of postoperative pain. In this context, non-steroidal anti-inflammatory drugs have been commonly used in studies that evaluated the efficacy of preemptive analgesia as a strategy for pain control. Thus, the aim of the present study was to evaluate the preemptive analgesic efficacy and anti-inflammatory effect of ibuprofen and etoricoxib in mandibular third molar surgery, compared with a placebo. A randomized, double-blind, placebo-controlled crossover trial was conducted with patients undergoing a surgical removal of mandibular third molars with similar pattern of bone inclusion and surgical difficult between right and left sides, requiring bone removal under local anesthesia. Eighteen eligible patients were allocated into three groups to receive 1 hour preoperatively a single dose of ibuprofen 400 mg, etoricoxib 120 mg, or placebo. Pain intensity, use of analgesic rescue medication, swelling and maximum mouth opening were evaluated. The overall median (minimum - maximum) of pain scores was different between groups ($p < 0.0001$): ibuprofen, 0.0 (0.0 – 5.5); etoricoxib, 0.0 (0.0 – 3.5); placebo, 1.0 (0.0 – 7.0). Etoricoxib reduced pain scores significantly in comparison with ibuprofen ($p < 0.05$). The pain score peak occurred 6 hours after surgery between 3 compared groups ($p < 0.0001$). Rescue medication was used in 83.33%, 75%, and 100% of surgical procedures receiving ibuprofen, etoricoxib, and placebo, respectively ($p = 0.1967$). The mean of consumed rescue medication was different between ibuprofen (1.7±2.0), etoricoxib (0.8±06), and placebo (1.0±2.7) groups over the study period ($p = 0.0052$), and was significantly lower in etoricoxib group by comparison with the placebo group ($p < 0.05$). Among study periods, there was no statistically significant difference between groups in relation to median values of facial swelling ($p > 0.05$) and mean values of maximum mouth opening ($p > 0.05$). In conclusion, ibuprofen and etoricoxib significantly reduced the intensity of postoperative pain and the need for use of rescue medication compared to placebo group. Etoricoxib showed a better preemptive analgesic activity than ibuprofen. Both drugs did not exert significant anti-inflammatory effect able to reduce swelling and trismus in comparison with placebo group.

Key words: third molar, clinical trial, pain, swelling, trismus.

LISTA DE ABREVIATURAS

DAINES	Drogas antiinflamatórias não esteroidais
COX	Ciclooxigenase
COX-2	Enzima ciclooxigenase tipo 2
COX-1	Enzima ciclooxigenase tipo 1
NSAIDs	Nonsteroidal anti-inflammatory drugs
ASA	America Society of Anesthesiologists
INR	International Normalized Ratio
VAS	Visual Analogue Scale
AM-Tr	Ângulo mandibular - *Tragus*
AM-ECE	Ângulo mandibular – canto externo do olho
AM-NB	Ângulo mandibular – asa do nariz
AM-LC	Ângulo mandibular – comissura labial
AM-SP	Ângulo mandibular – pogônio mole

SUMÁRIO

1. INTRODUÇÃO GERAL

A cirurgia para remoção de terceiros molares constitui-se um procedimento frequentemente realizado em Odontologia (Martin et al., 2005), estando associado a variados graus de dor pós-operatória (Benediktsdottir et al., 2004; Moller et al., 2005). Tal procedimento pode afetar significativamente a qualidade de vida dos pacientes, particularmente durante os três primeiros dias pós-operatórios, devido a intensidade da dor experimentada e aos eventos inflamatórios decorrentes do procedimento cirúrgico (Colorado-Bonnin et al., 2006).

Além de dor, os eventos pós-operatórios mais frequentemente relacionados à remoção de terceiros molares inferiores são o trismo e o edema decorrentes do processo inflamatório local, com as isoformas da ciclooxigenase (COX) e prostaglandinas desempenhando um importante papel em seu desenvolvimento (van Gool et al., 1977).

Nesse contexto, a analgesia preemptiva representa um tratamento antinociceptivo que previne a ocorrência do processamento alterado de um *input* aferente, o que amplificaria a dor pós-operatória (Kissin, 2000). O conceito de analgesia preemptiva data do século passado, tendo sido designado por Crile, em 1913, a partir de observações clínicas. O ressurgimento desse conceito foi associado a uma série de estudos experimentais, iniciados por Woolf em 1983 e destacados por Wall em 1988, na prevenção da dor pós-operatória. A partir disso, alguns ensaios de cunho clínico têm evidenciado a importância da analgesia preemptiva (Dahl, Kehlet 1993; Kissin, 2000). Segundo De Jean et al. (2008), acredita-se que essa estratégia, além de proporcionar conforto ao paciente, reduz o consumo de analgésicos para o controle da dor no período pós-operatório, o que abreviaria o tempo de recuperação do paciente.

Drogas anti-inflamatórias não-esteroidais (DAINEs) inibem a síntese de prostaglandinas e são comumente prescritas para alívio da dor e controle do edema após

cirurgia bucal (de Menezes, Cury 2010). Um dos agentes mais comumente utilizados para dor de origem dental é o ibuprofeno. Sua eficácia no tratamento de dor dental pós-operatória tem sido avaliada em diversos ensaios clínicos, sendo considerado um fármaco analgésico padrão ouro (Morse et al., 2006; Merry et al., 2010). Mais recentemente, outros autores têm demonstrado a eficácia do etoricoxib, um potente inibidor seletivo COX-2 com poucos efeitos gastrointestinais, para o tratamento de dor aguda oriunda de cirurgia buco-dentária, além de dismenorreia primária e alívio pós-operatório em cirurgia ortopédica (Daniels et al., 2011).

A analgesia preemptiva tem se tornado uma das mais promissoras estratégias no manejo farmacológico da dor (Grape, Tramer 2007). Até o presente momento, inexistem ensaios clínicos padronizados comparando a ação preemptiva entre ibuprofeno e etoricoxib em cirurgia para remoção de terceiros molares. Em adição, apenas um estudo avaliando o efeito preemptivo de etoricoxib em cirurgia de terceiros molares foi publicado até o momento (Sotto-Maior et al., 2011). Portanto, o objetivo do presente estudo foi avaliar a eficácia da analgesia preemptiva e ação anti-inflamatória do ibuprofeno e etoricoxibe em cirurgia de terceiros molares mandibulares em comparação a um placebo.

2. PROPOSIÇÃO

Objetivo Geral:

- Avaliar a eficácia da analgesia preemptiva e ação anti-inflamatória do ibuprofeno e etoricoxibe em cirurgia de terceiros molares mandibulares em comparação a um placebo.

Objetivos Específicos:

- Avaliar a eficácia analgésica preemptiva do ibuprofeno e etoricoxibe em cirurgias para remoção de terceiros molares mandibulares;
- Comparar a ação analgésica preemptiva do ibuprofeno e etoricoxibe em cirurgias para remoção de terceiros molares;
- Avaliar a ação do ibuprofeno e etoricoxibe sobre o edema e trismo no pós-operatório de cirurgias para remoção de terceiros molares mandibulares;
- Comparar a ação do ibuprofeno e etoricoxibe sobre o edema e trismo no pós-operatório de cirurgias para remoção de terceiros molares mandibulares.

