UNIVERSIDADE FEDERAL DO CEARÁ

FACULDADE DE FARMÁCIA, ODONTOLOGIA E ENFERMAGEM

PROGRAMA DE PÓS-GRADUAÇÃO EM ODONTOLOGIA

ERNEST CAVALCANTE POUCHAIN

ESTUDO COMPARATIVO DA AÇÃO DA NIMESULIDA E DO CETOPROFENO SOBRE OS EVENTOS INFLAMATÓRIOS EM CIRURGIAS DE TERCEIROS MOLARES: ESTUDO BOCA-DIVIDIDA, PROSPECTIVO, RANDOMIZADO, DUPLO-CEGO

FORTALEZA

2012

ERNEST CAVALCANTE POUCHAIN

ESTUDO COMPARATIVO DA AÇÃO DA NIMESULIDA E DO CETOPROFENO SOBRE OS EVENTOS INFLAMATÓRIOS EM CIRURGIAS DE TERCEIROS MOLARES: ESTUDO BOCA-DIVIDIDA, PROSPECTIVO, RANDOMIZADO, DUPLO-CEGO

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

Área de Concentração: Clínica Odontológica
Orientador: Prof. Dr. Eduardo Costa Studart Soares

FORTALEZA
2012

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

P894e Pouchain, Ernest Cavalcante.
Estudo comparativo da ação da nimesulida e do cetoprofeno sobre os eventos inflamatórios em cirurgias de terceiros molares: estudo boca-dividida, prospectivo, randomizado, duplo-cego / Ernest Cavalcante Pouchain. – 2012.
45 f. : il.

Dissertação (Mestrado) – Universidade Federal do Ceará, Faculdade de Farmácia, Odontologia e Enfermagem, Departamento de Clínica Odontológica, Programa de Pós-Graduação em Odontologia, Mestrado em Odontologia, Fortaleza, 2012.
Área de Concentração: Clínica Odontológica.
Orientação: Prof. Dr. Eduardo Costa Studart Soares.

1. Dente Serotino. 2. Anti-Inflamatórios. 3. Ensaio Clínico. 4. Dor. 5. Edema. 6. Trismo. I. Título.

CDD 617.66

ERNEST CAVALCANTE POUCHAIN

ESTUDO COMPARATIVO DA AÇÃO DA NIMESULIDA E DO CETOPROFENO SOBRE OS EVENTOS INFLAMATÓRIOS EM CIRURGIAS DE TERCEIROS MOLARES: ESTUDO BOCA-DIVIDIDA, PROSPECTIVO, RANDOMIZADO, DUPLO-CEGO

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

Aprovada em

BANCA EXAMINADORA

_____

Prof. Dr. Eduardo Costa Studart Soares

_____

Prof. Dr. Rodrygo Nunes Tavares

_____

Prof. Dr. Tácio Pinheiro Bezerra

Dedico este trabalho ao meu
tio e pai Sérgio Pouchain

“A vida esconde nos lugares mais simples sua
grande beleza que revela qual o significado de
porque persistimos em continuar vivendo”
(Pablo Neruda)
“Sábio é o homem que chega a ter
consciência de sua ignorância”
(Barão de Itararé)

AGRADECIMENTOS ESPECIAIS

A Deus, pela paz que vem me dando durante todos estes anos e, acima de tudo, pela minha saúde, que me possibilita desenvolver todas as atividades essenciais à minha vida pessoal, profissional e facilita, assim, a realização de todos os meus sonhos.

Ao tio, padrinho e, acima de tudo, o Pai, Sérgio Pouchain, pelo amor e carinho que recebo de forma sincera e dedicada. O homem que me encoraja a realizar todos os meus sonhos pessoais e profissionais. Um exemplo de vida para a minha profissional, pelo seu caráter admirável, dignidade, responsabilidade e compromisso com os seus pacientes. Peço a Deus todos os dias que ilumine os caminhos dele e que Ele possa dar ao meu pai uma vida longa e próspera, com muita saúde e amor.

Ao meu pai Tácito, minha mãe Ambrosina e meu padrasto Ronaldo, por todas as palavras de carinho e incentivo nos momentos de dificuldade e por compreenderem a minha ausência em diversas ocasiões.

Aos meus irmãos Sérgio e Raquel, por todo o amor que nutrem por mim e pela compreensão da minha ausência em nossos eventos familiares.

À minha namorada Nicole Moura, por todo o amor e carinho, além das palavras de incentivo na horas de grande dificuldade e pela compressão durante os momentos de ausência e de impaciência.

Aos sobrinhos Ednardo Neto, Ana Cecilia e Júlia pelo carinho que dão ao tio.

Aos cunhados Lucas Pinheiro e Kelma Lima, pelo acolhimento e respeito com que sempre me trataram.

À minha prima/irmã Maira Barreto e seu esposo e compadre Erick Araújo muito obrigado por compartilharem comigo momentos especiais na minha vida.

À senhora Maria do Carmo por todo o cuidado e a dedicação que vem dando a toda a minha família durante estes anos, desde o primeiro banho do neto mais velho (Ernest C. Pouchain), passando pelos cuidados de minha avó (Reine Pouchain), quando esteve enferma, até os dias de hoje.

À tia Mazé e ao tio Stênio, aos Hugo e Stefeson que me acolhem quando necessário em sua casa nos dias de maior dificuldade e correria no hospital.

Ao casal de amigos Wálbert Lima e Vanda Tomaz e às amigas Thayssa Tomaz Lima e Yana Tomaz Lima, pelas palavras de incentivo nos momentos de dúvida e angústia da vida profissional, além do carinho e respeito com que sempre fui tratado por esta família.

Ao professor, amigo e orientador Eduardo Costa Studart Soares, por toda a dedicação que tem e teve na orientação dos meus trabalhos, pela paciência que teve na condução desta caminhada e, principalmente, um muito obrigado por deixar eu fazer parte desta família científica que o senhor lidera tão brilhantemente e ainda por ter possibilitado a realização de um sonho que se iniciou em 2005 ainda como estagiário do curso de cirurgia da Academia Cearense de Odontologia.

Ao professor e grande amigo Alexandre Simões Nogueira, por todos os ensinamentos que me foi passado durante o período da graduação, pós-graduação e quando atuei como professor substituto em Sobral, onde iniciei as minhas primeiras atividades profissionais, inclusive como docente.

Ao professor e amigo Tácio Pinheiro Bezerra, pelos conselhos sempre valiosos na vida pessoal e profissional e pelo grande incentivo tanto no início como no final da construção deste trabalho.

Ao professor e amigo Fábio Wildson Gurgel Costa, pelos ensinamentos que vem me proporcionando durante todos estes anos assim como pela ajuda inexplicável ao final desta obra, o que me possibilitou a sua conclusão no tempo esperado. O meu muito obrigado!

Ao professor Wagner Freire, pelos primeiros ensinamentos dentro da Cirurgia Buco-Maxilo e pelas oportunidades que sempre me proporcionou.

Aos grandes amigos de fé e colegas de residência Carlos Bruno Nogueira e José Rômulo de Medeiros, pela compreensão em compartilhar as cirurgias e pela forma indistinta que sempre fui tratado, mesmo sendo aluno do mestrado, além do suporte necessário na realização das cirurgias.

Aos professores e amigos Marcelo Ferraro e Rafael Linard, por todos os conhecimentos e conselhos transmitidos.

Aos amigos, o residente Dr. Diego Esses e o dentista Dr. Erick Fontenele, pela ajuda insuperável da condução das cirurgias.

À amiga e companheira de residência Bárbara Carneiro, pela parceria e pela compreensão da minha ausência no período final deste trabalho.

Ao Dr. Paulo Beltrão, pela sua imensa disponibilidade na realização das cirurgias dos pacientes desta pesquisa em seu ambiente de trabalho, como também pelo conhecimento científico, o qual sempre me orientou em momentos de dificuldades, além das conversas informais descontraídas e bem humoradas nos intervalos de trabalho.

A todos os meus pacientes que participaram deste pesquisa e que se colocaram sempre à disposição nos momentos em que se fizeram necessários.

AGRADECIMENTOS

À Universidade Federal do Ceará, pelas oportunidades a mim oferecidas: o início da minha vida profissional como docente, a conclusão do mestrado e a possibilidade de realizar a residência em Cirurgia Buco-Maxilo.

À Universidade de Fortaleza e todo o corpo docente do curso de Odontologia, pela oportunidade de realizar a minha graduação em Odontologia.

À coordenadora do Programa de Pós-Graduação em Odontologia da Universidade Federal do Ceará, Profa. Dra. Lidiany Rodrigues pela grande contribuição na análise estatística deste trabalho, e em nome da qual agradeço a todos o professores do programa pelos ensinamentos e tempo de dedicação em prol da nossa formação.

Ao professor Dr. Henrique Scarparo, por todos os seus ensinamentos profissionais e pelos momentos de grande diversão em conversas informais.

Às professoras doutoras Andreá Aguiar e Cristiane Fonteles, por seu empenho em prol deste trabalho.

Ao colega de mestrado Paulo Goberlândio de Barros Silva, pela grande ajuda da interpretação e ajustes dos dados estatísticos.

Ao colega de residência Carlos Diego, pela troca de conhecimento sempre engrandecedora.

A todos os professores e servidores do curso de Odontologia da Universidade Federal do Ceará - Campus Sobral, pela oportunidade do convívio com todos e pelos conhecimentos que adquiri durante o período que com vocês compartilhei.

