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PROGRAMA DE PÓS-GRADUAÇÃO EM ODONTOLOGIA
MESTRADO EM CIRURGIA E TRAUMATOLOGIA BUCOMAXILOFACIAL

BERNARDO OTTONI BRAGA BARREIRO

Celecoxibe versus ibuprofeno no controle da sintomatologia pós-operatória em exodontias de terceiros molares: estudo clínico randomizado duplo-cego

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CELECOXIB VERSUS IBUPROFEN IN CONTROLLING POST-OPERATIVE SYMPTOMATOLOGY OF THIRD MOLAR EXTRACTION: A RANDOMIZED DOUBLE-BLIND CLINICAL TRIAL

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Orientadora: Profª. Drª. Karen Cherubini
Coorientadores: Prof. Dr. Claiton Heitz e Profª. Drª. Maria Martha Campos

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EPÍGRAFE

Somos o que fazemos repetidamente.
A excelência, portanto, não é um ato, mas um hábito.

Aristóteles (384 a.C. - 322 a.C.)

A todos aqueles que, de alguma forma, contribuíram

para minha formação

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RESUMO

RESUMO

A extração de terceiros molares constitui procedimento cirúrgico frequente e de significativa morbidade durante o período pós-operatório. O presente estudo teve por objetivo comparar o efeito pós-operatório dos fármacos celecoxibe (200 mg/dia) e ibuprofeno (1.800 mg/dia) sobre os parâmetros trismo, edema, dor e qualidade de vida em paciente submetidos a exodontias de terceiros molares. Um estudo clínico randomizado duplo-cego foi conduzido, em que 15 pacientes foram submetidos a exodontias de terceiros molares, dos lados direito e esquerdo, em diferentes momentos. Os pacientes receberam 8 mg de dexametasoan por via oral no pré-opratório e, para analgesia pós-operatória, celecoxibe foi administrado para um lado das extrações e ibuprofeno foi administrado para o outro. Dor, edema, trismo e qualidade de vida foram avaliados por meio de escala analogica visual (VAS), medidas faciais lineares e pelo inventário *Oral Health Impact Profile* (OHIP-14). O trismo não diferiu significativamente entre os grupos. A distância ângulo da mandíbula-asa do nariz (Go-Al) foi significativamente menor para o grupo ibuprofeno nos períodos de 0.5 h e 48 h. O escore total do OHIP-14 foi significativamente menor no grupo ibuprofeno no período de 48 h, sendo verificadas diferenças significativas para os domínios limitação funcional, dor física, e incapacidade física. Não ocorreram diferenças significativas para os demais períodos e domínios do OHIP-14. A VAS de dor foi significativamente menor no grupo ibuprofeno nos períodos 4, 8, 24, 48 e 72 h. A VAS de edema foi significativamente menor no grupo ibuprofeno nos períodos 2, 6, 12, 72 e 96 h. A frequência de uso da terapia analgésica de resgate foi maior no grupo celecoxibe, mas sem diferença significativa para o número de comprimidos usados. A frequência de infecção e a duração da cirurgia não diferiram significativamente entre os grupos.

Conclusão: O celecoxibe (200mg/day) exibiu desempenho similar ao do ibuprofeno (1.800 mg/dia) para controle do trismo, mas inferior para os parâmetros edema, dor e qualidade de vida.

Palavras-chave: terceiro molar; celecoxibe; ibuprofeno; dor; qualidade de vida

SUMMARY

SUMMARY

Third molar extraction is a surgical procedure with significant morbidity in the postoperative period. The aim of the present study was to compare postoperative effects of celecoxib (200 mg/day) and ibuprofen (1,800 mg/day) on trismus, swelling, pain and quality of life of patients subjected to extraction of third molars. A randomized double-blind clinical trial was conducted. Fifteen patients were submitted to extraction of impacted third molars, right and left, at different times. Oral dexamethasone (8 mg) was given preoperatively and for postoperative analgesia, celecoxib was administered for one side tooth extraction and ibuprofen for the other. Pain, swelling, trismus and quality of life were scored with a visual analogical scale (VAS), facial linear measurements and *Oral Health Impact Profile* questionnaire (OHIP-14). Trismus did not significantly differ between the groups. Angle of the mandible to the nasal border distance was significantly lower in the ibuprofen group at 0.5 h and 48 h. OHIP-14 total score was significantly lower in the ibuprofen group at 48 h, where differences occurred for functional limitation, physical pain and physical disability domains. No significant differences occurred at the other OHIP-14 times and domains. Pain VAS was significantly lower in the ibuprofen group at 4, 8, 24, 48 and 72 h. Swelling VAS was significantly lower in the ibuprofen group at 2, 6, 12, 72 and 96 h. Rescue medication was more often in the celecoxib group, but without significant difference considering the number of tablets used. Frequency of infection and duration of surgical procedure did not significantly differ between the groups.

Conclusion: Celecoxib (200mg/day) performance was similar to ibuprofen for trismus control but worse for swelling, pain and quality of life.

Key words: third molar; celecoxib; ibuprofen; pain; quality of life

LISTA DE SIGLAS E SÍMBOLOS

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AINE	Anti-inflamatório não esteroidal
AINEs	Anti-inflamatórios não esteroidais
AIE	Anti-inflamatório esteroidal
AIEs	Anti-inflamatórios esteroidais
CEP-PUCRS	Comitê de Ética em Pesquisa da Pontifícia Universidade Católica do Rio Grande do Sul
cm	Centímetro
COX	Ciclo-oxigenase
COX-1	Ciclo-oxigenase 1
COX-2	Ciclo-oxigenase 2
OHIP	Oral health impact profile
QV	Qualidade de vida
OMS	Organização Mundial da Saúde
mg	Miligrama
MMO	*Maximum mouth opening* - Máxima abertura bucal
PUCRS	Pontifícia Universidade Católica do Rio Grande do Sul
VAS	*Visual analogue scale* – Escala analógica visual
VSE	*Visual scale of edema* – Escala visual de edema

SUMÁRIO

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INTRODUÇÃO

1 INTRODUÇÃO

A extração de terceiros molares inclusos é a cirurgia oral mais frequente na Odontologia e, usualmente, acarreta dor, edema facial e trismo no período pós-operatório (Vegas-Bustamante *et al.*, 2008). Nesse período, um significativo número de pacientes relata dor moderada a severa, o que requer analgesia. O uso de fármacos para controle da dor e do edema é bastante difundido no meio médico-odontológico (Zandi *et al.*, 2016). Diversos medicamentos, de diferentes marcas comerciais, existem para esse propósito, destacando-se os analgésicos, os anti-inflamatórios esteroides e os anti-inflamatórios não-esteroides (Markíewicl *et al.*, 2008; Zandi *et al.*, 2016).