3. CAPÍTULO

Esta tese está baseada no Artigo 46, do Regimento Interno do Programa de Pós-Graduação da Universidade Federal do Ceará, que regulamenta o formato alternativo para trabalhos de conclusão (dissertações e teses) de mestrado e doutorado e permite a inserção de artigos científicos de autoria ou co-autoria do candidato.

Por se tratar de pesquisa envolvendo seres humanos, os protocolos utilizados neste trabalho foram submetidos à apreciação e foram devidamente aprovados pelo Comitê de Ética em Pesquisa em Seres Humanos do Centro de Educação Continuada da Academia Cearense de Odontologia, tendo sido aprovado e protocolado sob o no. 132/2010.

Desta forma, a presente tese é composta por um artigo científico redigido de acordo com a revista científica escolhida.

3.1 Capítulo 1

"Preemptive effect of Etoricoxib versus Ibuprofen on inflammatory parameters after mandibular third molar surgery: a randomized, double-blind, placebo-controlled crossover trial" Este artigo seguiu as normas de publicação do periódico *Journal of Oral and Maxillofacial Surgery* (ISSN 0278-2391)

Title page

Preemptive effect of Etoricoxib versus Ibuprofen on inflammatory parameters after mandibular third molar surgery: a randomized, double-blind, placebo-controlled crossover trial

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Competing interests: None declared

Funding: None

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Preemptive effect of Etoricoxib versus Ibuprofen on inflammatory parameters after mandibular third molar surgery: a randomized, double-blind, placebo-controlled crossover trial

***Purpose*.** The aim of the present study was to evaluate the preemptive analgesic efficacy and anti-inflammatory effect of ibuprofen and etoricoxib in mandibular third molar surgery compared with a placebo.

***Materials and Methods*.** A randomized, double-blind, placebo-controlled crossover trial was conducted in patients undergoing surgical removal of mandibular third molars, requiring bone removal under local anesthesia. Eighteen eligible patients were randomly allocated into three groups to receive 1 hour preoperatively a single dose of ibuprofen 400 mg, etoricoxib 120 mg, or placebo. Pain intensity, use of analgesic rescue medication, swelling and maximum mouth opening were evaluated.

***Results*.** Ibuprofen and etoricoxib reduced the pain scores in relation to placebo ($p < 0.0001$), and etoricoxib reduced pain scores significantly in comparison with ibuprofen ($p < 0.05$). The pain score peak occurred 6 hours after surgery ($p < 0.0001$). The mean of rescue medication consumed was different between ibuprofen (1.7±2.0), etoricoxib (0.8±06), and placebo (1.0±2.7) groups over the study period ($p = 0.0052$), and was significantly lower in etoricoxib group by comparison with the placebo group ($p < 0.05$). Among study periods, there was no statistically significant difference between groups related to swelling and trismus.

***Conclusions*.** Ibuprofen and etoricoxib significantly reduced the intensity of postoperative pain and the need for use of rescue medication compared to placebo group. Etoricoxib showed a better preemptive analgesic activity than ibuprofen. Both

drugs did not exert significant anti-inflammatory effect able to reduce swelling and trismus.

Key words. Preemptive analgesia, third molar, nonsteroidal anti-inflammatory drugs

INTRODUCTION

Third molar removal surgery is a frequent procedure in dentistry related to variable degrees of postoperative pain.[1,2] Removal of mandibular third molars can significantly affect patient's quality of life, especially in the following three days after operation, due to the intensity of pain experienced as well as the inflammatory events caused by the surgical procedure.[3] Following pain, the most common postoperative complications related to the removal of mandibular third molars are trismus and swelling, due to local inflammatory process, because the cyclooxygenase (COX) and prostaglandins isoforms play an important role in its development.[4]

In this context, preemptive analgesia represents an antinociceptive treatment which prevents the establishment of an altered afferent input process, something that would amplify postoperative pain.[5] According to De Jean et al.[6], it is believed that this strategy, besides providing patient comfort, reduces the ingestion of analgesic medication for pain control in the postoperative period, which would reduce patient recovery time.

Nonsteroidal anti-inflammatory drugs (NSAIDs) inhibit prostaglandin synthesis and are commonly prescribed for pain relief and swelling control after oral surgery.[7] One of the most commonly used agents for dental induced pain relief is ibuprofen. Its efficacy in postoperative dental pain has been evaluated in many clinical trials, being considered a gold standard analgesic drug.[8,9] More recently, other authors have demonstrated the Etoricoxib efficacy, a potent COX-2 selective inhibitor with few gastrointestinal effects, for the treatment of acute pain derived from oral surgery, primary dysmenorrhea and postoperative relief in orthopedic surgery.[10]

Preemptive analgesia has become one of the most promising strategies for pharmaceutical pain management.[11] To date, there are no standardized clinical trials comparing the preemptive action of ibuprofen and etoricoxib in mandibular third molar surgery. In addition, only one study evaluating preemptive effect of etoricoxib in third molar surgery has been published.[12] Therefore, the aim of the present study was to evaluate the preemptive analgesic efficacy and anti-inflammatory effect of ibuprofen and etoricoxib in mandibular third molar surgery, compared with a placebo.

MATERIALS AND METHODS

Study Design / Sample

This study was approved by the Ethics Committee of the Academia Cearense de Odontologia, Ceará, Brazil (protocol # 132), being in agreement with the Helsinki statements. The study protocol followed a prospective, single-center, crossover, randomized, double-blind, placebo-controlled clinical trial, and it was conducted on patients recruited from the Division of Oral and Maxillofacial Surgery, Walter Cantídio University Hospital, Federal University of Ceará, Brazil, who required bilateral lower third molar extraction. Patients recruitment was conducted between April / 2011 and September / 2012 according to CONSORT statement.[13]

Outpatients of both genders, aged from 18 to 35 years, were enrolled in this study. Inclusion criteria were healthy subjects (ASA, American Society of Anesthesiologists, classification I) who had indication for removal of the both lower third molars. These teeth should have been covered by osseous tissue, requiring bone removal and / or tooth sectioning for their extraction, and with similar patterns of root

formation, position, and impaction degree in both right and left sides of the mouth. Other inclusion criteria were absence of periodontal disease, subjects without swelling, hyperthermia, and trismus at the moment of the surgery, and those able to cooperate with the protocol and able and willing to sign an appropriate written informed consent.

Patients were excluded if they fulfilled at least one of the following criteria: smokers, pregnant or breast-feeding women, patients using medications that present interaction with the drugs used in this study; subjects having orthodontic bands on the second molars, known allergy to NSAIDs; systemic chronic diseases; signs of any pre-existing acute inflammatory or infectious condition; and history of NSAIDs use in the past 21 days, or patients that did not adhere to this study.