A todos os alunos dos curso de Odontologia da Universidade Federal do Ceará - Campus Sobral, pela oportunidade que recebi por ter atuado como professor substituto e pela confiança que em mim depositaram.

A todos os alunos dos curso de Odontologia da Universidade Federal do Ceará pelas contribuições que me deram e que me enriqueceram de forma pessoal e profissional, durante o período que estive como aluno do mestrado.

Aos estagiários Soraia Rodrigues, Karol Silveira, Mariana, Isabela, Fabricio, Eduardo Emim, pela ajuda nas cirurgias.

Às atendentes Sônia (Soninha da Estomato), Lucineide (a Lu do CEO) e Sandra Velma, pela forma dedicada e atenciosa com que me trataram durante a triagem e o acompanhamento dos pacientes desta pesquisa.

À professora Marivan Ferraro, pela revisão gramatical do presente trabalho.

Às secretárias do Programa de Pós-Graduação em Odontologia, pela atenção e pelo apoio sempre prestados.

E, finalmente, a todos que, mesmo não citados aqui, de alguma forma, direta ou indiretamente, contribuíram para a realização deste trabalho.

RESUMO

A remoção cirúrgica dos terceiros molares é considerado um procedimento relativamente comum em odontologia, no qual uma reação inflamatória aguda é particularmente observada durante os três primeiros dias pós-operatórios. Diversos ensaios clínicos têm utilizado o modelo farmacológico com a cirurgia de terceiros molares, para avaliar o efeito de medicamentos nos eventos pós-operatórios. No entanto nenhum estudo comparando o cetoprofeno e a nimesulida administrados por via oral foi publicado. O objetivo do presente trabalho foi comparar o efeito do cetoprofeno e da nimesulida sobre parâmetros inflamatórios relacionados à remoção de terceiros molares. Foi realizado um estudo piloto duplo-cego, randomizado, prospectivo, do tipo "boca-dividida" em pacientes submetidos à remoção de quatro terceiros molares sob anestesia local. A amostra foi composta por 18 pacientes que seguiram os critérios de inclusão e exclusão do presente estudo. Cada paciente recebeu dois procedimentos cirúrgicos, sendo um lado experimental e outro controle. A escolha dos tratamentos foi de forma aleatória a qual indicava o uso de nimesulida 100 mg (controle) ou cetoprofeno 100 mg (experimental) duas vezes por dia durante 3 dias após o primeiro procedimento. Após a segunda cirurgia o outro medicamento era utilizado seguindo-se a mesma posologia. O número de medicamentos de resgate, intensidade de dor, edema e abertura bucal máxima foram avaliados. Os períodos da intensidade de dor foram avaliados com 6, 12, 24, 72 horas e 7 dias enquanto que edema e abertura bucal foram avaliados com 24, 72 horas e 7 dias. Em relação à dor, o pico máximo ocorreu 6 horas após o procedimento cirúrgico e não houve diferença estatisticamente significante entre os grupos. O sexo feminino foi o mais prevalente (88,8%). O tempo médio das cirurgias foi de 29 minutos (± 7,2 min). Nenhum paciente necessitou de medicação de resgate. Não houve diferença estatisticamente significante entre os grupos com relação ao edema e o trismo, porém, quando os grupos de medicamentos foram avaliados individualmente, este mostraram redução significante no limite de abertura após 72 horas e 7 dias ($P < 0.0001$) para ambos os grupos. De acordo com os resultados do presente estudo piloto, tanto o cetoprofeno quanto a nimesulida mostraram-se eficazes no controle da dor, edema e trismo após cirurgia para remoção de terceiros molares.

Palavras-chave: Dente serotino, Antiinflamatórios, Ensaio clínico, Dor, Edema, Trismo.

ABSTRACT

This study aimed to compare the effect of nimesulide and ketoprofen on inflammatory parameters related to the surgical removal of third molars. A split-mouth, prospective, randomized, double-blind study was conducted in patients undergoing removal of four third molars. Eighteen eligible patients were allocated to one of two groups to receive treatment two times a day with either ketoprofen 100 mg or nimesulide 100 mg for a period of 3 days. The rescue medication intake (number) and pain intensity were evaluated at 6, 12, 24, and 48 h, and at 7 days postoperative. Swelling and maximum mouth opening were evaluated at 24 h, 72 h, and 7 days postoperatively. The peak pain score occurred at 6 h (nimesulide group) and 12 h (ketoprofen group) after surgery. There was no statistically significant difference between the groups, although pain relief was observed after 48 h in the nimesulide group and after 7 days in the ketoprofen group. In each group, there was a statically significant difference in pain scores among the studied periods ($P < 0.0001$). None of the patients required rescue medication. There was a statistically significant difference in maximum mouth opening between the preoperative and postoperative periods ($P < 0.0001$). Ketoprofen and nimesulide were effective at controlling pain, swelling, and trismus after the surgical removal of third molars.

Keywords: Third molar, Anti-inflammatory drugs, Clinical trial, Pain, Swelling, Trismus.

LISTA DE ABREVIATURAS

AINES	Anti-inflamatório não esteroidal
COX-2	Enzima cicloxigenase tipo 2
COX-1	Enzima cicloxigenase tipo 1
NSAIDS	Non-steroidal anti-inflammatory drugs
ASA	America Society of Anesthesiologists
INR	International Normalized Ratio
VAS	Visual Analogue Scale
Tr-Gn	*Tragus-Gnatio*
Tr-Exo	*Tragos-Exocanthio*
Tr-Al	*Tragus-Alare*
Tr-Che	*Tragus-Cheilio*
Go-Gn	*Gonio-Gnatio*
Go-Exo	*Gonio-Exocanthio*
Go-Al	*Gonio-Alare*
Go-Che	*Gonio-Cheilio*
CPMP	Committee for Proprietary Medicinal Products
EMEA	European Medicines Agency

SUMÁRIO

1. INTRODUÇÃO GERAL

Um dente impactado é aquele que não consegue erupcionar na arcada dentária dentro do tempo esperado. Ele se torna impactado devido aos dentes adjacentes, recobrimento por osso denso, excesso de tecidos moles, ou uma anomalia genética que evita a erupção (HUPP, 2009).

Os terceiros molares são os dentes que mais frequentemente apresentam-se em situações de inclusão, sendo que os estudos epidemiológicos mostram maior prevalência de inclusões dentárias de terceiros molares inferiores (NESS; PETERSON, 2008). Segundo MARZOLA (1995), a menor frequência de inclusões de terceiros molares superiores é explicada pela estrutura anatômica da maxila, mais esponjosa que a mandíbula. Sendo assim, o tecido ósseo que envolve este dente é mais delgado, sendo facilmente reabsorvido pelas forças de erupção aplicadas pelos terceiros molares superiores.

A remoção de dentes impactados é um dos procedimentos cirúrgicos mais realizados pelos cirurgiões buco-maxilo-faciais, sendo considerada por muitos uma das cirurgias mais desafiadoras (NESS; PETERSON, 2008).

Um dente impactado pode causar ao paciente problemas de média e alta complexidade se permanecer nesse estado. Nem todo dente impactado causa um problema clínico significante, ainda que tenha potencial para tanto (NESS; PETERSON, 2008). Não existe um consenso na literatura sobre a indicação de exodontia profilática dos terceiros molares inclusos assintomáticos, sendo a pericoronarite, a principal indicação da exérese dos terceiros molares inferiores sintomáticos (PORTO et al., 2009).

A extração cirúrgica de um terceiro molar impactado é geralmente seguida por dor aguda pós-operatória (LEVRINI et al., 2008). O controle da dor e da inflamação pós-operatórias das cirurgias de terceiros molares pode ser feita com uso de anti-inflamatórios não esteroidais (AINES), considerando que estes previnem a dor e o edema (LEONE et al., 2007).

Não existe na literatura uma indicação absoluta de qual AINES deve ser usado no pós-operatório de cirurgia de terceiros molares (LEVRINI et al., 2008).

Os AINES desenvolvem sua ação sobre os nociceptores, seja por meio da inibição da enzima cicloxigenase ou das prostaglandinas. Decorrente desta sua ação, os AINES podem ser indicados como medicação pré e pós-operatória, nas intervenções odontológicas, onde haja expectativa de resposta inflamatória de maior intensidade, com o objetivo de prevenir a dor e o edema excessivo, (ANDRADE; RANALI; VOLPATO, 2002) como acontece nas cirurgias de terceiros molares.

O cetoprofeno é um AINES da classe do ácido propiônico bastante utilizado no tratamento de condições inflamatórias agudas e crônicas, que variam de dor pós-operatória à artrite reumatóide (BJORNSSON et al., 2003). Este medicamento, considerado um AINES tradicional, reduz não apenas o edema pós-operatório (BJORNSSON et al., 2003), mas também proporciona alívio da dor em dose única, variando de 12,5 mg até 100 mg (COOPER; GELB; GOLDMAN, 1984; COOPER; BERRIER; COHN, 1988; SUNSHINE; OLSON; ZIGHELBOIM, 1993; SEYMOUR; KELLY, 1996).