Os glicocorticoides constituem uma classe de corticosteroides que têm propriedades anti-inflamatórias importantes no pós-operatório de cirurgias, e cuja ação está relacionada à modulação microvascular e seus efeitos celulares (Kester *et al.*, 2008). Os glicocorticoides mais usados em cirurgia bucal são a metilprednisona e a dexametasona (Alexsanden; Throndson, 2000). Esta última, quando administrada no pré-operatório de cirurgia dos terceiros molares, exibe eficácia na redução do edema e da dor (Alcântara *et al.*, 2014; Antunes *et al.*, 2011; Bhargava *et al.*, 2014).

Anti-inflamatórios não-esteroides (AINEs) orais são comumente prescritos para dor aguda pós-operatória e possuem, aparentemente, vantagens sobre os analgésicos opioides, incluindo menos efeitos colaterais, apesar de sua associação a problemas gastrointestinais (Niebler; Dayno, 2016). Os anti-inflamatórios não-esteroides não-seletivos exercem efeito por meio da inibição da ciclo-oxigenase (COX) 1 e/ou 2 (FitzGerald, 2002). Os anti-inflamatórios não-esteroides seletivos foram desenvolvidos em função da associação da COX-1 com proteção gástrica. Dessa forma, os AINEs seletivos inibem apenas a COX-2, apresentando menos efeitos adversos sobre o trato

gastrointestinal. Todavia, quando administradas por tempo prolongado, como no tratamento da osteoartrite, essa classe de medicamentos eleva o risco de alterações cardiovasculares, visto que, com a inibição da COX-2, ocorre um desequilíbrio entre a produção de prostaciclinas e de tromboxano A2, favorecendo a ocorrência de eventos tromboembólicos. Por conseguinte, há aumento do risco de infarto do miocárdio ou acidente vascular cerebral (Bresalier *et al.*, 2005; Nussmeier *et al.*, 2005; Solomon *et al.*, 2005). O celecoxibe é um exemplo de anti-inflamatório não-esteroide seletivo (COX-2) indicado para o alívio dos sinais e sintomas da osteoartrite e da artrite juvenil, bem como para o manejo da dor aguda pós-operatória (Celecoxibe, 2008).

A cirurgia de terceiros molares acarreta desconforto ao paciente e pode comprometer sua qualidade de vida (Vegas-Bustamante *et al.*, 2008; Zandi, 2008), motivo pelo qual o controle dos sinais e dos sintomas de dor, edema e trismo é de suma importância nesse procedimento cirúrgico e constitui problemática relevante para pesquisas científicas. Embora o uso de fármacos seja um método eficaz para o controle dos sinais e sintomas inflamatórios da região da face, existem muitas controvérsias no que diz respeito aos protocolos de terapia pós-operatória para a cirurgia de terceiros molares. O presente estudo teve por objetivo investigar o manejo pós-operatório de pacientes submetidos a exodontias de terceiros molares. O trabalho está estruturado sob a forma de dois artigos: o artigo 1 corresponde à fundamentação teórica do tema, enquanto o artigo 2 apresenta um estudo clínico duplo-cego randomizado que foi desenvolvido para comparar a eficácia dos fármacos celecoxibe e ibuprofeno no controle da sintomatologia pós-operatória de terceiros molares impactados.


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Manejo clínico do paciente submetido a exodontia de terceiros molares: revisão da literatura

Clinical management of the patient undergoing third molar extraction: a literature review

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RESUMO

A extração de terceiros molares constitui procedimento cirúrgico frequente, cujo pós-operatório implica considerável morbidade. Os autores apresentam uma revisão da literatura enfocando eventos mórbidos envolvidos e algumas das alternativas de manejo clínico pós-operatório do paciente submetido à extração de terceiro molar. A literatura cita o uso tanto de drogas anti-inflamatórias esteroides, quanto de não-esteroides para o controle da sintomatologia pós-operatória, entre as quais destacam-se a dexametasona, o ibuprofeno, o paracetamol e, mais recentemente, tem sido investigado o uso do celecoxibe. Os resultados divergem entre os estudos, em parte, porque não existe entre os mesmos padronização de métodos de análise e da posologia dos fármacos. Novos estudos aplicando padronização dos métodos, rigoroso controle de vieses e avaliação custo/benefício e risco/benefício fazem-se necessários.

Palavras-chave: terceiros molares; terapia pós-operatótia; drogas anti-inflamatórias esteroides; drogas anti-inflamatórias não-esteroides; qualidade de vida

ABSTRACT

Third molar extraction is a frequent surgical procedure, whose postoperative period has significant morbidity. The authors present a literature review focusing on the morbid events involved and some options of postoperative clinical management of patient undergoing third molar extraction. Both steroid and non-steroid drugs are reported as options for postoperative symptomatology control. Dexamethasone, ibuprofen, paracetamol and, most recently, celecoxib have been investigated. There is some disagreement between the studies because of lack of standardization of dosages of the drugs and methods of analysis. Further studies applying standardized methods of analysis, rigorous bias control and cost/benefit and risk/benefit evaluation are needed.

Key words: third molars; postoperative therapy; steroidal antiinflammatory drugs; non-steroidal antiinflammatory drugs; quality of life

INTRODUÇÃO

Consideram-se impactados os dentes que não irromperam na cavidade bucal no seu prazo de erupção normal (Ellis *et al.*, 2015). A incidência de terceiros molares impactados é alta, maior que a de qualquer outro dente, tendo em vista que são os últimos dentes a erupcionar na cavidade bucal e, em geral, há falta de espaço para eles no arco dentário (Ellis *et al.*, 2015; Santosh, 2015). A exodontia precoce reduz a morbidade pós-operatória e permite melhor cicatrização. Pacientes jovens toleram bem o procedimento, recuperam-se mais rapidamente e com menos interferência em seu cotidiano (Santosh, 2015). O momento ideal para a remoção dos terceiros molares é quando apresentam um terço de raiz formada, geralmente na adolescência, entre 17 e 20 anos de idade (Ellis *et al.*, 2015; Santosh, 2015). A cirurgia para a remoção desses dentes é invasiva, e o trauma cirúrgico é consideravelmente maior que o da cirurgia para remoção de um dente erupcionado em função da ostectomia (Juodzbalys; Daugela, 2013). O período pós-operatório é delicado e, em geral, o paciente experimenta intensidade moderada de edema na área da cirurgia por três a quatro dias, com a dissipação após sete dias (Pouchain *et al.*, 2015). Geralmente, quadro de desconforto sucede ao procedimento, e o trismo está presente. A incapacidade de abrir a boca compromete a higienização bucal e os hábitos alimentares e predispõe à infecção local e perda de peso. O trismo resolve-se em cerca de dez dias (Balakrishnan *et al.*, 2017). O grau de intensidade dessas manifestações inflamatórias é diretamente proporcional ao trauma cirúrgico que, no caso, é considerável. Em função disso, a administração de fármacos é importante para prevenir e controlar a inflamação, o que reduz a morbidade dos quadros (Alcântara *et al.*, 2014). O presente estudo faz uma revisão da literatura enfocando eventos mórbidos envolvidos e algumas das alternativas de manejo clínico pós-operatório do paciente submetido à extração de terceiro molar.