Criteria for withdrawal from the study were: intolerance to the pharmacological regimen, surgical procedure exceeding 2 hours, patients who did not follow the indicated recommendations or whose in which a infectious process was installed after the third molar extraction. Patients who did not return for reassessment were also removed.

Preoperatively, data about patients were recorded according to a standardized clinical examination, including gender, age, systemic condition, periodontal status, hemogram parameters, platelet count, International Normalized Ratio (INR) value, and plasmatic glucose. Orthopantomography was required to evaluate teeth variables such as position through Pell and Gregory[14] and Winter[15] classifications, teeth/root formation grade, and degree of impaction.

Patients were scheduled for surgery on two separate clinical sessions (one tooth per session) at least with a three weeks interval. Subjects were allocated into 3 groups, according to the medication received 1 hour before surgery (Group 1: Ibuprofen 400

mg; Group 2: Etoricoxib 120 mg; and Group 3: placebo). Placebo and ibuprofen were dispensed as identical capsules by a blind collaborator. There were 6 combinations of sequence in the prescription of the drugs to which provided the crossover:

	First surgery	*Second surgery*
1.	Ibuprofen	Etoricoxib
2.	Etoricoxib	Ibuprofen
3.	Ibuprofen	Placebo
4.	Placebo	Ibuprofen
5.	Etoricoxib	Placebo
6.	Placebo	Etoricoxib

The selected subjects who meet the eligibility criteria were randomly allocated to 1 of the 6 combinations according to a computer generated randomization code (Microsoft Excell®). Prior to surgical procedure, the method of allocation concealment of the right and left sides of the mouth was followed as described by Bezerra et al.[16] Antibiotic prophylaxis was not given to the patients. After surgery, ibuprofen 300 mg was allowed as rescue analgesic medication in each 8 hours if necessary.

Blinding

All patients, the surgeon who carried out the operative procedure, the collaborator who carried out the follow-up examination and outcome measurements, and the statistician were unaware of the medication given to each voluntary.

Surgical Overview

All patients were submitted to standardized surgical technique performed in an outpatient setting under local anesthesia, followed by strict biosafety control. One surgeon with 10-year experience in dentoalveolar surgery performed all surgical procedures. The same surgical procedure was adopted for both sides of the mouth, aiming to reduce differences in the level of transoperatory trauma. The extraction of lower third molars was performed under local anesthesia with mepivacaine 2% and epinephrine 1:200,000 (Mepivalem AD®, Dentsply, USA), using 2 or 3 1.8-mL cartridges. A full-thickness flap followed by bone removal using a drill cooled with bi-distilled water was performed. Surgical wound was closed using a 4-0 silk suture.

Recommendations were carefully read and explained (especially liquid and cold diet for 24 hours, rigorous oral hygiene and to avoid vigorous mouthwashes aiming to prevent the occurrence of post-surgical blending) for all subjects. Patients were informed that they must contact the surgeon by telephone in case of persistent bleeding or any other complications such as fever. In addition, patients were also asked to report any physical symptoms experienced during the study period, e.g., nausea, vomiting, dizziness, headache, insomnia and infection signs.

Outcome Measure

The primary outcome of the study was the occurrence of postoperative pain. Measurements of this outcome considered pain intensity and need for rescue analgesia. Postoperative pain intensity was measured using a 10 cm Visual Analogue Scale (VAS).[7-10,12] Before starting the treatment, each patient received explanation about how to measure pain intensity on this scale. At the end of surgery, patients received a standardized form to record the values of postoperative pain, and this form should be

returned to the researcher on the day of suture removal. The VAS consisted of an interval scale ranging from 0 (absence of pain or discomfort) to 10 (maximum pain or discomfort). Study participants were asked to record the pain intensity score at 0, 2, 4, 6, 8, 10, 12, 24, 48, 72 h, 5 and 7 days following surgery. Additional analyses included the evaluation of time to remedication, which was defined by Ong et al.[17] as " the time from the end of surgery until the intake of rescue medication became necessary for the patient". The number of patients requiring ibuprofen after the initial postoperative two days was also recorded, as well as the amount of analgesic required during the study period.

The secondary outcome was the occurrence of postoperative inflammatory events. Some measurements were performed to evaluate postoperative swelling on the facial side of surgery including: distance from angle of the mandible to tragus (distance AM-Tr); distance from angle of the mandible to external corner of the eye (distance AM-ECE); distance from angle of the mandible to nasal border (distance AM-NB); distance from angle of the mandible to labial commissure (distance AM-LC); distance from angle of the mandible to soft pogonion (distance AM-SP). Differences obtained between preoperative values (baseline) and those after 24, 72 h, 5 and 7 days of surgery were compared. The maximum mouth opening ability was measured to estimate trismus in millimeters between the upper and lower central incisors using a calibrated ruler preoperatively, and on every period of observation in this study (initial, and 24, 72 h, 5 and 7 days postoperatively).

Statistical Analysis

Data was initially submitted to the Kolmogorov-Smirnov normality test. The parametric data was analyzed via ANOVA/Bonferroni test, paired or no paired, unifactorial or multifactorial, depending on the indication and expressed as a mean ± SD (standard deviation). The non-parametric data was analyzed via Kruskall-Wallis/Dunn or Friedman/Dunn depending on the indication and expressed as average (minimum - maximum). The Kaplan-Meyer method was utilized for the evaluation of the rescue medication through chi-square test. GraphPad Prism 5.0® software was used for all analyses and a significance rate of $p < 0.05$ was considered in all of the evaluations.

Sample size calculation

Based on the results from Al-Shukun et al.[18] who observed a failure rate (negative response) of 58% in the placebo group and 18% in the therapeutic group, it was possible to estimate a sample size of 12 surgical procedures per group, considering a confidence interval of 95% and a power of at least 80% with a type I error of 0.05 (chi-square test without correction).

RESULTS

A total of 644 patients were assessed for eligibility in this study (Figure 1), being 622 excluded because they did not meet the study criteria, 1 developed an infection process following the first surgery, and 3 lost the follow-up visits. The final sample was constituted by a total of 18 volunteers, being 12 male (66.67%) and 6 female (33.33%) equally distributed among three groups ($p = 0.7581$). Each experimental group had six patients (n = 6) and, as each patient was submitted to two surgical procedures for the

removal of the inferior third molars, a total of 12 surgeries per group was performed, totalizing 36 surgical procedures.

According to Table 1, there was no statistically significant difference in relation to main baseline characteristics of the 3 compared groups. Local anesthetic (mepivacaine 2% and epinephrine 1:200,000) was injected at all appropriate sites before surgery, and its injected quantity was measured as the number of dental cartridges. The median value (minimum – maximum) in the ibuprofen, etoricoxib, and placebo was 2.50 (2.00 – 2.50), 2.00 (2.00 – 3.00), and 2.50 (2.00 – 3.00) dental cartridges, respectively, and these values did not differ between the 3 compared groups (p = 0.3575). Mean duration of operation was 14.85±1.22 minutes for ibuprofen group, 15.15±2.49 minutes for etoricoxib group, and 15.03±1.93 minutes for placebo group, and no statistically significant difference was detected between groups (p = 0.9307).