A nimesulida é uma AINES de modo de ação únicox (RAINSFORD, 2006). Esta droga tem ação preferencial nas prostaglandinas produzidas pela enzima cicloxigenase tipo 2 (COX-2), altamente expressa nos processos inflamatórios. Ao mesmo tempo, a nimesulida inibe minimamente a cicloxigenase tipo 1 (COX-1), a qual desempenha papel importante na manutenção da integridade da mucosa gástrica (WARNER et al., 1999). O uso da nimesulida no tratamento da dor após cirurgia buco-maxilo-facial, incluindo àquela associada a cirurgia de dentes inclusos, têm sido amplamente documentada em ensaios clínicos, do tipo randomizados e duplo-cegos. (STEFANONI; SACCOMANNO; SCARICABAROZZI, 1990; ARBEX; WASSAL; NUNES, 1992; FERRARI-PARABITA; ZANETTI; SCALVINI, 1993)

Diante do exposto, faz-se necessário a realização de estudos que identifiquem medicamentos que minimizem os eventos inflamatórios associados à cirurgia de terceiros molares. Embora um número reduzido de trabalhos tenha se dedicado a avaliar o efeito do cetoprofeno e da nimesulida sobre a dor pós-operatória em cirurgias de terceiros molares, muito pouco se sabe acerca da ação de tais drogas sobre os demais eventos inflamatórios desencadeados por tais procedimentos cirúrgicos. Desta forma, o objetivo deste trabalho é comparar o efeito do cetoprofeno e da nimesulida sobre a dor, o edema e o trismo após a exodontia de terceiros molares.

2. PROPOSIÇÃO

Objetivo Geral:

- Avaliar o efeito do cetoprofeno e da nimesulida sobre os eventos inflamatórios associados as cirurgias de terceiros molares.

Objetivos Específicos:

- Avaliar o efeito clínico do cetoprofeno sobre a dor, edema, máxima abertura bucal após a realização de cirurgias para a remoção de terceiros molares.

- Avaliar o efeito clínico da nimesulida sobre a dor, edema, máxima abertura bucal após a realização de cirurgias para a remoção de terceiros molares.

- Comparar os efeitos clínicos do cetoprofeno com o da nimesulida sobre a dor, edema, máxima abertura bucal após a realização de cirurgias para a remoção de terceiros molares.

3. CAPÍTULO

Esta dissertação está baseada no Artigo 46, do Regimento Interno do Programa de Pós-Graduação da Universidade Federal do Ceará, que regulamenta o formato alternativo para dissertações de Mestrado 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 do Hospital Universitário Walter Cantídio (Anexo 1).

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

3.1 Capítulo 1

"Comparative study about the effect of nimesulide and ketoprfen on inflammatory events in third molars surgeries: a split-mouth, prospective, randomized, double-bind study." Este artigo seguiu normas de publicação do periódico *Journal of Oral and Maxillofacial Surgery* (ISSN 0278-2391)

Comparative study about the effect of nimesulide and ketoprofen on inflammatory events in third molars surgeries: a split-mouth, prospective, randomized, double-bind study

TITLE PAGE

Comparative study about the effect of nimesulide and ketoprofen on inflammatory events in third molars surgeries: a split-mouth, propective, randomized, double-blid study

Authors:

Ernest Cavalcante POUCHAIN – DDS, MS

Fábio Wildson Gurgel COSTA – DDS, MS

Tácio Pinheiro BEZERRA – DDS, MS, PhD

Eduardo Costa STUDART-SOARES – DDS, MS, PhD

Intitutional Affiliation:

Post-Graduation Program in Dentistry of the Federal University of Ceará

Address: St. Monsenhor Furtado, without number. Rodolfo Teófilo

60.430-350 – Fortaleza – Ceará – Brazil

Corresponding Author: Ernest C. Pouchain

Address: St. Amelia Benebiem 333, apto 801. Papicu. 60.176-010 – Fortaleza – Ceará– Brazil

Phone: 55-85-99981426 55-85-32653792

e-mail: ernestpouchain@gmail.com ernestpouchain@me.com

Keywords:

Third molar, Anti-inflammatory drugs, Clinical trial, Pain, Swelling, Trismus.

Abstract

This study aimed to compare the effect of nimesulide and ketoprofen on inflammatory parameters related to the surgical removal of third molars. A split-mouth, prospective, randomized, double-blind study was conducted in patients undergoing removal of four third molars. Eighteen eligible patients were allocated to one of two groups to receive treatment two times a day with either ketoprofen 100 mg or nimesulide 100 mg for a period of 3 days. The rescue medication intake (number) and pain intensity were evaluated at 6, 12, 24, and 48 h, and at 7 days postoperative. Swelling and maximum mouth opening were evaluated at 24 h, 72 h, and 7 days postoperatively. The peak pain score occurred at 6 h (nimesulide group) and 12 h (ketoprofen group) after surgery. There was no statistically significant difference between the groups, although pain relief was observed after 48 h in the nimesulide group and after 7 days in the ketoprofen group. In each group, there was a statically significant difference in pain scores among the studied periods ($P < 0.0001$). None of the patients required rescue medication. There was a statistically significant difference in maximum mouth opening between the preoperative and postoperative periods ($P < 0.0001$). Ketoprofen and nimesulide were effective at controlling pain, swelling, and trismus after the surgical removal of third molars.

Key words: analgesia, third molar, nimesulide, ketoprofen, split-mouth

Introduction

The surgical removal of impacted third molars is considered the most common outpatient procedure among oral surgeries[1–3]. Normally, an inflammatory reaction with pain, swelling, and trismus is observed as a result of this procedure[1–3]. The removal of third molars is commonly associated with a significant change in quality of life[4], particularly during the first three postoperative days[5]. Therefore, it is necessary to take measures to control the

postoperative inflammatory events. Such measures include cryotherapy[6], laser application[7], and NSAIDs (non-steroidal anti-inflammatory drugs)[8,9].

Nimesulide (4-nitro-2-phenoxy methane sulfonanilide) belongs to the group of sulfanilamide derivatives, differing from other NSAIDs by presenting a sulfonanilide radical rather than a carboxylic radical[9]. This drug is a partially selective cyclooxygenase 2 enzyme (COX-2) inhibitor, used for the treatment of acute pain, such as that associated with osteoarthritis. It is currently accepted for use in countries of different regions of the world, including Europe, Latin America, and Asia. Nimesulide has shown efficacy in the treatment of acute pain associated with different diseases, such as back pain, toothache, postoperative pain and inflammation, and headache and migraine[9–13]. Its efficiency has been evaluated in more than 200 clinical studies, which have included more than 90,000 patients with inflammatory and acutely painful conditions[9]. The use of nimesulide in the symptomatic treatment of inflammatory pain is supported by the rapid onset of the analgesic drug effect, which becomes apparent at 15 min after its administration. Thus, nimesulide is a valuable option when the rapid relief of pain is required[14,15].

Ketoprofen is an effective inhibitor of cyclooxygenase and prostaglandin synthesis[16], demonstrating antipyretic, analgesic, and anti-inflammatory properties[17,18]. This drug has been used in the treatment of musculoskeletal disorders, and evidence from clinical studies suggests that ketoprofen is as effective as other anti-inflammatories in the reduction of postoperative pain and discomfort[8]. Following third molar removal, this drug relieves pain approximately 25.5 min after its administration[19].

Several clinical trials have been conducted to compare the action of acetaminophen[1,19,20], ibuprofen[19], ketorolac[21], meloxicam[22], ketoprofen[8,20,23,24], and nimesulide[22,24] in the control of inflammatory events after third molar surgery. To date, only one study has been performed to compare the effects of nimesulide and ketoprofen on the

inflammation caused by this surgical procedure, and the drugs were administered rectally[25]. Therefore, we present the results of a split-mouth, prospective, randomized, double-blind trial aimed at assessing and comparing the effects of orally administered nimesulide and ketoprofen on pain, swelling, and trismus in patients undergoing the surgical removal of four third molars under local anaesthesia.

Materials and methods

Study design and sample

The present prospective, single-centre, randomized, double-blind pilot study using a split-mouth design was conducted on patients recruited from the division of oral and maxillofacial surgery of the university hospital who required third molar extraction. This study was approved by the university hospital ethics committee and was performed in accordance with the Declaration of Helsinki. Patient recruitment was conducted between April 2011 and June 2012 and followed the guidelines of the CONSORT statement[26].

This study included healthy subjects (ASA classification I; American Society of Anesthesiologists) of both genders, aged 18 to 35 years, with an indication for removal of their four third molars and no periodontal disease. The subjects were able and willing to cooperate with the protocol and to sign an appropriate written informed consent form. Furthermore, to standardize the sample, each patient had to have similar patterns of tooth and root formation, position, and impaction degree between the upper and lower third molars of the right and left sides of the mouth[27]. Patients were excluded if they fulfilled at least one of the following criteria: smoker, pregnant or breast-feeding, using medications that interact with the drugs used in this study, have orthodontic bands on the second molars, a known allergy to NSAIDs, a systemic chronic disease, signs of any pre-existing acute inflammatory or infectious condition, or a history of NSAID use in the past 21 days. Patients who did not

follow the indicated recommendations or whose surgery exceeded 2 h were removed from this study. Patients who did not return for reassessment were also removed.

Patient data were recorded postoperatively and according to a standardized clinical examination, and included gender, age, systemic conditions, periodontal status, haemogram parameters, platelet count, international normalized ratio (INR) value, and blood glucose. Orthopantomograms were required to evaluate tooth variables such as position, Pell and Gregory[28] and Winter[29] classifications, tooth/root formation, and degree of impaction.