Processo inflamatório e drogas anti-inflamatórias

A inflamação é uma reação biológica do organismo a um dano tecidual (Bilate, 2007). A etiologia da agressão pode variar, podendo ser de origem física, química ou microbiológica (Bilate, 2007; Darwiche *et al.*, 2013). Em geral, em pequena escala, a inflamação restaura o equilíbrio homeostático, combate o agente agressor e estimula a cicatrização (Bilate, 2007). Por outro lado, a inflamação em escala exacerbada conduz ao desenvolvimento de diversas doenças, como asma, artrite, gota e ateroesclerose (Bilate, 2007; Darwiche *et al.*, 2013).

A resposta inflamatória a um trauma agudo ocorre em três fases: (i) aguda, caracterizada por vasodilatação, aumento da permeabilidade vascular e aumento de líquido no interstício (edema), mediado principalmente pela histamina; (ii) subaguda, com forte quimiotaxia atraindo leucócitos e fagócitos; (iii) crônica proliferativa, iniciando 36 a 48 horas após o trauma com sinais de regeneração e deposição de matriz conjuntiva (Wannmaker; Ferreira, 2007). Na via das ciclo-oxigenases, há a síntese de prostaglandinas e tromboxanos. Essas enzimas podem ser classificadas em: constitutiva ou fisiológica (COX-1), expressa na maioria dos tecidos, especialmente nas plaquetas, mucosa gástrica e rins; e a ciclo-oxigenase induzível ou inflamatória (COX-2), que tem sua expressão aumentada nos sítios de inflamação (Khan; Fraser, 2012).

O dano tecidual causa vasodilatação, aumento da permeabilidade capilar, acúmulo de células inflamatórias no local da lesão e dor, bem como estimula a liberação de uma variedade de mediadores inflamatórios como histamina, citocinas e neuropeptídeos para manter a resposta inflamatória mediante a agressão (Bilate, 2007; Church; Church, 2013; Darwiche *et al.*, 2013; Zhang; Han, 2013). Em circunstâncias normais, há reversão espontânea do quadro inflamatório, após ser removida a causa da inflamação; por outro lado, a manutenção do processo inflamatório indica um estado

patológico persistente (Bilate, 2007; Darwiche *et al.*, 2013; Wannmaker; Ferreira, 2007).

A compreensão e identificação dos mecanismos biológicos de regulação do processo inflamatório levou ao desenvolvimento de fármacos para controle e modulação da inflamação. Os fármacos mais comumente empregados no controle do processo inflamatório distribuem-se em dois grupos, esteroides e não-esteroides (Kester *et al.*, 2008).

Anti-inflamatórios não-esteroides (AINEs)

Em geral, os anti-inflamatórios não-esteroides (AINEs) são usados como agentes anti-inflamatórios, antipiréticos, analgésicos e antitrombóticos, apesar de nem todos possuírem essas quatro ações em graus semelhantes. O efeito dos AINEs se dá pela inibição da síntese de prostaglandinas e tromboxanos, via bloqueio das ciclo-oxigenases 1 (COX-1) e 2 (COX-2). A maioria dos AINEs atua pela inibição não-seletiva das duas isoformas da ciclo-oxigenase. Assim, com o objetivo de ter-se o mesmo efeito benéfico anti-inflamatório, porém evitando o risco de sangramento gástrico causado pela inibição da COX-1 foram desenvolvidos inibidores específicos da COX-2 (Khan; Fraser, 2012). Entretanto, relatos da literatura associam os inibidores da COX-2 ao aumento de eventos cardiovasculares adversos. Esse fato levou à retirada do mercado de vários membros dessa classe farmacológica. Os medicamentos ainda disponíveis necessitam de prescrição medicamentosa para sua venda (Cannon; Cannon, 2012; Funk; FitzGerald, 2007).

Os AINEs COX-2 seletivos são empregados em várias situações clínicas como osteoartrite, dor pós-operatória, cefaleia, odontalgia. No entanto, apresentam efeitos adversos importantes principalmente por ocasião do uso crônico. Pacientes com úlcera

ou sangramento gastrointestinal devem evitar os AINES não-seletivos, pois esses fármacos podem exacerbar tais condições (Monteiro *et al.*, 2008).

Celecoxibe

O celecoxibe é um anti-inflamatório e analgésico pertencente ao grupo de medicamentos denominados inibidores seletivos da enzima COX-2. Está indicado para o tratamento sintomático da osteoartrite e artrite reumatoide; alívio dos sinais e sintomas da espondilite anquilosante (doença inflamatória crônica que atinge as articulações da coluna e grandes articulações, como dos quadris e ombros reduzindo a sua mobilidade); alívio da dor aguda, principalmente no pós-operatório de cirurgia ortopédica ou dental, e em afecções musculoesqueléticas como, por exemplo, entorse do tornozelo e dor nas costas; alívio dos sintomas de dismenorreia primária. Quando se necessita de analgesia aguda, a dose de impregnação é de 400 mg, seguida de uma dose de 200 mg, após 12 horas no primeiro dia do tratamento. Nos dias subsequentes, deve-se administrar 200 mg duas vezes ao dia. O celecoxibe é bem absorvido em jejum, atingindo concentrações plasmáticas máximas após, aproximadamente, 2 a 3 horas. A biodisponibilidade oral das cápsulas é de cerca de 99% em relação à administração em suspensão. Em condições de jejum, tanto os níveis plasmáticos máximos como as áreas sob a curva são quase proporcionais à dose de até 200 mg duas vezes ao dia (Celecoxibe, 2008).