The peak pain score recorded was at postoperative six hours for the three groups (Figure 2), and statistically significant difference was detected between groups (p < 0.0001). According to table 2, median value at 6-hour postoperative period was significantly lower in etoricoxib (0.5; 0.0 – 2.0) and ibuprofen (0.9; 0.0 – 5.5) groups by comparison with the placebo (4.5; 2.0 – 7.0) group. Both etoricoxib and ibuprofen showed significantly lower median values in comparison to placebo group at the 6-hour period (p < 0.05). The median pain scores of the etoricoxib group were lower than the placebo group from the end of the surgical procedure to the 72-hour evaluation period (p < 0.05). The ibuprofen group did not differ from the placebo group at the 4 and 48-hours postoperative periods (p > 0.05). Cumulative effect over 7 days showed significantly lower median pain scores for ibuprofen (0.0; 0.0 – 5.5), etoricoxib (0.0; 0.0 – 3.5) groups in comparison with placebo (1.0; 0.0 – 7.0) group (p < 0.05). Furthermore,

etoricoxib showed a significantly lower median value in comparison to ibuprofen group ($p < 0.05$).

Rescue medication was used in 75%, 83.33%, and 100% of surgical procedures receiving etoricoxib, ibuprofen, and placebo, respectively (table 3). Kaplan-Meyer method (Figure 3) showed that proportion of patients requiring rescue analgesic medication was a significantly higher in the placebo group, followed by ibuprofen and etoricoxib groups ($p = 0.0035$). According to Table 3, time (mean±SD) to first rescue medication intake was statistically different between etoricoxib (8.0±6.1 hours), ibuprofen (5.0±2.2 hours), and placebo (3.7±2.1 hours) groups ($p = 0.0239$). The mean of consumed rescue medication was different between ibuprofen (1.7±2.0), etoricoxib (0.8±06), and placebo (1.0±2.7) groups over the study periods ($p = 0.0052$). Overall medication consumption was lower in the etoricoxib group by comparison with placebo group ($p < 0.05$). Patients from the etoricoxib group ingested fewer rescue medicaments than the patients from placebo group on the day of surgery (0.7±0.5) and over a 24-hour period (0.2±0.4). Ibuprofen group showed a significantly lower rescue medication intake on the postoperative day 1 (0.3±0.7) by comparison with placebo group (1.3±0.9) with $p < 0.05$ (Table 3).

The swelling peak occurred 24 hours after surgical procedure in relation to all the facial measurements, showing elevated values when compared to baseline values (Table 4). There was no statistically significant difference between postoperative periods of evaluation in relation to the facial land markers AM-Tr ($p = 0.9640$), AM-ECE ($p = 0.9914$), AM-NB ($p = 0.1272$), AM-LC ($p = 0.3108$), and AM-SP ($p = 0.3298$) for the 3 compared groups (Repeated-Mensures-ANOVA-Two-way/Bonferroni test).

The AM-Tr and AM-NB measurements showed significant reduction on the etoricoxib group 72 hours after surgical procedure in relation to 24 h postoperative period ($p < 0.001$), and in the ibuprofen and placebo group reduction was seen only after the fifth postoperative day ($p < 0.001$). All of the studied groups presented significant reduction of the AM-ECE measurements after the fifth postoperative day in relation to 24-hour postoperative period ($p < 0.001$). The AM-LC measurements showed significant reduction in the etoricoxib and ibuprofen five days after surgery ($p < 0.001$), and in the placebo group this reduction occurred within seven days ($p < 0.001$). The AM-SP measurements of the placebo and etoricoxib groups decreased significantly 72 hours after surgery ($p < 0.001$) and in the ibuprofen group only after 5 days ($p < 0.001$) (Repeated-Mensures-ANOVA/Bonferroni). The cumulative effect of all facial measurements did not show significant difference between the evaluated groups in any of the postoperative moments as showed in the table 2 (Kruskall-Wallis/Dunn test).

Among study periods, there was no statistically significant difference between the 3 studied groups considering the postoperative measurements of maximum mouth opening ($p = 0.6973$). Cumulative effect showed a mean value of opening limitation significantly higher in the placebo group (39.2±6.9) than in etoricoxib (44.2±9.9) and ibuprofen (46.0±9.1) groups. There was no statistically significant difference between ibuprofen and etoricoxib groups (Table 5).

DISCUSSION

The present study evaluated the efficacy of NSAIDs drugs orally administrated, which represent commonly prescribed drugs in dentistry.[19] For this purpose, mandibular third molar surgery was chosen as a clinical model. The existence of different types of

models to evaluate the efficacy of oral analgesics is based on the relative frequency of the three types of pain: chronic (i.e.cancer patients), postpartum/episiotomy and postsurgical (i.e. orthopedic and dental surgery).[20]

Pain dental model can be allocated according to Cooper[21] in three procedure categories: complicated oral surgery, periodontal surgery and impacted third molar removal surgery. Since third molar removal surgery is associated with the occurrence of moderated postoperative pain in 40% of the cases and severe pain in 60% of the procedures,[22-24] pain after third molar removal has become the most utilized pharmaceutical model in clinical trials about acute pain, not differing on the analgesic efficacy potential when compared to other non-dentistry postsurgical models.[25]

In the present model of acute pain, a clinical double blinded, randomized and placebo controlled trial was performed to decrease bias occurrence that could interfere with the results.[26] Due to the fact that the interpretation of comparable pain experiences can differ not only from one person to the next, but within the same person at different time periods,[20] in the present research it was performed a crossed study where the patients acted as controls of themselves allowing reduction of the variables related to perception of pain and possible alterations derived from physiologic and psychological causes.[27] Besides, to decrease difference in each patient, the left and right sides should be “mirrored”, which is, similar with radicular formation pattern, position and degree of dental impactation.[28] Data homogeneity between the three groups in the present research was found due to the absence of statistically significant difference in relation to gender, age, number of surgical procedures, surgery duration, bone removal and/or tooth sectioning, postoperative bleeding and teeth position. According to Pozos-Guillen

et al.[29], the absence of significant difference in relation to the pain intensity found in between the studied groups is a result of the drug effect itself.