Patients were scheduled for surgery at two separate clinical sessions (one side at a time) at least 3 weeks apart. Each person had both upper and lower third molars removed at the same time on the involved side. Subjects were allocated to one of two groups according to a computer-generated randomization code to receive treatment two times a day with either ketoprofen 100 mg or nimesulide 100 mg (one tablet every 12 h for 3 days). The study drugs were dispensed as identical tablets by a blinded collaborator. Prior to the surgical procedure, the method of allocation concealment of the right and left sides of the mouth was followed, as described by Bezerra et al.[27]. Antibiotic prophylaxis was not adopted for the surgical procedure.

Surgical overview

All patients were submitted to a standardized surgical technique performed in an outpatient setting under local anaesthesia, followed by strict biosafety control. One surgeon with 5 years of experience in dentoalveolar surgery performed all of the surgical procedures. The same surgical procedure was adopted for both sides of the mouth, aiming to reduce the bias related to the intraoperative trauma. Local anaesthesia with 2% mepivacaine associated with 1:200,000 epinephrine (three cartridges) was administered. A mucoperiosteal flap followed by bone removal and/or tooth sectioning was performed. The surgical wound was closed using a 4–0 silk suture.

After surgery, 750 mg of acetaminophen was allowed as rescue medication for 7 days if necessary. The postoperative recommendations were carefully read and explained to the patient, in particular the need for a liquid and cold diet for 24 h, rigorous oral hygiene, and to avoid mouthwash. Patients were informed that they should contact the surgeon by telephone in the case of persistent bleeding or any other complications such as fever.

Outcome measures

The primary outcome of the study was the occurrence of postoperative pain. Measurement of this outcome considered both the pain intensity and the need for rescue analgesia. Postoperative pain intensity was measured using a 10-cm visual analogue scale (VAS) ranging from 0 (absence of pain or discomfort) to 10 (maximum pain or discomfort). Before starting the treatment, each patient received an explanation about how to measure pain intensity on this scale. Study participants were asked to record the pain intensity score at 6, 12, 24, 48, and 72 h, and 7 days following surgery. Additional analyses included the evaluation of time to re-medication, which was defined by Ong et al.[30] as "the time from the end of surgery until the intake of rescue medication became necessary for the patient". The number of patients requiring acetaminophen after the surgical procedure and the number of analgesics consumed during the study period were recorded.

The secondary outcome was the occurrence of postoperative inflammatory events. The following measurements were performed to evaluate postoperative swelling on the facial side receiving surgery (Fig. 1): tragus to the soft pogonion (Tr–Pog'), tragus to the external corner of the eye (Tr–Exo), tragus to the nasal border (Tr–Al), tragus to the labial commissure (Tr–Che), angle of the mandible to the external corner of the eye (Go–Exo), angle of the mandible to the nasal border (Go–Al), angle of the mandible to the soft pogonion (Go–Pog'), and angle of the mandible to the labial commissure (Go–Che). The differences between the preoperative values (baseline) and those measured at 24 h, 72 h, and 7 days after surgery were compared.

To estimate trismus, maximum mouth opening was measured in millimetres between the upper and lower central incisors using a calibrated sliding caliper (TheraBite Range-of-Motion Scales), preoperatively (baseline) and at 24 h, 72 h, and 7 days after surgery.

Statistical analysis

Standard statistical evaluation included the Kolmogorov–Smirnov test to evaluate the normality of the distributions. Pain scores and facial distances did not follow the Gaussian pattern of normality, differing from maximum mouth opening, which did. The Mann–Whitney test was used for comparisons of pain scores and facial distances between the ketoprofen and nimesulide groups. The Friedman test (Dunn post-hoc test) was used to assess the same variables (pain score and facial distances) among each of the fixed postoperative time intervals. One-way analysis of variance (ANOVA; Tukey post-hoc tests) and the *t*-test were used to assess the means of maximum mouth opening. All data was expressed as mean ± SD (standard deviation). Statistical significance was set at $P < 0.05$.

Results

The composition of the final sample in the present study was in accordance with the characteristics of clinical trials using ‘split-mouth’ as the study design. The experimental units randomly allocated to interventions in split-mouth models are expressed by divisions of the mouth (e.g. dental arches/sides), allowing better control of individual biological responses with a reduced number of recruited individuals. A total of 744 patients were assessed for eligibility in this study (Fig. 2); 724 did not meet the study criteria, one was removed because orthodontic treatment was started with banding of the second molars, and one did not return for follow-up. Among the excluded persons, there were cases with overlapping exclusion criteria. Thus, an order of priority was adopted for the exclusion criteria.

The study sample comprised 18 patients. There were 16 females (88.9%) and two males (11.1%) and they ranged in age from 18 to 35 years (mean age 19 ± 4.4 years). The lower third molars (n = 36) were characterized as 1A (n = 16), 1B (n = 10), 2A (n = 4), and 2B (n = 6) according to the Pell and Gregory classification ($P > 0.05$; Chi-square test), and as horizontal (n = 2), mesioangular (n = 16), and vertical (n = 18) according to the Winter classification ($P > 0.05$; Chi-square test). The upper third molars (n = 36) were characterized as A (n = 22), B (n = 8), and C (n = 6) according to the Pell and Gregory classification ($P > 0.05$; Chi-square test), and as mesioangular (n = 2), vertical (n = 10), and distoangular (n = 24) according to the Winter classification ($P > 0.05$; Chi-square test). The average duration of surgery was 29.9 (± 7.2) min; extractions on the left side took 30.4 (± 7.3) min, while those on the right side took 29.4 (± 7.3) min.

Pain intensity

Comparisons of pain intensity between the groups at each observation time point did not reveal any statistically significant difference (Table 1). Fig. 3 illustrates the change in the mean postoperative pain scores across the different observation time points of the study (6, 12, 24, 48, and 72 h, and 7 days). The comparison of all observation periods among each group and between the groups showed a statistically significant difference using the Friedman test ($P < 0.0001$). In the ketoprofen group, the Dunn post-hoc test identified a difference between the time points of 6 h and 7 days, and between 12 h and 7 days (Fig. 4A). In the nimesulide group, a statistically significant difference was found between the time points of 6 h and 48 h, 6 h and 72 h, and 6 h and 7 days (Fig. 4B).

Time to rescue analgesia

After the standardized administration of the study drugs in both groups, only one of the patients required a drug for rescue analgesia during the observation period of the study. The

patient requiring a rescue drug was removed from the analyzed sample because she took a drug other than acetaminophen 750 mg.

Facial swelling and trismus

At each observation point, there was no statistically significant difference in the mean linear distances between the two studied groups ($P > 0.05$). However, comparing all observation periods between themselves and by group (Table 2), a statistically significant difference was observed for the distances Tr–Al (ketoprofen, $P = 0.0029$), Tr–Che (ketoprofen, $P = 0.0026$; nimesulide $P < 0.0001$, Tr– Pog' (ketoprofen, $P < 0.0001$; nimesulide, $P = 0.0008$), Go–Exo (nimesulide, $P = 0.0437$), Go–Al (nimesulide and ketoprofen, $P < 0.0001$), Go–Pog' (ketoprofen, $P = 0.0087$; nimesulide, $P < 0.0001$), and Go–Che (ketoprofen, $P = 0.0004$; nimesulide, $P < 0.0001$). Table 3 shows the differences between measurements in the preoperative and postoperative periods.

With regard to maximum mouth opening, there was no statistically significant difference ($P > 0.05$) between the preoperative (baseline) and postoperative periods (24 h, 72 h, and 7 days) of observation when ketoprofen was compared with nimesulide (Table 4). Individually, ketoprofen and nimesulide showed a statistically significant difference in the maximum mouth opening when the preoperative value was compared to the postoperative periods (24 h, 72 h, and 7 days) ($P < 0.0001$; one-way ANOVA and Turkey post-hoc test). For both groups, there was a statistically significant difference at 24 h and 72 h after surgery ($P < 0.05$; *t*-test) in comparison with the baseline value for maximum mouth opening (Fig. 4C, D). In addition, there was a statistically significant difference in maximum mouth opening at 72 h and 7 days postoperative ($P < 0.05$; *t*-test) when compared with the 24 h postoperative period (Fig. 4C, D).

Discussion

The main objective of this research was to conduct a study on two COX-2 partially selective drugs to compare their analgesic efficacy and to analyze their anti-inflammatory effects through a third molar surgery model, with a split-mouth methodology and without a placebo group. The third molar surgery model was chosen because it has been used widely in pharmacological tests since 1976[31] and is a procedure commonly performed in dentistry in which postoperative pain is usually observed in the early stages after the surgical procedure[32]. This model has been considered important in clinical investigations to distinguish the analgesic effects of different drugs, as performed in this study, and even between different dosages of a single drug[33,34]. Because some patients have bilaterally impacted third molars, they can be the control for themselves. This study design, known as 'split-mouth'[32], enables adequate control of individual variability and requires a smaller number of patients[35]. Moreover, we agree with Anderson and Cranswick[36] and Merry et al.[37] about the unnecessary and unethical use of a placebo in studies using drugs with well-known effects.

In Brazil, both ketoprofen and nimesulide are drugs that are used widely following procedures such as orthopaedic, thoracic, abdominal, and oral surgery, which justifies the interest in studying these two drugs[38–40]. In a multicenter prospective study involving nine Italian universities, assessing the local protocols of the study services, nimesulide was the most prescribed NSAID, used in 68% of the cases, whereas ketoprofen was used in only 9% of the cases[24]. No study comparing the effects of both of these drugs administered orally using the methodology adopted in the present study has been published to date.