Saito *et al.* (2012) relatam uso de dose inicial de 400 mg de celecoxibe, uma hora após a cirurgia, no pós-operatório de extração de terceiros molares. Após essa dose, também administraram, nos períodos de cinco e doze horas, 200 mg de celecoxibe ou placebo. De acordo com os autores, o uso de celecoxibe 400 mg seguido da administração de celecoxibe 200 mg, nos períodos de cinco e doze horas de pós-operatório, é significativamente superior para controle da dor pós-operatória do que

somente a dose inicial de 400 mg do fármaco associada ao placebo nos mesmos períodos.

Al-Sukhun *et al.* (2012) conduziram o primeiro estudo a relatar efeito analgésico superior do celecoxibe em relação ao ibuprofeno na dor aguda pós-operatória da remoção de terceiros molares impactados. Os autores compararam uma dose única de 200 mg de celecoxibe com 400 mg de ibuprofeno, administradas uma hora antes da cirurgia, com analgesia de resgate, quando necessário, de 1.000 mg de paracetamol. Yamashita *et al.* (2014) compararam o uso de 60 mg loxoprofeno sódico ao de 400 mg de celecoxibe, em dose única, após cirurgias de terceiros molares inferiores. Os autores não verificaram diferença entre o efeito analgésico dos dois medicamentos. Nesse estudo, foi administrada terapia antibiótica para prevenção de infecção e analgesia de resgate, quando necessário, com celecoxibe 200 mg.

Aoki *et al.* (2016) avaliaram, por meio de escala visual analógica da dor, o tempo de início e duração da analgesia de 400 mg de celecoxibe após a extração de 103 terceiros molares. Segundo os autores, o tempo decorrido desde a ingestão do medicamento até o seu efeito analgésico foi de 35 minutos, sendo que esse efeito perdurava por seis horas.

Zamiri *et al.* (2009) compararam a eficácia analgésica de ibuprofeno (n=14), celecoxibe (n=15) e tramadol (n=12) em 41 pacientes após a extração dos terceiros molares inferiores. O grupo 1 recebeu ibuprofeno (600 mg) e os grupos 2 e 3 receberam celecoxibe (200 mg) e tramadol (100 mg), respectivamente, uma hora antes da extração dos terceiros molares e após oito horas. Os pacientes relataram a intensidade da dor (VAS) nos tempos de quatro e oito horas após a extração dentária. Para avaliar os efeitos secundários do fármaco, os pacientes foram solicitados a relatar se haviam desenvolvido algum efeito adverso com o uso da droga. Não houve diferença significativa, embora o

ibuprofeno apresentasse menores índices de dor, seguido pelo celecoxibe, e ficando o tramadol com o pior resultado (Zamiri *et al.*, 2009).

Não houve efeitos secundários indesejáveis nos grupos ibuprofeno e celecoxibe, mas efeitos secundários tais como cefaleia, náusea, vômito, xerostomia, sonolência, tremor e vertigem foram observados no grupo tramadol. Todos os pacientes que usaram este fármaco se mostraram insatisfeitos em função de o mesmo ter perturbado suas atividades diárias. Os autores concluíram que o celecoxibe exibe efeitos secundários leves, quando administrado em períodos curtos, com bom efeito analgésico, sendo, portanto, uma droga de escolha na Odontologia (Zamiri *et al.*, 2009).

Manvelian *et al.* (2012) avaliaram uma nanoformulação de diclofenaco (35 mg ou 18 mg) comparando o uso de dose única desse fármaco com os grupos celecoxibe (400 mg) e placebo. Os pacientes foram submetidos a extrações de terceiros molares com anestesia local associada a sedação com óxido nitroso. A diferença analgésica (VAS) entre os fármacos e o placebo foi estatisticamente significativa.

Ibuprofeno

O ibuprofeno é um AINE não seletivo, atua em COX-1 e COX-2, e representa o padrão-ouro para avaliação de novos agentes analgésicos em Odontologia. Os AINEs não-seletivos são apropriados para tratamento de odontalgia aguda em curto prazo, a despeito de sua toxicidade gastrointestinal (Nagi *et al.*, 2015), sendo prescritos regularmente para o primeiro e segundo dias de pó-operatório. Uma das limitações desse grupo de fármacos é o efeito de teto, ou seja, depois que o teto analgésico foi atingido, o aumento da dose só aumenta os efeitos secundários, sem alcançar analgesia adicional. No entanto, esse problema pode ser superado pela combinação de medicamentos com

mecanismo de ação diferentes como, por exemplo, a associação de paracetamol ao ibuprofeno ou ao diclofenaco (Munir *et al.*, 2007).

Au *et al.*, em revisão sistemática de 2015, chegaram à conclusão de que o ibuprofeno apresentou efeitos analgésicos superiores no pós-operatório de remoção cirúrgica de terceiros molares, comparado com diversas posologias de paracetamol e ácido acetilsalicílico. Segundo Bailey *et al.* (2014), há evidências de que o ibuprofeno 400 mg é superior ao paracetamol 1.000 mg para analgesia pós-operatória da remoção cirúrgica de terceiros molares. Nesse trabalho de revisão sistemática com metanálise, padrão *Cochrane*, foram selecionados sete estudos que incluíam um total de 2.241 participantes inscritos.

A associação de ibuprofeno com paracetamol no alívio da dor pós-operatória é promissora (Bailey *et al.*, 2014), além disso, a associação de ibuprofeno com oxicodona (analgésico opioide, análogo semissintético da morfina) representa alternativa eficaz para controle da dor pós-operatória moderada e severa na extração de terceiros molares (Litkowski *et al.*, 2005).

Anti-inflamatórios esteroides

Os glicocorticoides são definidos como agentes esteroides com ação anti-inflamatória e imunossupressora, que podem ser empregados em inúmeras doenças na prática médica diária (Kester *et al.*, 2008). O glicocorticoide produzido pelos seres humanos é o cortisol e está associado diretamente com a resposta ao estresse. Nas situações de emergência, o cortisol é liberado, o que aumenta a pressão arterial e a glicemia, propiciando energia muscular (Cheifetz, 2013; Kwon; Hermayer, 2013). Os maiores níveis de cortisol ocorrem durante o sono, antes de acordar, e os menores níveis à noite, antes do início do sono. O cortisol é secretado intermitentemente ao longo do dia, por períodos que duram somente uns poucos minutos (Cheifetz, 2013). Entre esses pulsos de secreção, o córtex

adrenal pode permanecer sem secretar qualquer cortisol por minutos a horas (Kwon; Hermayer, 2013).