The clinical model adopted in the present study had as primary objective relief the antinociceptive action of NSAI preoperatively administrated. Besides being considered effective drugs in the management of pain after third molar removal,[19] NSAI have been commonly used in studies that evaluated the efficacy of preemptive analgesia as a strategy for pain control.[8,12,26,30,31] From the physiological point of view, NSAI would act reducing peripheral and central sensitivity. This last one would occur due to the reduction of the sensory inflow from the periphery to central nervous system.[32,33] Among the NSAI, there are ibuprofen and etoricoxib, non-selective COX-2 inhibitor and selective COX-2 inhibitor drugs respectively.[34] Due to the non-existence of study that evaluated the efficacy of the preemptive analgesic action of these drugs between themselves in third molar removal surgeries models, there is a lack of information regarding comparative results. To date, only one study has used preoperative etoricoxib.[12]

Pain intensity was considerably reduced when treated with Ibuprofen and mostly with etoricoxib. In a general evaluation, and in the mean postsurgical times, the pain scores were statistically inferior in the experimental groups in comparison to the placebo group in the present study. Morse et al.[8], comparing the preemptive analgesic efficacy between ibuprofen, rofecoxib (NSAI selective COX-2 inhibitor) and placebo observed that in all of the evaluation periods of the study, ibuprofen provided pain relief significantly superior to placebo. Rofecoxib also provided similar results except on the 1, 3 and 4 hour period when pain relief was not inferior to placebo. Besides that, the authors have shown that there was no significant difference between ibuprofen and

rofecoxib in any postoperative period. In the present study over a 72-hour period, ibuprofen did not show statistical difference in relation to placebo during the periods of 4 and 48 h, while etoricoxib display difference during this period of evaluation. Differently, Chiu et al.[30] performed a study with preemptively administrated ibuprofen and rofecoxib, and observed that in relation to placebo, ibuprofen did not show statistically significant reduction of pain scores in any of the periods evaluated, while rofecoxib showed significant reduction only in the postoperative first 6 hours. Besides that, it was seen on the present clinical trial that the cumulative effect of pain scores of the etoricoxib group was better than placebo 6 h and 7 days post operation. Ibuprofen displayed difference in the cumulative effect only after 7 days in relation to placebo. Therefore, despite no difference in between groups is seen, a better behavior of Etoricoxib in relation to ibuprofen should be taken under consideration. Contrary to this data observed in the present clinical trial, Sotto-Maior et al.[12] did not see a significant difference regarding pain when etoricoxib 120mg was used.

All the 3 studied groups in the present trial displayed a pain peak 6 hours after the surgical procedure, but this peak was statistically lower in the group treated with etoricoxib in relation to placebo group, which reinforces its role in preemptive analgesia. In studies that evaluated preoperatively administrated ibuprofen, not comparing with selective COX-2 inhibitor NSAIs, pain peaks during the postsurgical period between 0 and 1 hour,[35] 2 hours,[36] 3 hours,[37] 6 hours,[31] and 8 hours[26] were observed. In other two preemptive analgesia studies comparing ibuprofen with selective COX-2 inhibitor drugs the peak occurred 6 hours after the surgical procedure,[8,30] which was similar to the present work. In the Sotto-Maior et al.[12] study where preemptive Etoricoxib was utilized there is no information on the achieved pain peak.

The time elapsed between the end of surgical procedure and the use of the first rescue medication was different in the groups analyzed in the present work. The average for the etoricoxib group was statistically superior to placebo and ibuprofen group, in other words, patients who had etoricoxib took longer to require postoperative analgesic medication. This fact may reflect the drug pharmacokinetic in relation to its preemptive analgesic action. Ibuprofen is a drug rapidly absorbed by the gastrointestinal system and its maximum plasmatic concentration is 15.4 μg mL^{-1}. The time needed to reach the maximum plasmatic peak is 1.3 hours and the elimination half-life is 2.7 hours in average.[38] On the other hand, Etoricoxib is a drug that acts faster and for a longer period in the organism. Its maximum plasmatic concentration is 1.36 μg mL^{-1}. The time needed to reach this maximum plasmatic concentration is 1 hour and the elimination half-life is 24.9 hours.[39]

The apparent analgesic efficacy of the etoricoxib can also be reflected in the reduced number of rescue medication consumed during the evaluation period. It was seen on day 0, period with higher medication consumption, as well as during the overall postoperative period, that etoricoxib presented the lower medication ingestion rate by patients when compared to placebo. Ibuprofen also showed significant reduction of supplementary analgesic usage frequency two days after surgical procedure when compared to placebo. The ibuprofen and etoricoxib groups did not differ between themselves, though etoricoxib displayed lower improvement in this aspect. Morse et al.[8] also noted that the preemptive use of NSAIs significantly reduced the need for rescue medication and, similarly to results of the present paper, there was no difference between ibuprofen and the selective COX-2 inhibitor drug utilized. Chiu et al.[30] observed that the patients who utilized the selective COX-2 inhibitor drug required a smaller quantity of medication than the ones who utilized ibuprofen. Besides, the

superiority hypothesis of the etoricoxib sustained by the present research can also be reinforced when the group's average intensity of pain can be correlated with the number of rescue medication ingested. Both placebo and ibuprofen groups exhibited a direct relation between pain and medication consumption.

It is recognized that the inflammatory response is mediated by prostaglandins and its synthesis is initiated by the release of arachidonic acid from the cellular membrane phospholipids through the cyclooxygenase action. The consequence of this physiologic process includes interlinked events that are represented by pain, swelling and trismus.[40] It is important to observe that, even with a reduction of the pain scores in the groups treated with etoricoxib and ibuprofen, no interference with swelling and with maximum mouth opening was seen in the present research.

Etoricoxib showed an apparently good anti-inflammatory activity in relation to some facial measurements (AM-NB e AM-SP). However, in relation to the AM-SP measurement there was no difference to the placebo group. Besides that, ibuprofen had a worse outcome in that measurement, suggesting a reduced anti-inflammatory action. The multivariable analysis test did not show significance between groups therefore there was no important impact of the preemptive administration of etoricoxib or ibuprofen on swelling. All measurements displayed swelling peak in 24 hours and the reduction of swelling only occurred significantly from the fifth postoperative day despite the previous institution of NSAIs. Sotto-Maior et al.[12] did not observe significant difference of swelling with the preemptive use of Etoricoxib. Curiously, the authors concluded that during the 48-hour evaluation period there was an increase on facial swelling despite trismus reduction.

In summary, ibuprofen and etoricoxib significantly reduced the intensity of postoperative pain and the need for use of rescue medication compared to placebo group. Etoricoxib showed a better preemptive analgesic activity than ibuprofen. Both drugs did not exert significant anti-inflammatory effect able to reduce swelling and trismus in comparison with placebo group.

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FIGURES AND LEGENDS

Figure 1. Flow chart of patients recruited for study groups according to CONSORT statement.