The efficacy of nimesulide and ketoprofen in the control of postoperative pain after dental extraction has been well described in clinical trials. Bjornsson et al.[20], comparing the use of ketoprofen 75 mg with acetaminophen 1000 mg, showed a statistically significant difference between the drugs, with the least amount of pain in the group of patients who

received ketoprofen. De Menezes and Cury[22], comparing nimesulide 100 mg and meloxicam 75 mg, observed lower pain intensity for the nimesulide group. However, the present study did not find any statistically significant difference between the drugs studied in relation to pain scores. This is in agreement with the results of the study by Seymour et al.[8], who evaluated the analgesic efficacy of different doses of ketoprofen (12.5 and 25 mg) and acetaminophen (500 and 1000 mg). Likewise, Leone et al.[41] did not find any statistical difference when comparing ketoprofen with methylprednisolone in the control of pain following third molar surgery, even though these drugs are from different groups and have different actions, which highlights the good efficacy of ketoprofen. Furthermore, the greatest pain intensity occurred within the first 12 h with the use of both drugs in this study, which is in agreement with the results of De Menezes and Cury[22]. In particular, it was observed that the pain scores were the same for the two drugs at 6 h, but different at 12 h. Bjornsson et al.[20] observed a similar pain intensity reduction between 4 and 9 h after surgery in the ketoprofen group, differing from Seymour et al.[8] who found that the reduction in pain scores occurred at 1 h after the surgical procedure.

In the present study, both drugs were administered immediately after the surgical procedure and the use of rescue medications for pain was found to be unnecessary. This is in contrast to the studies by Seymour et al.[8] and Olmedo et al.[21]. The results of the present study could suggest that nimesulide and ketoprofen control pain in therapeutic doses and that the routine use of additional postoperative analgesics is unnecessary in third molar surgery. Levrini et al.[24] observed that 75% of patients used rescue medication during the early onset of pain (3 h after the surgical procedure) and that 24% of patients used rescue medication immediately after the surgical procedure.

In the study by Levrini et al.[24], those patients who used the drug after the onset of pain experienced their peak pain at around 4 h and 10 min after surgery; in contrast, the peak

maximum pain occurred at 6 h and 30 min after surgery in patients who received medication before the onset of pain. Considering the time intervals assessed in the present study to evaluate postoperative pain (6, 12, 24, and 48 h, and 7 days), the peak in pain occurred at 6 h after the surgical procedure in the nimesulide group and 12 hours postoperatively in the ketoprofen group. The pain values decreased significantly after the sixth hour postoperative in the nimesulide group, whereas in the ketoprofen group the pain decreased significantly after the 12th postoperative hour. In addition, nimesulide showed lower pain scores at the 24 h, 48 h, and 72 h intervals than the ketoprofen group, demonstrating a better analgesic efficacy in comparison with ketoprofen. These data show that although complete pain relief was not observed, the pain level was tolerable to patients and they did not require rescue medication.

Regarding oedema, a significant increase was observed in the first 24 h after the surgical procedure for both drugs evaluated, whereas in the studies of Troullos et al.[42] and De Menezes and Cury[22], the maximum swelling occurred at 48 h and 72 h, respectively, after the extraction of the third molars. There was no statistically significant difference when the groups in this study were compared with each other, which is in contrasts to the results from the study of Bjornsson et al.[20]; they found a statistically significant reduction in swelling on the third and sixth postoperative days for the ketoprofen group. In that study, the reduction in swelling with ketoprofen use was 27.8% on the third day, increasing to 70.8% on the sixth day of observation. De Menezes and Cury[22] observed that the group using nimesulide (100 mg twice a day) had less pronounced swelling compared to the meloxicam group (7.5 mg twice a day) during the periods studied. No statistically significant difference in swelling was observed between the nimesulide and ketoprofen groups in relation to the assessed interval periods in the present study.

In both groups studied, *P*-values were less than 0.05 for the differences in measurements between the preoperative period and the postoperative period for six facial

measurements. Additionally, five of them (Tr–Pog', Tr–Che, Go–Al, Go–Pog', and Go–Che) showed *P*-values less than 0.0001. In the study by De Menezes and Cury[22], the distance Go–Che was the most affected. These authors observed statistically significant differences for nimesulide in comparison with meloxicam in the Go–Exo distance at 24 h postoperative, the Go–Exo and Go–Pog' distances at 48 h postoperative, and the Go–Exo, Go–Al, Go–Che, and Go– Pog' distances at 72 h postoperative. These findings are not supported by the present research, since at 72 h nimesulide did not show any statistically significant difference compared to ketoprofen for all facial swelling measurements.

The assessment of trismus was done by measuring the difference in maximum mouth opening between the postoperative and preoperative periods. A decrease in mouth opening was observed in the first 72 h after surgery both in this study and in the study performed by De Menezes and Cury[22]. However, in this study there was no statistically significant difference in the comparison between the nimesulide and ketoprofen groups. A significant increase in mouth opening occurred at 72 h and at 7 days after surgery in the patients of both groups. This was also found in the study of De Menezes and Cury[22], whose patients used nimesulide, as well as in the study of Bjornsson et al.[20], whose patients used ketoprofen.

Several pharmacological studies have aimed to investigate the tolerability of different drugs. Olmedo et al.[21] recruited patients to analyze the drug safety of ketorolac and ketoprofen. Adverse effects were transient in all patients who presented one, and none of the patients required adjuvant treatment. In the study by Olmedo et al.[21], 37.3% of the patients reported some type of adverse effect, with drowsiness being the most prevalent (10.7% of cases), followed by gastric disturbances (8%) and dizziness (5.3%). The most prevalent adverse effect related to ketoprofen was pyrosis (10.3%). Three serious adverse effects were reported by Olson et al.[19], with two of these events related to ibuprofen and one related to acetaminophen. No adverse effect, such as gastrointestinal discomfort, dizziness, or nausea,

was related to the use of ketoprofen in this study. Bjornsson et al.[20] stated that the adverse effects that deserve special attention are those associated with the gastrointestinal tract (stomach ache and diarrhoea). In that study, all adverse effects were reported to be of mild to moderate intensity[20]. Ketoprofen and other strong NSAIDs have been associated with a risk of gastric irritation[43–45]. Unlike those studies, none of the patients evaluated in the present clinical trial experienced adverse effects related to the use of drugs during the study period. This fact is probably due to the short period (3 days) that was adopted in the methodology. It is reasonable to assume that a relatively short duration of the ketoprofen drug regimen represents a limited risk to the patient who has had no previous experience of gastrointestinal problems or reactions to other NSAIDs[20].

De Menezes and Cury[22] described no adverse effects in the patients who used nimesulide. In a review of hepatic adverse effects, a greater number and severity of hepatotoxic events was demonstrated for patients who used nimesulide in relation to other NSAIDs[45]. Mació et al.[45] found that the patients with a higher risk of hepatotoxicity with nimesulide use were older, female, and had a median of 62 days using this drug. Different from that work, the patients in the research by De Menezes and Cury[22] and in the present study were younger (average age around 20 years) and used nimesulide for a very short period of time.

The present research was a comparative study of ketoprofen and nimesulide administered orally following surgery for the removal of third molars. In summary, patients who received ketoprofen 100 mg or nimesulide 100 mg showed good control of pain, swelling, and trismus after the extraction of the third molars.

Funding

None.

Competing interests

None declared.

Ethical approval

This study was approved by the Ethics Committee of the Walter Cantídio University Hospital, Ceará, Brazil (protocol number 084.08.11) and was conducted in accordance with the Helsinki statements.

Patient consent

The patient consented to the use of the photo in this publication.

References

1. Seymour RA, Meechan JG, Blair GS. An investigation into post-operative pain after third molar surgery under local analgesia. Br J Oral Maxillofac Surg 1985: 23: 410–418.

2. Clauser C, Barone R. Effect of incision and flap reflection on postoperative pain after the removal of partially impacted mandibular third molars. Quintessence Int 1994: 25: 845–849.

3. Berge TI, Egil O. Predictor evaluation of postoperative morbidity after surgical removal of mandibular third molar. Acta Odontol Scand 1994: 52: 162–169.

4. McGrath C, Comfort MB, Lo EC, Luo Y. Changes in life quality following third molar surgery—the immediate postoperative period. Br Dent J 2003: 194: 265–268.

5. Colorado-Bonnin M, Valmaseda-Castellón E, Berini-Aytés L, Gay-Escoda C. Quality of life following lower third molar removal. Int J Oral Maxillofac Surg 2006: 35: 343–347.

6. Sortino F, Messina G, Pulvirenti G. Evaluation of postoperative mucosa and skin temperature after surgery of impacted third molar. Minerva Stomatol 2003: 57: 393–399.

7. Markovic AB, Todorovic L. Postoperative analgesia after lower third molar surgery: contribution of the use of long-acting local anesthetics, low-power laser and diclofenac. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2006: 12: e4–e8.

8. Seymour RA, Kelly PJ, Hawkesford JE. The efficacy of ketoprofen and paracetamol (acetaminophen) in postoperative pain after third molar surgery. Br J Clin Pharmacol 1996: 41: 581–585.

9. Rainsford KD. Nimesulide: a multifactorial approach to inflammation and pain: scientific and clinical consensus. Curr Med Res Opin 2006: 2: 1161–1170.

10. Binning A. Nimesulide in the treatment of postoperative pain: a double-blind, comparative study in patients undergoing arthroscopic knee surgery. Clin J Pain 2007: 23: 565–570.