Fazendo a introdução de um grupo metila, hidroxila, ou flúor na posição 9-alfa da cortisona, pode-se produzir, por meios sintéticos, corticosteroides com diferentes potências anti-inflamatórias e de retenção de sódio (Kim *et al.*, 2009). Ao contrário dos AINEs, que inibem diretamente enzimas que geram segundos mensageiros inflamatórios derivados de lipídios, os corticosteroides são lipofílicos, ligando-se a receptores esteroides citosólicos que se translocam para o núcleo da célula e exercem seu efeito nos genes responsivos aos glicocorticoides (Dexametasona, 2015). Dessa forma, determinam modificação conformacional nos receptores e sua translocação ao núcleo celular, onde ativam a transcrição gênica por meio de interação com sequências de DNA específicas. Assim, processa-se mRNA no citoplasma, que ativa a síntese de proteínas específicas que, por sua vez, regulam e controlam o processo inflamatório (Wannmaker; Ferreira, 2007). Entre as proteínas corticoinduzidas, estão a vasocortina e a lipocortina, que inibem, respectivamente, a liberação de substâncias vasoativas e fatores quimiotáticos (responsáveis por edema), bem como a enzima fosfolipase A2, responsável pela transformação de lipídeos da membrana celular em ácido araquidônico. Dessa maneira, fica bloqueada a síntese subsequente de prostaglandinas, prostaciclinas e leucotrienos, mediadores da resposta inflamatória (Dexametasona, 2015; Wannmaker; Ferreira, 2007).

Os corticosteroides exercem importante ação anti-inflamatória, inibindo a vasodilatação e reduzindo fatores como transudação e formação de edema, exsudato e depósitos de fibrina circunjacentes à área inflamada. Os mecanismos responsáveis por esses efeitos incluem a inibição da quimiotaxia de leucócitos para o foco inflamatório, a inibição da função de fibroblastos e células endoteliais, e a supressão da produção ou

dos efeitos dos mediadores inflamatórios (Herrera-Briones *et al.*, 2013). O uso prolongado de glicocorticoides sistêmicos leva ao desenvolvimento de um estado cushingoide caracterizado por obesidade central, face arredondada, hiperglicemia, osteoporose e perda da integridade estrutural da pele, bem como perda de massa muscular (Kim *et al.*, 2009).

O uso de corticosteroides em determinadas dosagens e vias de administração tem sido recomendado como alternativa de tratamento para reduzir a resposta inflamatória no pós-operatório odontológico (Paiva-Oliveira *et al.*, 2016). Em função de atenuarem a disponibilidade de mediadores inflamatórios no local da agressão, com consequente efeito analgésico e anti-inflamatório, esses fármacos passaram a ser investigados no pós-operatório de terceiros molares. Segundo Skjelbred e Iokken (1982), a injeção intramuscular pré-operatória de 9 mg de betametasona determinou significativa diminuição do edema pós-operatório em cirurgias de terceiros molares retidos. Laureano Filho *et al.* (2008) também relataram melhora do edema e do trismo após administração pré-operatória de 4 mg de dexametasona por via oral.

Herrera-Briones *et al.* (2013) conduziram metanálise que chegou a 28 artigos. Os autores observaram que a administração de corticosteroides em diferentes dosagens é eficaz para controlar a dor, a inflamação e o trismo, o que melhora a experiência pós-operatória do paciente. Além disso, concluíram que os maiores efeitos parecem ser alcançados com a administração do corticosteroide por via parenteral e antes da cirurgia. Segundo Alcântara *et al.* (2014) a administração pré-operatória de dexametasona 8 mg determina melhor controle do edema facial e do trismo em comparação à metilprednisolona 40 mg. Entretanto, essas duas drogas não se diferenciam em relação ao parâmetro dor.

Dexametasona

A dexametasona é um corticosteroide 25 a 30 vezes mais potente que a hidrocortisona, que é a forma sintética do cortisol (Kester *et al.*, 2008; Wannmaker; Ferreira, 2007). A dexametasona é empregada quando os efeitos anti-inflamatórios e imunossupressores dos corticosteroides são desejados, especialmente para tratamento intensivo durante períodos mais curtos (Pedersen, 1985). Esse medicamento é indicado para o tratamento de várias condições, tais como controle de afecções alérgicas; controle de inflamação aguda e crônica; situações inflamatórias graves ou incapacitantes (Almeida *et al.*, 2000; Laureano Filho *et al.*, 2008). A dexametasona está contraindicada nos casos de hipersensibilidade ao fármaco, micoses sistêmicas, coadministração com vacinas de vírus vivos (Majid, 2011; Messen; Keller, 1975), casos de doença de Cushing, amebíase, estrongiloidíase, diverticulite e herpes simples (Lambert *et al.*, 2013; Messen; Keller, 1975).

De acordo com Paiva-Oliveira *et al.* (2016), a dexamentasona (8 mg) e o cetorolaco de trometamina (10 mg), ambos administrados a intervalos de oito horas durante dois dias, foram eficazes no pós-operatório. Não houve diferença significativa para edema e controle da dor entre as drogas, porém, em relação à limitação de abertura de boca, a dexametasona teve melhor resultado. Alcântara *et al.* (2014) compararam a dexametasona (8 mg) e a metilprednisolona (40 mg), administradas em dose única, uma hora antes do procedimento cirúrgico. Os autores constataram melhor desempenho da dexametasona no controle do edema e da limitação da abertura de boca. Não houve diferença significativa para o parâmetro dor.

Sabhlok *et al.* (2015) compararam o uso de dexametasona (4 mg) via oral por cinco dias e dexametasona (4 mg) intramassetérica imediatamente após o procedimento

cirúrgico. A via oral foi superior à via intramuscular nos critérios dosagem, biodisponibilidade do medicamento e limitação da abertura de boca.

A dexametasona é um corticosteroide de longa duração que mantém dose terapêutica plasmática adequada durante o período pós-operatório imediato (Sabhlok *et al.*, 2015). Seu efeito anti-inflamatório diminui o edema e melhora as funções do sistema mastigatório, o que resulta em maior conforto no pós-operatório do paciente (Barbalho *et al.*, 2017).