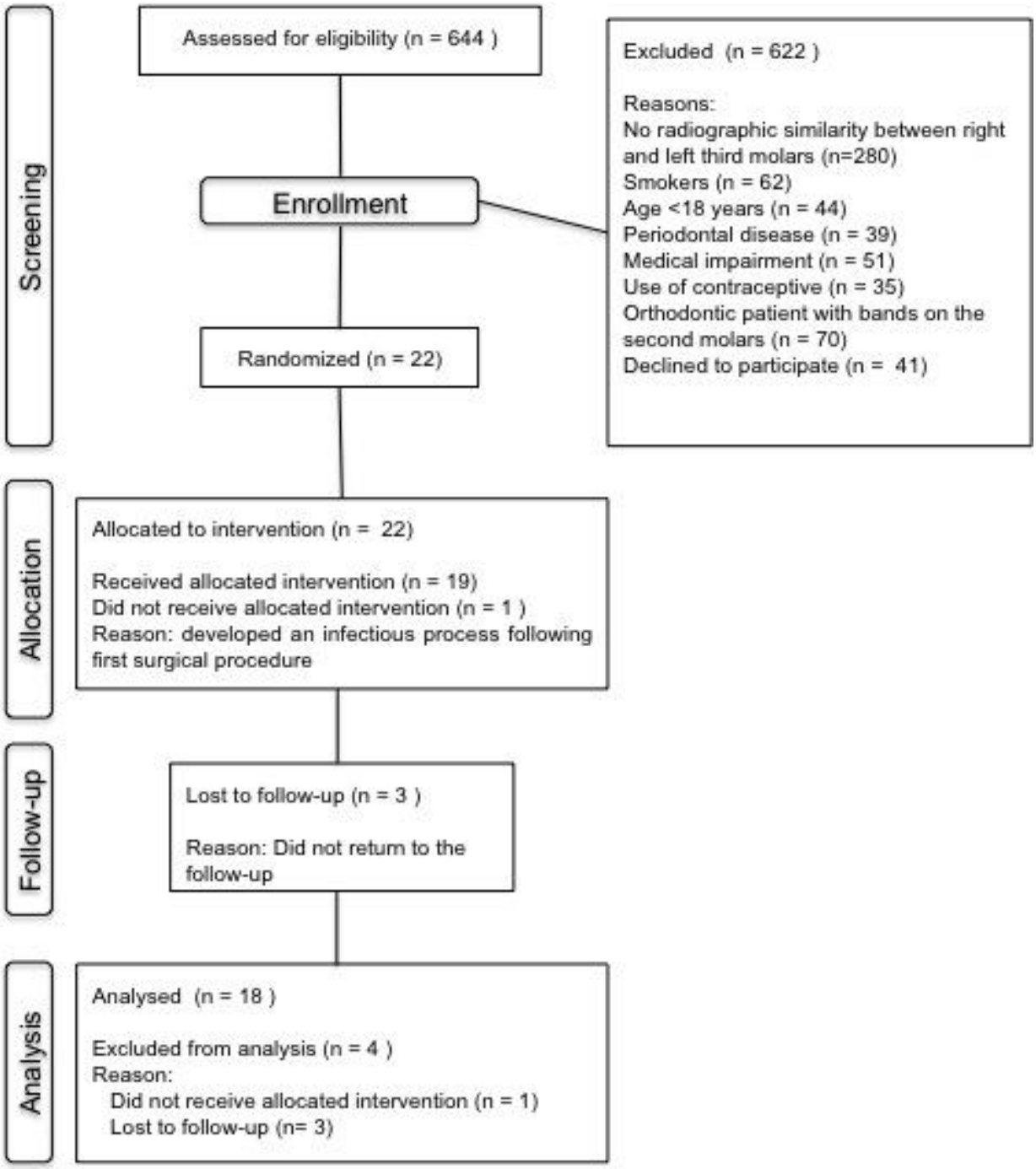


Figure 2. VAS pain intensity (mm) of the 3 drug groups recorded at specific time intervals postoperative. *p < 0.05 in relation to Placebo (Kruskall-Wallis/Dunn test). Data expressed as median (minimum – maximum).

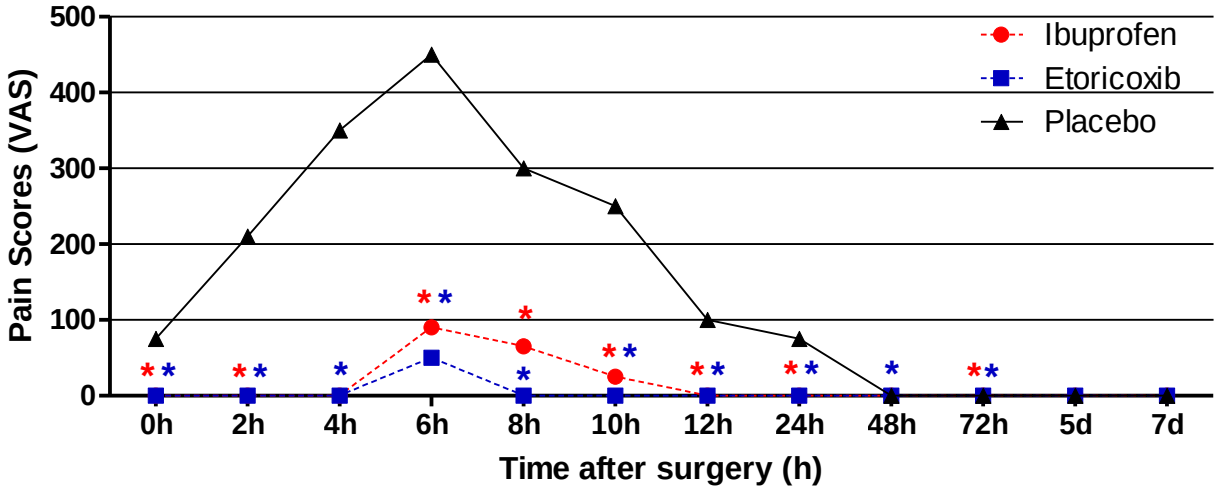
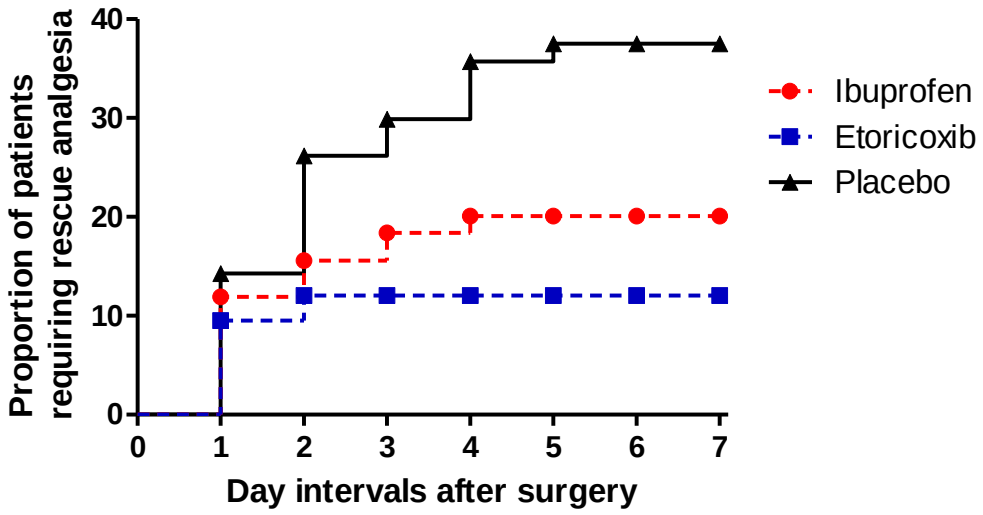


Figure 3. Kaplan-Meyer plot for ibuprofen, etoricoxib, and placebo groups, representing the proportion of patients in each group who required rescue analgesia (X^2=11.29, p=0.0035, Df=2).