11. Ferrari A, Pasciullo G, Savino, Cicero AF, Ottani A, Bertolini A, Sternieri E. Headache treatment before and after the consultation of a specialized center: a pharmacoepidemiology study. Cephalalgia 2004: 24: 356–362.

12. Pohjolainen T, Jekunen A, Autio L, Vuorela H. Treatment of acute low back pain with the COX-selective anti-inflammatory drug nimesulide: results of a randomized, double-blind comparative trial versus ibuprofen. Spine (Phila Pa 1976) 2000: 25: 1579–1585.

13. Wober W. Comparative efficacy and safety of nimesulide and diclofenac in patients with acute shoulder, and a meta-analysis of controlled studies with nimesulide. Rheumatology (Oxford) 1999: 38: 33–38.

14. Bianchi M, Broggini M. A randomised, double-blind, clinical trial comparing the efficacy of nimesulide, celecoxib and rofecoxib in osteoarthritis of the knee. Drug 2003: 63: 37–46.

15. Bianchi M, Broggini M. Anti-hyperalgesic effects of nimesulide: studies in rats and humans. Int J Clin Pract 2002: 128: 11–19.

16. Jamali F, Brocks DR. Clinical pharmacokinetics of ketoprofen and its enantiomers. Clin Pharmacokinet 1990: 19: 197–217.

17. Fossgreen J. Ketoprofen—a survey of current publications. Scand J Rheumatol 1976: 14: 7–32.

18. Kantor TG. Ketoprofen: a review of its pharmacologic and clinical properties. Pharmacotherapy 1976: 6: 93–103.

19. Olson NZ, Otero AM, Marrero I Tirado S, Cooper S, Doyle G, Jayawardena S, Sunshine A. Onset of analgesia for liquigel ibuprofen 400 mg, acetaminophen 1000 mg, ketoprofen 25 mg, and placebo in the treatment of postoperative dental pain. J Clin Pharmacol 2001: 41: 1238–1247.

20. Bjornsson GA, Haanaes HR, Skoglund LA. Ketoprofen 75 mg qid versus acetaminophen 1000 mg qid for 3 days on swelling, pain and other postoperative events after third molar surgery. J Clin Pharmacol 2003: 43: 305–314.

21. Olmedo MV, Gálvez R, Vallecillo M. Double-blind parallel comparison of multiple doses of ketorolac, ketoprofen and placebo administered orally to patients with postoperative dental pain. Pain 2001: 90: 135–141.

22. De Menezes SA, Cury PR. Efficacy of nimesulide versus meloxicam in the control of pain, swelling and trismus following extraction of impacted lower third molar. Int J Oral Maxillofac Surg 2010: 39: 580–584.

23. Seymour RA, Watkinson H, Hawkesford JE, Moore U. The efficacy of buffered ketoprofen in postoperative pain after third molar surgery. Eur J Clin Pharmacol 2006: 55: 801–806.

24. Levrini L, Carraro M, Rizzo S, Salgarello S, Bertelli E, Pelliccioni GA, Garau V, Bandettini M, Caputi S, Lörincz A, Szûcs A. Prescriptions of NSAIDs to patients undergoing third molar surgery: an observational, prospective, multicentre survey. Clin Drug Invest 2008: 28: 657–668.

25. Pierleoni P, Tonelli P, Scaricabarozzi I. A double-blind comparison of nimesulide and ketoprofen in dental surgery. Drugs 1993: 46: 168–170.

26. Moher D, Hopewell S, Schulz KF, Montori V, Gøtzsche PC, Devereaux PJ, Elbourne D, Egger M, Altman DG; Consolidated Standards of Reporting Trials Group. CONSORT 2010 explanation and elaboration: updated guidelines for reporting parallel group randomised trials. J Clin Epidemiol 2010: 63: e1–e37.

27. Bezerra TP, Studart-Soares EC, Scaparo HC, Pita-Neto IC, Batista SH, Fonteles CS. Prophylaxis versus placebo treatment for infective and inflammatory complications of surgical third molar removal: a split-mouth, double-blind, controlled, clinical trial with amoxicillin (500 mg). J Oral Maxillofac Surg 2011: 69: e333–e339.

28. Pell GJ, Gregory BT. Impacted mandibular third molars: classification and modified techniques for removal. Dent Digest 1933: 39: 330–338.

29. Winter GB. Principles of exodontia applied to the impacted mandibular third molar. Saint Louis: American Books, 1926.

30. Ong KS, Seymour RA, Chen FG, Ho VC. Preoperative ketorolac has a preemptive effect for postoperative third molar surgical pain. Int J Oral Maxillofac Surg 2004: 33: 771–776.31. Cooper SA, Beaver WT. A model to evaluate mild analgesics in oral surgery outpatients. Clin Pharmacol Ther 1976: 20: 241–250.

32. Meechan JG, Seymour RA. The use of third molar surgery in clinical pharmacology. Br J Oral Maxillofac Surg 1993: 31: 360–365.

33. Forbes JA. Oral surgery. In: Max ME, Portenoy RK, Laska EM, eds.: Advances in pain research and therapy. The design of analgesic clinical trials. New York: Raven Press, 1991: 347.

34. Van Aken H, Thys L, Veekman L, Buerkle H. Assessing analgesia in single and repeated administrations of propacetamol for postoperative pain: comparison with morphine after dental surgery. Anesth Analg 2004: 98: 159–165.

35. Lesaffre E, Garcia Zattera MJ, Redmond C, Huber H, Needleman I. ISCB Subcommittee on Dentistry. Reported methodological quality of split-mouth studies. J Clin Periodontol 2007: 34: 756–761.

36. Anderson B, Cranswick N. The placebo (I shall please) – is it so pleasing in children? Pediatr Anaesth 2005: 15: 809–813.

37. Merry AF, Gibbs RD, Edwards J, Ting GS, Frampton C, Davies E, Anderson BJ. Combined acetaminophen and ibuprofen for pain relief after oral surgery in adults: a randomized controlled trial. Br J Anaesth 2010: 104: 80–88.

38. Arrais PS, Coelho HL, Batista MC, Carvalho ML, Righi RE, Arnau JM. [Profile of self-medication in Brazil] (in Portuguese). Rev Saude Publica 1997: 31: 71–77.

39. Pereira FS, Bucarethi F, Stephan C, Cordeiro R. Self-medication in children and adolescents. J Pediatr (Rio J) 2007: 83: 453–458.

40. Castilho LS, Paixão HH, Perini E. Prescription patterns of drugs of systemic use by dentists. Rev Saude Publica 1999: 33: 287–294.

41. Leone M, Richard O, Antonini F, Rousseau S, Chabaane W, Guyot L, Martin C. Comparison of methylprednisolone and ketoprofen after multiple third molar extraction: a randomized controlled study. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2007: 103: e7–e9.

42. Troullos ES, Hargreaves KM, Butler DP, Dionne RA. Comparison of nonsteroidal anti-inflammatory drugs, ibuprofen and flurbiprofen, with methylprednisolone and placebo for acute pain, swelling, and trismus. J Oral Maxillofac Surg 1990: 48: 945–952.

44. Henry D, Lim LL, Rodrigues LA, Perez Gutthann S, Carson JL, Griffin M, Savage R, Logan R, Moride Y, Hawkey C, Hill S, Fries JT. Variability in risk of gastrointestinal complications with individual non-steroidal anti-inflammatory drugs: results of a collaborative meta-analysis. Br Med J 1996: 312: 1563–1566.

44. Lanza FL, Codispotti JR, Nelson EB. An endoscopic comparison of gastroduodenal injury with over-the-counter doses of ketoprofen and acetaminophen. Am J Gastroenterol 1998: 93: 1051–1054.

45. Mació MA, Carvajal A, Vera E. Hepatotoxicity associated with nimesulide: data from the Spanish pharmacovigilance system. Clin Pharmacol Ther 2001: 72: 696–697.