Qualidade de vida no pós-operatório

A expressão *qualidade de vida* apresenta diversos significados e, apesar de ainda não haver um consenso, a Organização Mundial da Saúde (OMS) a define como *a percepção do indivíduo de sua posição na vida, no contexto da cultura e sistema de valores nos quais ele vive e em relação aos seus objetivos, expectativas, padrões e preocupações* (WHOQOL Group, 1994). A OMS refere, ainda, que a saúde física e psicológica, bem como o nível de independência, as relações sociais, as crenças pessoais e a relação com o meio ambiente podem interferir na qualidade de vida (WHOQOL Group, 1997). A partir dessa concepção, fica implícito que o conceito de qualidade de vida é subjetivo, multidimensional e que inclui elementos de avaliação tanto positivos, quanto negativos (Fleck, 2000; Fleck *et al.,* 1999).

A *qualidade de vida* é reconhecida não só como a ausência de doença ou enfermidade, mas também como a capacidade de uma pessoa de levar uma vida produtiva e agradável. A qualidade de vida inclui domínios da saúde física, funcional, mental, social, satisfação com o tratamento, preocupações sobre o seu futuro e bem-estar geral (El Achhab *et al.*, 2008).

A relação entre saúde bucal e qualidade de vida tem chamado a atenção dos profissionais da Odontologia pelos impactos físicos e psicossociais que os problemas bucais

podem acarretar na vida dos indivíduos. De acordo com Leão *et al.* (1998), os problemas bucais podem causar dor, desconforto, limitações e outras condições decorrentes de fatores estéticos que afetam a vida social, a alimentação, as atividades diárias e o bem-estar do indivíduo, causando problemas significativos na qualidade de vida dos mesmos. Esse fato torna essencial entender como o indivíduo percebe a própria condição bucal, pois seu comportamento é condicionado por essa percepção (Barrêtto *et al.*, 2004).

A qualidade de vida tem sido cada vez mais aceita como uma medida muito importante na avaliação de qualquer tratamento ou intervenção de saúde (Skevington, 1998). Pode ser mensurada por meio de instrumentos genéricos e de instrumentos específicos. Os genéricos abordam aspectos relacionados à saúde e refletem o impacto de uma doença sobre o indivíduo. Podem ser usados para estudar indivíduos da população em geral, de grupos específicos, além de portadores de doenças crônicas. Assim, permitem comparar a qualidade de vida de indivíduos sadios com doentes ou de portadores da mesma doença vivendo em diferentes contextos sociais e culturais (Fayers; Machin, 2000).

O oral health impact profile (OHIP) foi desenvolvido por Slade e Spencer e caracteriza-se por ser um meio de avaliação de disfunção, desconforto e incapacidade das condições bucais em relação à qualidade de vida dos indivíduos. Inicialmente, era composto por 49 questões, agrupadas em sete domínios (Slade; Spencer, 1994). Em 1997, foi desenvolvida uma versão mais concisa com 14 questões e composta pelos seguintes domínios: limitação funcional, dor física, desconforto psicológico, deficiência física, deficiência psicológica, limitação social e incapacidade (Göelzer *et al.*, 2014). Cada questão possui cinco possibilidades de resposta, às quais são atribuídas pontuações de 1 a 5, em que 1 corresponde à melhor condição e 5 à pior condição (Beluci; Genaro, 2016). Dessa forma, o oral health impact profile– 14 (OHIP-14) mostra-se como alternativa para a avaliação subjetiva da saúde bucal e da qualidade de vida no pós-operatório (Matijevic *et*

al., 2014), pois tem-se demonstrado confiável e compatível com diversas culturas, além de ser suscetível a mudanças (Ibikunle; Adeyemo, 2016).

Estudo realizado por Negreiros *et al.* (2012) revelou que 86 pacientes que se submeteram a cirurgia de terceiros molares impactados apresentaram piora significativa da qualidade de vida nos primeiros dois dias e, após, tiveram uma rápida recuperação. De acordo com os autores, a dor física e o desconforto psicológico fazem parte do quadro. O estudo faz referência ao uso de um protocolo medicamentoso, mas sem especificá-lo. Chopra *et al.* (2009), em estudo com metodologia semelhante, porém com amostra menor (n=72), verificaram piora significativa da qualidade de vida nos primeiros cinco dias de pós-operatório. Os autores comentam que os pacientes receberam ibuprofeno como terapia pós-operatória, mas não informam por quantos dias.

CONSIDERAÇÕES FINAIS

A exodontia de terceiros molares é um dos procedimentos mais frequentes em cirurgia dento-alveolar. Constitui procedimento previsível, se bem planejado, porém, possui impacto sobre os hábitos e qualidade de vida dos indivíduos no período pós-operatório, pois pode causar dor, aumento de volume e limitação da abertura de boca, o que faz o indivíduo diminuir suas atividades e isolar-se do convívio social. As complicações pós-operatórias dependem da resposta inflamatória de cada indivíduo, da intensidade do trauma e da manipulação dos tecidos (Sabhlok *et al.*, 2015). Embora a resposta inflamatória seja fisiológica, o quadro de dor, edema e limitação da abertura de boca demanda terapia medicamentosa (Alcântara *et al.*, 2014). O uso de fármacos analgésicos e anti-inflamatórios tem sido rotina no pós-operatório de terceiros molares impactados com o objetivo de melhorar as condições clínicas do paciente. Inúmeras pesquisas têm testado o uso de drogas anti-inflamatórias, esteroides e não-esteroides, no intuito de estabelecer protocolos-padrão. Entretanto, a diversidade de fármacos e protocolos, bem como falta de

padronização dos métodos de análise tem gerado considerável controvérsia entre os estudos publicados. Novas pesquisas com padronização tanto dos métodos de análise, quanto da seleção da amostra e técnica cirúrgica devem ser encorajados a fim de que se estabeleçam protocolos medicamentosos adequados para o controle da sintomatologia pós-operatória da extração de terceiros molares impactados.

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ARTIGO 2

2 ARTIGO 2

O artigo a seguir intitula-se ***Celecoxib versus ibuprofen in controlling postoperative symptomatology of third molar extraction: a randomized double-blind clinical trial*** e foi formatado de acordo com as normas do periódico *International Journal of Oral and Maxillofacial Surgery* (Anexos A e B).

Celecoxib versus ibuprofen in controlling postoperative symptomatology of third molar extraction: a randomized double-blind clinical trial

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Short title: *Celecoxib versus ibuprofen*

Key words: third molar; celecoxib; ibuprofen; pain; quality of life

ABSTRACT

Objective: To compare the postoperative effects of celecoxib and ibuprofen on pain, swelling, trismus and life quality of patients submitted to extraction of impacted third molars.