TABLES AND LEGENDS

Table 1. Baseline characteristics of the 3 compared drug groups

	Placebo	Ibuprofen	Etoricoxib	*p*-value
Gender (male/female)	4/2	5/1	4/2	0.7581‡
Age (years)				
Mean±SD	24.42±4.98	23.00±4.09	24.08±4.66	0.7340*
Number of surgical procedures per group	12	12	12	1.0000‡
Duration of surgery (min)				
Mean±SD	15.03±1.93	14.85±1.22	15.15±2.49	0.9307*
Bone removal (yes/no)	12/0	12/0	12/0	1.0000‡
Tooth sectioning (yes/no)	8/4	8/4	5/7	0.3575‡
Number of dental cartridges	2.50 (2.00 - 3.00)	2.50 (2.00 - 2.50)	2.00 (2.00 - 3.00)	0.3038†
Postoperative bleeding (yes/no)	3/55	4/54	3/55	0.8993‡
Day 0	0/12	1/11	0/12	0.3575‡
Day 1	3/7	3/7	3/7	1.0000‡
Day 3	0/12	0/12	0/12	1.0000‡
Day 5	0/12	0/12	0/12	1.0000‡
Day 7	0/12	0/12	0/12	1.0000‡
Pell&Gregory position (I/II/III)	7/5/0	8/4/0	5/7/0	0.4598‡
Pell&Gregory position (A/B/C)	0/12/0	0/12/0	0/12/0	1.0000‡
Winter position (mesioangular/vertical)	8/4	9/3	10/2	1.0000‡

*ANOVA/Bonferroni test. Data expressed as mean ±SD.

†Kruskall-Wallis/Dunn test. Data expressed as median (minimum – maximum).

‡Chi-square test or Fisher exact test. Data expressed as absolute frequency.

Table 2. Values of postoperative VAS pain intensity (cm) of the 3 compared drug groups (n = 36 surgical procedures).

Period	Drug groups			*p*-value
	Placebo	Ibuprofen	Etoricoxib	
0 h	0.7 (0.0 - 2.0)	0.0 (0.0 - 1.0)*	0.0 (0.0-0.0)*	0.0012
2 h	2.1 (0.0 - 7.0)	0.0 (0.0 - 5.0)*	0.0 (0.0-0.5)*	0.0024
4 h	3.5 (0.0 - 6.5)	0.0 (0.0 - 4.5)	0.0 (0.0-3.5)*	0.0051
6 h	4.5 (2.0 - 7.0)†	0.9 (0.0 - 5.5)*†	0.5 (0.0-2.0)*	<0.0001
8 h	3.0 (1.5 - 5.6)	0.7 (0.0 - 5.0)*	0.0 (0.0-0.8)*	<0.0001
10 h	2.5 (0.5 - 5.0)	0.3 (0.0 - 5.0)*	0.0 (0.0-0.5)*	<0.0001
12 h	1.0 (0.0 - 4.0)	0.0 (0.0 - 4.7)*	0.0 (0.0-0.5)*	0.0006
24 h	0.7 (0.0 - 5.0)	0.0 (0.0 - 4.5)*	0.0 (0.0-1.0)*	0.0065
48 h	0.0 (0.0 - 4.5)‡	0.0 (0.0 - 2.0)‡	0.0 (0.0-0.0)*	0.0333
72 h	0.0 (0.0 - 3.0)‡	0.0 (0.0 - 0.0)*‡	0.0 (0.0-0.0)*	0.0128
5 days	0.0 (0.0 - 0.5)‡	0.0 (0.0 - 0.0)‡	0.0 (0.0-0.0)	0.3679
7 days	0.0 (0.0 - 0.0)‡	0.0 (0.0 - 0.0)‡	0.0 (0.0-0.0)	1.0000
Cumulative effect over 6 h	2.0 (0.0 - 7.0)	0.0 (0.0 - 5.5)*	0.0 (0.0 - 3.5)*	<0.0001
Cumulative effect over 7 days	1.0 (0.0 - 7.0)	0.0 (0.0 - 5.5)*	0.0 (0.0 - 3.5)*§	<0.0001

*$p < 0.05$ in relation to Placebo group (Kruskall-Wallis/Dunn test). Data expressed as median (minimum – maximum).
†$p < 0.05$ in relation to immediate postoperative period (Friedman/Dunn test). Data expressed as median (minimum – maximum).
‡$p < 0.05$ in relation to 6 h pain peak (Friedman /Dunn test). Data expressed as median (minimum – maximum).
§$p < 0.05$ in relation to Ibuprofen group (Kruskall-Wallis/Dunn test). Data expressed as median (minimum – maximum).

Table 3. Rescue analgesic medication consumption after surgical procedures (n = 36).

	Placebo	**Ibuprofen**	**Etoricoxib**	***p*-value**
Rescue medication intake (yes/no)	12/0	10/2	9/3	0.1967
Time to first rescue medication (hour)				
Median (minimum – maximum)	3 (2 - 8)	5 (2 - 8)	6 (4 - 24)†	0.0239
Mean±SD	3.7±2.1	5.0±2.2	8.0±6.1	
Number of rescue medication consumed (Mean±SD)				
Day 0	1.5±0.5	1.0±0.6	0.7±0.5†	0.0210
Day 1	1.3±0.9	0.3±0.7†	0.2±0.4†	0.0065
Day 2	0.5±1.0	0.3±0.8	0.0±0.0	0.2955
Day 3	0.4±0.7	0.1±0.3	0.0±0.0	0.1017
Day 4	0.1±0.3	0.0±0.0	0.0±0.0	0.4531
Day 5	0.0±0.0	0.0±0.0	0.0±0.0	1.0000
Day 6	0.0±0.0	0.0±0.0	0.0±0.0	1.0000
Day 7	0.0±0.0	0.0±0.0	0.0±0.0	1.0000
Overall medication consumption	1.0±2.7	1.7±2.0	0.8±0.6†	0.0052
Side effects (yes/no)	0/12	0/12	0/12	1.0000

†$p < 0.05$ in relation to Placebo group. There was no statisticaly significant difference for the number of patients taking rescue medication between Ibuprofen and Etoricoxib groups (Kruskall-Wallis/Dunn test). Data expressed as median (minimum – maximum).