FIGURES AND LEGENDS

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

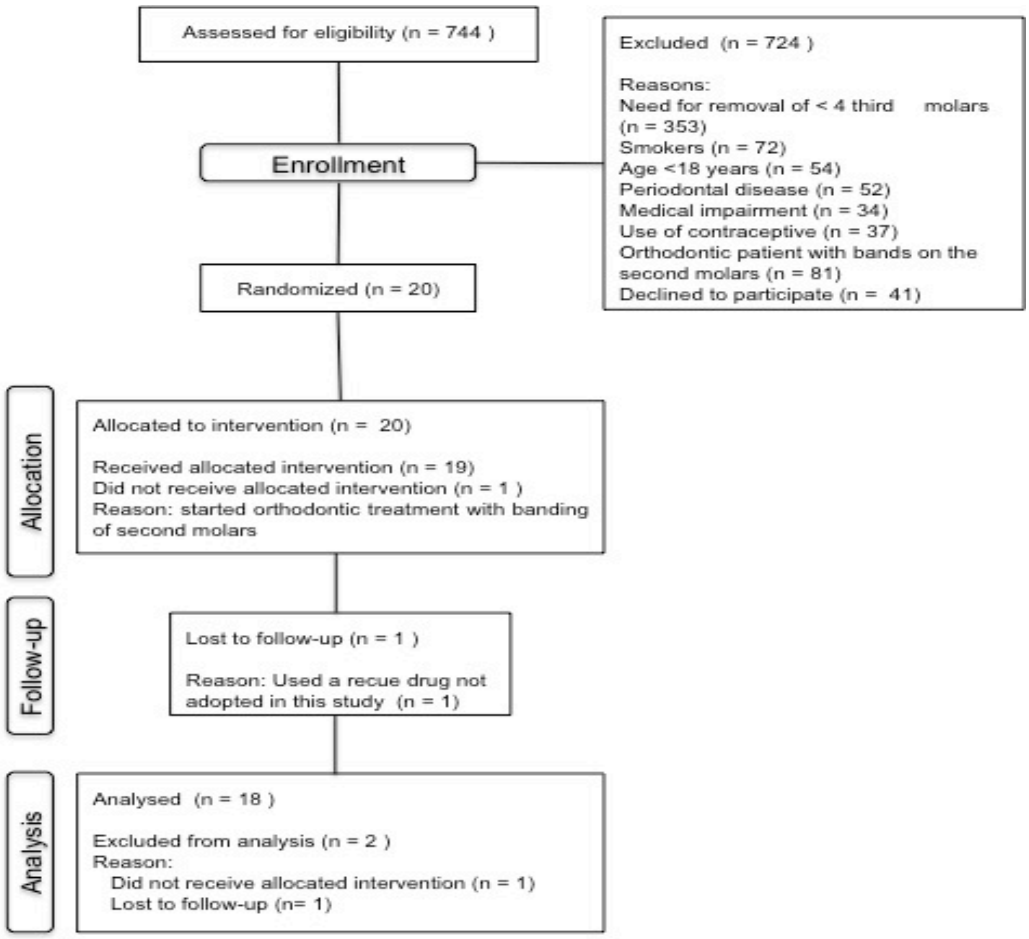


Figure 2. Graph about the mean pain intensity scores over study period.

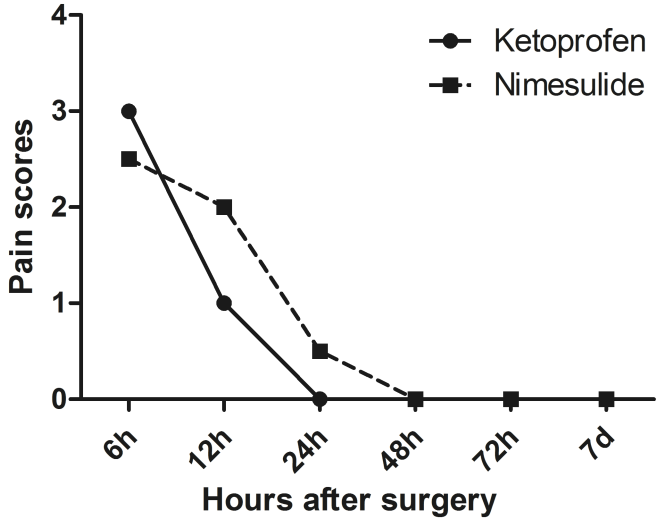
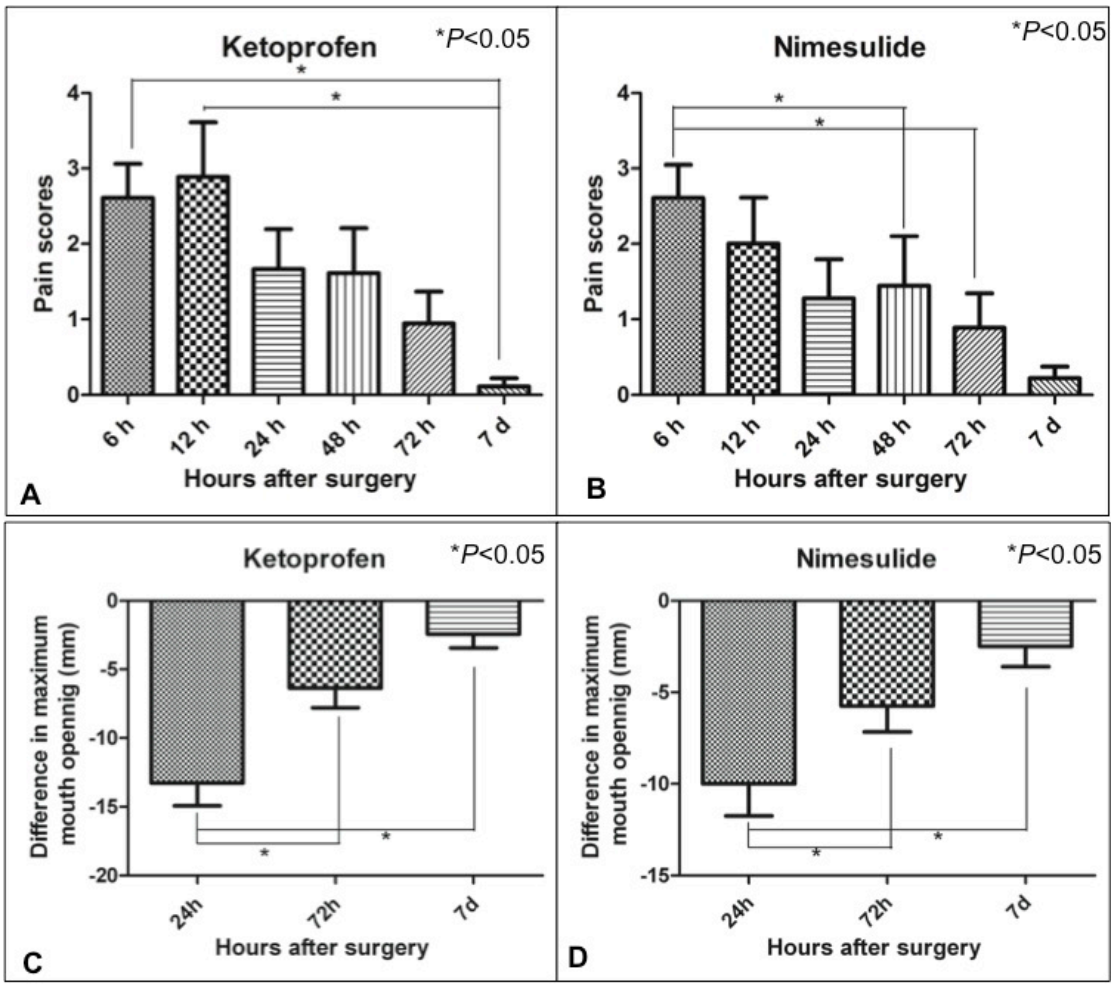


Figure 3. Pain intensity scores between Ketoprofen (A) and Nimesulide (B) groups; Difference in maximum mouth opening (mm) between Ketoprofen (C) and Nimesulide (D). (*P<0.05).



TABLES AND LEGENDS

Table 1. Pain intensity scores over study period according to Ketoprofen and Nimesulid groups.

Hours after surgery	Pain scores (Mean ± SD)		*P*-value	Test
	Ketoprofen	Nimesulide		
6	2.611 ± 1.914*	2.611 ± 1.852§#	0.9872	Mann-Whitney
12	2.889 ± 3.085†	2.000 ± 2.612	0.4395	Mann-Whitney
24	1.667 ± 2.249	1.278 ± 2.191	0.4856	Mann-Whitney
48	1.611 ± 2.547	1.444 ± 2.791§	0.5836	Mann-Whitney
72	0.9444 ± 1.798	0.8889 ± 1.937#	0.7707	Mann-Whitney
7d	0.1111 ± 0.4714*†	0.2222 ± 0.6468	0.5744	Mann-Whitney
Total	1.639 ± 2.318	1.407 ± 2.209	0.4653	Mann-Whitney
P-value	<0.0001	<0.0001		Friedman/Post-hoc Dunn

Abreviation: SD, standard deviation. *Statiscally significant comparison between 6h and 7d; § Statiscally significant comparison between 6h and 48h; #Statiscally significant comparison between 6h and 72h; †Statiscally significant comparison between 12h and 7d.

Table 2. *P*-value of the measurements between groups in all postoperative periods.

Distances	*P*-value		Test
	Ketoprofen	Nimesulide	
Tr-Exo	0.1873	0.9311	Friedman/Post-hoc Dunn
Tr-Al	0.0029*	0.1621	Friedman/Post-hoc Dunn
Tr-Che	0.0026 *	<0.0001*	Friedman/Post-hoc Dunn
Tr-Gn	<0.0001 *	0.0008*	Friedman/Post-hoc Dunn
Go-Exo	0.0775	0.0437*	Friedman/Post-hoc Dunn
Go-Al	<0.0001*	<0.0001*	Friedman/Post-hoc Dunn
Go-Gn	0.0087*	<0.0001*	Friedman/Post-hoc Dunn
Go-Che	0.0004*	<0.0001*	Friedman/Post-hoc Dunn

Abbreviations: Tr-Exo, tragus to the external corner of the eye ; Tr-Al, tragus to the nasal border; Tr-Che, tragus to the labial commissure; Tr-Gn, tragus to the angle of the mandible; Go-Exo, soft pogonion to the external corner of the eye; Go-Al, soft pogonion to the nasal

border; Go-Gn, soft pogonion to the angle of the mandible; Go-Che, soft pogonion to the labial commissure.
*Statiscally significant.

Table 3. Difference in the facial distance measurements before surgery in comparison to preoperative values.