Methods: Fifteen patients were submitted to extraction of impacted third molars, right and left, at different times. Oral dexamethasone (8 mg) was given preoperatively, and for postoperative analgesia, oral celecoxib was administered for one side tooth extraction and ibuprofen for the other. Pain, swelling, trismus and life quality were scored with a visual analogical scale (VAS), facial linear measurements and Oral Health Impact Profile questionnaire (OHIP-14).

Results: Trismus did not significantly differ between groups. Angle of mandible to nasal border was significantly less in the ibuprofen group at 0.5 and 48 h. OHIP-14 score only differed (lower) for ibuprofen at 48 h. Pain VAS was lower in the ibuprofen group at 4, 8, 24, 48 and 72 h. Swelling VAS was lower in the ibuprofen group at 2, 6, 12, 72 and 96 h. Rescue medication was more often in the celecoxib group, but not significantly, considering the number of tablets used.

Conclusion: Celecoxib (200 mg/day) performance was similar compared to ibuprofen for trismus but worse for swelling, pain and life quality parameters.

Key words: third molar; celecoxib; ibuprofen; pain; quality of life

INTRODUCTION

Third molar extraction is the most frequent intervention in oral and maxillofacial surgery. It usually results in pain, facial swelling and trismus, which compromises patients' quality of life.[1,2] Since a substantial number of patients report moderate to severe pain in such situation, requiring analgesics,[3] this kind of surgery has become a widely applied validated model for evaluating analgesia in postoperative pain.

Drugs are often administered to control pain and swelling in oral surgery,[3] where the most used are analgesic and antiinflammatory agents, either steroids or non-steroids.[4,5] Corticosteroids are a class of drugs with important antiinflammatory properties for the surgical postoperative period. They comprise a group of antiinflammatory steroid hormones produced by the adrenal gland or synthesized in the laboratory and produced by pharmaceutical companies[6,7,8], which exert various functions in the human body, with a key role in water balance and metabolic regulation.[6] Disturbances in the production of this hormone lead to diseases such as Addison's disease and Cushing's syndrome[9,10]. Methylprednisolone and dexamethasone are the most used glucocorticoids in oral surgery,[11] resulting in efficacious reduction of swelling and pain when administered preoperatively in third molar surgery.[12,13,14]

Oral non-steroidal antiinflammatory drugs (NSAIDs), in turn, are extensively prescribed for acute postoperative pain, overcoming opioid analgesics, with more benefits and less adverse effects. However, NSAIDs are sometimes associated with gastrointestinal disturbances[15], since non-selective NSAIDs exert effects by means of cyclooxygenase 1 (Cox1) and/or cyclooxygenase 2 (Cox2) inhibition[6]. A prototype of these is ibuprofen, the most commonly prescribed and used NSAID, which is a non-selective inhibitor of Cox-1 and Cox-2[16].

Considering the association of Cox-1 with gastric protection, selective NSAIDs were developed. Celecoxib is a selective NSAID (Cox-2) that was approved and has been commercialized worldwide to alleviate signs and symptoms of osteoarthritis and juvenile arthritis and to manage acute postoperative pain[17,18]. Such agents inhibit only Cox-2, showing less adverse effects on the gastrointestinal tract. Nevertheless, if used long-term, such as in

osteoarthritis treatment, these drugs increase the risk of cardiovascular problems, since Cox-2 inhibition causes an imbalance in prostacyclin and thromboxane-A2 production, favoring the occurrence of thromboembolic events. Therefore, there is an increased risk of myocardial infarction or stroke related to their use[19].

Third molar surgeries cause discomfort to the patient[1,3] with pain, swelling and trismus, whose control is crucial for patient well-being. Drug prescription is the most used method for control of inflammatory signs and symptoms in the orofacial region. Celecoxib is furthermore a medication with good efficacy for postoperative analgesia[17,20]. However, there are no reports in the literature regarding the value of this drug in swelling control. On the other hand, even though the efficacy of dexamethasone to control postoperative pain and swelling is well known,[12,13,14] there are no investigations about its association with celecoxib. Considering these points, the aim of the present study was to compare the efficacy of postoperative administration of celecoxib *versus* ibuprofen on pain, swelling, trismus and quality of life of patients having undergone extraction of impacted third molars.

MATERIAL AND METHODS

This work was conducted in accordance with the guidelines of Helsinki Protocol, and approved by the Research Ethics Committee of Pontifical Catholic University of Rio Grande do Sul (CEP-PUCRS, protocol #62935716.9.0000.5336). Patients were informed about the aims and procedures of the study and signed a consent form. The study was performed in a double-blind randomized split-mouth manner. The sample was composed of 15 patients needing extraction of their third molars (upper and mandibular; left and right). The sample size was determined by using Gpower 3.1.9.2 software, with power of 80% and significance level of 5%. The criteria of inclusion were: (a) patients between 18 and 25 years of age, having indication of extraction of the third molars for orthodontic reasons; (b) lower third molars (left and right) of the same patient should be mirrored in position of class I/B or II/B of Pell & Gregory[21]; (c) upper

third molars extraction should also be indicated, these teeth should be in bilateral mirrored position, fully covered by bone and mucosa, and with vertical inclination; (d) healthy patients, without local or systemic signs of infection and not under analgesic and/or antiinflammatory medication in the 15 days previous to the surgery (15-day washout period; ASA I and II patient). Exclusion criteria were: (a) local or systemic diseases, including cardiopathy; (b) allergy to sulfa or to the medications used in the study; (c) pregnancy and lactation; (d) surgery duration difference between the left and the right side in the same patient surpassing 20%.

Randomization was managed by an individual not directly involved with patient surgery and evaluation. It used sealed envelopes sequentially numbered, each one indicating the therapy combination (dexamethasone and celecoxib or dexamethasone and ibuprofen) and the side to be operated (right or left) for each patient. The same person was responsible for the administration of the medications to the patients. Patient and researcher were blinded to the drug used.

Medication

All patients received 8 mg oral dexamethasone one hour before the tooth extraction. The same patient also received 100 mg celecoxib every 12 h for one side of extraction alternating with 600 mg ibuprofen every 8 h for the other side, both medications administered for three days. For rescue analgesia, in case of no pain control with the medication administered, 750 mg paracetamol was given every 6 h.