Table 4. Values of facial swelling of the 3 compared drug groups according to postoperative period (n = 36 surgical procedures).

Facial measurements	Period	Drug groups			*p*-value
		Placebo	Ibuprofen	Etoricoxib	
AM-Tr	Baseline	5.70±0.81	5.58±0.53	5.58±0.52	*0.9640
	24 h	6.49±0.74	6.33±0.56	6.36±0.64	
	72 h	6.33±0.80	6.19±0.63	6.07±0.65†	
	5 days	5.95±0.75†	5.77±0.60†	5.77±0.55†	
	7 days	5.73±0.78†	5.62±0.52†	5.60±0.52†	
AM-ECE	Baseline	9.90±0.81	9.98±0.56	9.98±0.56	*0.9914
	24 h	10.73±0.89	10.77±0.81	10.65±1.02	
	72 h	10.42±0.79	10.55±0.86	10.38±0.74	
	5 days	10.15±0.82†	10.28±0.67†	10.14±0.62†	
	7 days	9.98±0.80†	10.06±0.61†	9.99±0.58†	
AM-NB	Baseline	5.70±0.81	5.58±0.53	5.58±0.52	*0.1272
	24 h	6.49±0.74	6.33±0.56	6.36±0.64	
	72 h	6.33±0.80	6.19±0.63	6.07±0.65†	
	5 days	5.95±0.75†	5.77±0.60†	5.77±0.55†	
	7 days	5.73±0.78†	5.62±0.52†	5.60±0.52†	
AM-LC	Baseline	8.38±0.52	8.86±0.48	8.56±0.59	*0.3108
	24 h	9.11±0.60	9.77±0.79	9.30±0.90	
	72 h	9.14±0.61	9.68±0.77	9.05±0.62	
	5 days	8.98±0.82†	9.23±0.50†	8.77±0.60†	
	7 days	8.45±0.51†	8.92±0.42†	8.56±0.56†	
AM-SP	Baseline	10.03±0.67	10.25±0.24	10.08±0.60	*0.3298
	24 h	11.03±0.82	11.11±0.62	11.14±0.79	
	72 h	10.60±0.76†	10.89±0.56	10.48±0.70†	
	5 days	10.35±0.72†	10.49±0.46†	10.21±0.65†	
	7 days	10.05±0.67†	10.32±0.21†	10.08±0.60†	
Cumulative effect	Baseline	9.4 (4.5 - 12.0)	9.8 (4.9 - 11.4)	9.5 (4.6 - 11.3)	**0.4957
	24 h	10.1 (5.5 - 12.6)	10.7 (5.3 - 12.6)	10.3 (5.1 - 12.6)	**0.5969
	72 h	9.8 (5.4 - 12.2)	10.6 (5.1 - 12.8)	9.8 (4.8 -11.8)	**0.2685
	5 days	9.5 (5.2 - 11.9)‡	10.2 (4.9 - 12.0)‡	9.5 (4.6 -11.3)‡	**0.3748
	7 days	9.4 (4.6 - 11.9)‡	10.0 (4.9 - 11.6)‡	9.5 (4.6 - 11.3)‡	**0.3708

*Repeated-Measures-ANOVA-Two-way/Bonferroni test (row factor x colunn factor). Data expressed as mean ±SD.

** Kruskall-Wallis/Dunn test. Data expressed as median (minimum – maximum).

†$p < 0.001$ in relation to 24h postoperative period (Re-ANOVA/Bonferroni test). Data expressed as mean ±SD.

‡$p < 0.001$ in relation to 24h postoperative period (Friedman/Dunn test). Data expressed as median (minimum – maximum).

Table 5. Maximum mouth opening mean values (n = 36 surgical procedures).

Period	Drug groups			*p*-value
	Placebo	**Ibuprofen**	**Etoricoxib**	
0 h	43.8±5.2	48.9±8.3	48.2±9.3	
24 h	32.8±5.4	41.3±9.8	37.5±8.9	
72 h	35.6±5.9	44.1±9.7	41.8±9.9†	*0.6973
5 days	40.4±6.1†	47.0±8.4†	45.5±9.4†	
7 days	43.4±5.3†	48.8±8.3†	48.0±9.4†	
Cumulative effect	39.2±6.9	46.0±9.1‡	44.2±9.9‡	< 0.0001

*Repeated-Measures-ANOVA-Two-way/Bonferroni test (row factor x column factor). Data expressed as mean±SD.

†$p < 0.001$ in relation to 24h postoperative period (Re-ANOVA/Bonferroni test). Data expressed as mean ± SD.

‡$p < 0.001$ in relation to Placebo group (ANOVA/Bonferroni test). Data expressed as mean ± SD.

4. CONCLUSÃO GERAL

Em resumo, ibuprofeno e etoricoxib reduziram significativamente a intensidade da dor pós-operatória e a necessidade do uso de medicação de resgate quando comparados ao grupo placebo. Etoricoxib mostrou uma melhor atividade analgésica preemptiva do que o ibuprofeno. Ambas as drogas não exerceram significante efeito anti-inflamatório capaz de reduzir edema e trismo. Estudos futuros com um maior número de pacientes devem ser realizados a fim de se confirmar os resultados do presente estudo.

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ANEXO

Anexo 1 – Aprovação do Comitê de Ética em Pesquisa com Seres Humanos

MINISTÉRIO DA SAÚDE - Conselho Nacional de Saúde – Comissão Nacional de Ética em Pesquisa - CONEP

Academia Cearense de Odontologia
Centro de Educação Continuada
"A Excelência do Ensino Pós-Graduado na Odontologia Cearense"

COMITÊ DE ÉTICA EM PESQUISA – ACO/CEC

O Comitê de Ética em Pesquisa da Academia Cearense de Odontologia autoriza ao Dr. Fábio Wildson Gurgel Costa a modificação do título do seu projeto de pesquisa "Avaliação da Analgesia Pré-Emptiva do Ibuprofeno e Nimesulida em cirurgia de Terceiros Molares: Um ensaio clínico randomizado, duplo-cego, placebo-controlado, cruzado". A Nimesulida foi substituída por Etoricoxib, que é um medicamento da mesma classe farmacológica e com ação semelhante. A mudança do medicamento Nimesulida por Etoricoxib deveu-se ao fato deste último apresentar um efeito mais potente sob o controle da dor pós-operatória se comparado à Nimesulida. Sendo assim, acreditamos que o Etoricoxib seria mais benéfico aos voluntários da pesquisa. Além disso, essa mudança não acarreta alteração nenhuma na metodologia do estudo, apenas a substituição de um medicamento por outro. Desse modo, o novo título será: **"Avaliação da Analgesia Pré-Emptiva do Ibuprofeno e Etoricoxib em cirurgia de Terceiros Molares: Um ensaio clínico randomizado, duplo-cego, placebo-controlado, cruzado".**

Fortaleza, 05 de março de 2013.

Marlene Lopes Cidrack
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