Distances	Difference measurement in cm (Mean ± SD)		*P*-value	Test
	Ketoprofen	Nimesulide		
24h				
Tr-Exo	0.05 ± 0.08	0.03 ± 0.05	0.2576	Friedman test
Tr-Al	0.17 ± 0.50	0.18 ± 0.19	0.9356	Friedman test
Tr-Che	0.35 ± 0.25	0.33 ± 0.29	0.5112	Friedman test
Tr-Gn	0.38 ± 0.34	0.33 ± 0.32	0.3627	Friedman test
Go-Exo	0.21 ± 0.33	0.12 ± 0.26	0.4090	Friedman test
Go-Al	0.33 ± 0.33	0.30 ± 0.33	0.9235	Friedman test
Go-Gn	0.14 ± 0.29	0.28 ± 0.26	0.1637	Friedman test
Go-Che	0.38 ± 0.28	0.33 ± 0.94	0.5033	Friedman test
72h				
Tr-Exo	0.04 ± 0.15	0.01 ± 0.10	0.2863	Friedman test
Tr-Al	0.89 ± 0.32	0.12 ± 0.12	0.2313	Friedman test
Tr-Che	0.25 ± 0.28	0.25 ± 0.26	0.7000	Friedman test
Tr-Gn	0.33 ± 0.27	0.28 ± 0.27	0.4718	Friedman test
Go-Exo	0.12 ± 0.35	0.07 ± 0.25	0.6295	Friedman test
Go-Al	0.24 ± 0.30	0.22 ± 0.28	0.8978	Friedman test
Go-Gn	0.06 ± 0.24	0.12 ± 0.23	0.7347	Friedman test
Go-Che	0.27 ± 0.32	0.24 ± 0.91	0.7484	Friedman test
7d				
Tr-Exo	0.02 ± 0.15	0.02 ± 0.08	0.9151	Friedman test
Tr-Al	0.33 ± 0.42	0.08 ± 0.13	0.1026	Friedman test
Tr-Che	0.89 ± 0.26	0.09 ± 0.16	0.6861	Friedman test
Tr-Gn	0.07 ± 0.23	0.09 ± 0.20	0.6015	Friedman test
Go-Exo	0.03 ± 0.09	0.01 ± 0.20	0.7558	Friedman test
Go-Al	0.03 ± 0.09	0.00 ± 0.17	0.2135	Friedman test
Go-Gn	0.02 ± 0.07	0.00 ± 0.12	0.1448	Friedman test

Go-Che	0.04 ± 0.17	0.05 ± 0.82	0.9487	Friedman test

Abbreviations: SD, standard deviation; Tr-Exo, tragus to the external corner of the eye ; Tr-Al, tragus to the nasal border; Tr-Che, tragus to the labial commissure; Tr-Gn, tragus to the angle of the mandible; Go-Exo, soft pogonion to the external corner of the eye; Go-Al, soft pogonion to the nasal border; Go-Gn, soft pogonion to the angle of the mandible; Go-Che, soft pogonion to the labial commissure.

Table 4. Difference in maximum mouth opening (mm) before surgery and postoperatively at 7 days.

Hours after surgery	Max. mouth opening difference (Mean ± SD)		*P*-value	Test
	Ketoprofen	Nimesulide		
24	-13.28 ± 6.96	-10 ± 7.396	0.1799	t test
72	-6.361 ± 6.96	-5.75 ± 6.006	0.7629	t test
7d	-2.444 ± 6.96	-2.5 ± 4.719	0.9705	t test
P-value	<0.0001*†	<0.0001*†		1-way ANOVA[a]

Abreviation: SD, standard deviation. *Statiscally significant comparison between 24h and 72h; †Statiscally significant comparison between 24h and 7d. [a]Turkey post-hoc test.

4. CONCLUSÃO GERAL

Nas condições do presente trabalho, os principais achados do presente estudo piloto foram que os pacientes que receberam 100mg de cetoprofeno ou 100mg de nimesulida apresentaram um bom controle da dor, edema, e trismo após a exodontia de terceiros molares. Observamos, ainda, que o uso destes medicamentos logo após o término dos procedimentos cirúrgicos apresentaram um melhor tempo de analgesia, prolongando assim o sua ação e minimizando os efeitos inflamatórios e dolorosos do procedimento. Não foi observado diferença estatisticamente significante entre os grupos do cetoprofeno e da nimesulida para os eventos de dor, máxima abertura bucal, edema e número de medicamentos de resgate utilizado. Porém o grupo da nimesulida apresentou melhor comportamento para os eventos inflamatórios, como controle da dor e do edema. Entretanto, estudos clínicos envolvendo uma amostra maior de pacientes são necessários para confirmação, ou não, dos resultados encontrados nesta pesquisa, que para o nosso conhecimento trata-se do primeiro estudo comparativo entre essas duas drogas administradas oralmente em cirurgias para remoção de terceiros molares.

REFERÊNCIAS

HUPP, J. R. Princípios do tratamento de dentes impactados. In: Hupp, J. R. Ellis, III E, Tucker, M. R. **Cirurgia oral e maxilofacial contemporânea**. 5ª ed. Rio de Janeiro: Elsevier; 2009. p. 153-177.

NESS, G. M.; PETERSON. L. J. Dentes impactados. In: Miloro M, Larsen E, Waite PD. **Princípios de cirurgia bucomaxilofacial de Peterson**. 2ª ed. São Paulo: Santos; 2008. p. 139-155.

MAZOLLA, C. **Retenção dental**. 2ª ed. São Paulo: Pancast; 1995.

PORTO, G. G.; VASCONCELOS, B. C. E.; CARNEIRO, S. C. A. S.; et al. **Princípios bioéticos na cirurgia de terceiro molar incluso em adolescentes e adultos jovens**. *Rev Cir Traumatol Buco-Maxilo-Fac,* Pernambuco, v. 9, n 1, p. 103-114, 2009.

ANDRADE, E. D.; RANALI, J.; VOLPATO, M. C. Uso de medicamento na prevenção e controle da dor. In: Andrade ED. **Terapêutica medicamentosa em odontologia**. 1ª ed. São Paulo: Artes Médicas; 2002. p. 46-64.

COOPER, S. A.; GELB S. B.; GOLDMAN E.H. **An analgesic relative potency assay comparing ketoprofen and aspirin in postoperative dental pain**. *Adv Ther,* Metuchen, v. 1, p. 410-418, 1984.

COOPER, S. A.; BERRIE R.; COHN, P. **Comparison of ketoprofen, ibuprofen, and placebo in a dental surgery pain model.** *Adv Ther,* Metuchen, v. 5, p. 43, 1988.

SUNSHINE, A.; OLSON N.Z.; ZIGHELBOIM, I. et al. **Ketoprofen , acetominophen plusoxycodone, and acetominophen in the relief of postoperative pain**. *Clin Phamacol Ther,* St. Louis , v.54, p. 546-555, 1993.

WARNER, T. D.; GIULIANO, F.; VOJNOVIC, I. et al. **Nonsteroid drug selectivities for cyclo-oxygenase-1 rather than cyclo-oxygenase-2 are associated with human**

gastrointestinal toxicity: a full in vitro analysis. *Proc Natl Acad Sci U S A,* Washington, v. 96, n. 13, p. 7563-7568, 1999.

STEFANONI, G.; SACCOMANNO, F.; SCARICABAROZZI, I. **Efficacia clinica della nimesulide in confronto a diclofenac sodico nella prevenzione e nel trattamento della sintomatologia algico-flogistica postchirurgica**. *Minerva Chir* , Torino, v. 45, p. 41-45, 1990.

ARBEX S. T.; WASSAL T.; NUNES E. L. **An assessment of nimesulide by comparison with naproxen in the treatment of pain following oral surgery**. *Rev Bras Odontol,* Rio de Janeiro, v.1, p. 15-18, 1992.

FERRARI PARABITA, G.; ZANETTI, U.; SCALVINI, F. **A controlled clinical study of the efficacy and tolerability of nimesulide vs naproxen in maxillo-facial surgery**. *Drugs,* England, v.46 Suppl. 1, p. 171-173, 1993.

ANEXO

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

UNIVERSIDADE FEDERAL DO CEARÁ
HOSPITAL UNIVERSITÁRIO WALTER CANTÍDIO
COMITÊ DE ÉTICA EM PESQUISA
Rua Capitão Francisco Pedro, 1290 – Rodolfo Teófilo – 60.430-370 – Fortaleza-CE
FONE: (85) 3366-8589 / 3366.8613 E-MAIL: cephuwc@huwc.ufc.br

Protocolo n°: 084.08.11
Pesquisador(a) Responsável: Eduardo Costa Studart Soares
Departamento / Serviço:
Título do Projeto: "Estudo comparativo do uso da nimesulida e do cetaprofeno sobre eventos inflamatórios de cirurgias de terceiros molares."

O Comitê de Ética em Pesquisa do Hospital Universitário Walter Cantídio analisou na sessão do dia 29/08/11 o projeto de pesquisa supracitado e baseando-se nas normas que regulamentam a pesquisa em seres humanos, do Conselho Nacional de Saúde (Resoluções CNS 196/96, 251/97, 292/99, 303/00, 304/00, 347/05, 346/05), resolveu classificá-lo como: APROVADO.

Salientamos a necessidade de apresentação de relatório ao CEP-HUWC da pesquisa dentro de 12 meses (data prevista: 29/08/12).

Fortaleza, 30 de agosto de 2011.

Maria de Fátima de Souza
Dra. Maria de Fátima de Souza
Coordenadora do CEP - HUWC