Surgical technique

The impacted teeth were extracted under local anesthesia using 2% lidocaine with 1:100,000 epinephrine (DFL, Rio de Janeiro, Brazil) at a maximum volume of 6.3 mL. A standardized technique was applied for all surgeries. First, an incision on the alveolar ridge in maxillary tuberosity and an intrasulcular incision encircling the second molar

were performed. The mucoperiosteal flap was raised, and the overlying bone and third molar were removed. Next, a triangular incision in the region of the mandibular third molar was made, and after raising the mucoperiosteal flap, an ostectomy was performed in the jaw; the mandibular third molar was then sectioned and removed. The surgical wound was then closed with a 4-0 nylon suture. The upper and lower third molars on the same side were extracted in the same surgical procedure. Thirty days later, the contralateral third molars were also extracted. The variables swelling, pain, trismus and quality of life were analyzed as described below.

Trismus

Maximum mouth opening was measured taking as reference the distance between incisal edge of upper and lower central incisors using a digital caliper (0-300 mm range, 0.01 mm accuracy; Digimess, São Paulo, SP, Brazil) at 4 times: immediate preoperative time, immediate postoperative time, and 2 and 7 postoperative days[22-25].

Swelling

Swelling was evaluated using linear measurements at reference points on the operated side of the face: Tr-Che (tragus to the labial commissure); Tr-Al (tragus to the nasal border); Tr-Pog' (tragus to the soft pogonion); Go-Exo (angle of the mandible to the external corner of the eye); Go-Al (angle of the mandible to the nasal border); Go-Pog' (angle of the mandible to the soft pogonion); Go-Che (angle of the mandible to the labial commissure); Tr-Tr (right tragus to the left tragus passing right under the nasal base).[22,23,26] These were taken with a measuring tape at 4 times: immediate preoperative time, immediate postoperative time and 2 and 7 postoperative days. The visual analogue scale (VAS) of swelling was also applied. Patients chose on a 0 to 10 cm scale with graphic figures representing the intensity of swelling (absent, mild, moderate, severe, very severe) the one corresponding to their perception. These data were collected at the

immediate postoperative time and 2, 6, 12, 24, 48 and 72 h after the surgery and also on the 4th, 5th, 6th and 7th postoperative days[22,23,26-28].

Pain

A pain VAS was administered to the patients right after the surgery. They indicated pain intensity on the scale (0 to 10 cm), where 0=no pain and 10=the strongest pain. The scale was applied at the immediate preoperative time, immediate postoperative time, and 1, 2, 4, 6, 8, 12, 24, 48 and 72 h after surgery and also on 4th, 5th, 6th and 7th postoperative days[22,23,25-28].

Quality of life

A simplified Oral Health Impact Profile questionnaire (OHIP-14) was applied. It is composed of 14 questions covering seven domains: (a) functional limitation, (b) physical pain, (c) psychological discomfort, (d) physical disability, (e) psychological disability, (f) social disability and (g) handicap. Each question has five options for answer, graduated from 0 to 4 points, where higher scores represent greater negative impact on quality of life. The evaluation was performed at preoperative time and 2 and 7 days of postoperative period[2,29-31].

Statistical analysis

Data were analyzed by means of descriptive and inferential statistics. For quality of life data analysis, we used a Likert scale to grade the answers for OHIP-14[22]. Generalized estimating equations (GEE) and Bonferroni test were used for pain and swelling VAS analysis; the Mann-Whitney test was used for OHIP-14, trismus and swelling variation (mm). Frequency of rescue medication and infection was analyzed by the Fisher exact test. The Student t-test was applied for number of tablets used during rescue medication and duration of the surgical procedure. Data were analyzed in SPSS 17.0 at a significance level of 5%.

RESULTS

Demographic data

The inclusion criteria were fulfilled by 16 patients; one of them was excluded from the study because of having only one side of the mandible/maxilla operated and no return for the surgical procedure on the opposite side. The final sample therefore comprised 15 patients ranging in age from 18 to 24 years (mean age of 20.4 years, 6 males and 9 females). Regarding race, 10 patients were white (66.6%), 4 were black (26.6%) and 1 was mulatto (6.6%). A total of 60 teeth were extracted in 30 distinct surgical procedures. Twelve (80%) of the 15 patients had bilateral third mandibular molars classified as II/B Pell and Gregory[21] and 3 (20%) had bilateral third mandibular molars classified as II/A. In the ibuprofen group, 7 surgeries were performed on the right and 8 on the left side; whereas in the celecoxib group, 8 surgeries were performed on the right and 7 on the left side. Undesirable side effects were reported neither in the ibuprofen nor the celecoxib group.

Trismus (maximum mouth opening) and swelling linear measurements

Trismus did not show any significant difference between the groups at the times evaluated, with the greatest variation occurring in both groups at 48 h postoperatively (Table 1, Fig. 1A). Swelling features significantly differed between the groups only for the variable Go-Al, which was greater for celecoxib at 0.5 and 48 h. No significant differences were observed for the other measurements of swelling at the different times evaluated (Table 1, Mann-Whitney test, $\alpha=0.05$).

Table 1 - Variation in maximum mouth opening (mm) and facial measurements (mm) in relation to baseline in the ibuprofen and celecoxib groups at the different times evaluated

Time	Group										*P**
	Ibuprofen					Celecoxib					
0.5 h	Mean	SD	MD	P25	P75	Mean	SD	MD	P25	P75	
Trismus	-5.31	7.25	-4.26	-8.70	0.00	-6.40	8.87	-6.45	-14.81	-2.33	0.436
Tr–Che	0.94	1.21	0.83	0.00	0.89	0.45	0.61	0.00	0.00	0.90	0.486
Tr–Al	0.54	0.72	0.00	0.00	0.87	0.23	0.52	0.00	0.00	0.00	0.25
Tr–Pog’	1.09	0.97	0.00	0.00	0.87	0.57	0.98	0.66	0.00	1.21	0.174
Go–Exo	0.42	2.53	0.00	0.00	1.46	0.60	1.37	0.00	0.00	1.90	0.775
Go–Al	0.46	1.64	0.00	0.00	0.96	1.66	1.31	1.77	0.89	2.59	**0.023**
Go–Pog’	0.44	1.55	0.00	0.00	0.95	0.97	1.34	0.93	0.00	2.06	0.161
Go–Che	0.91	1.74	0.00	0.00	1.33	1.32	1.85	1.19	0.00	2.60	0.539
Tr-Tr	0.25	0.42	0.00	0.00	0.65	0.40	0.55	0.00	0.00	0.96	0.539
48 h											
Trismus	-17.94	16.97	-11.32	-35.09	-5.17	-26.22	18.21	-27.66	-41.38	-9.43	0.217
Tr–Che	2.52	2.17	1.75	0.90	4.39	2.81	1.84	2.63	1.68	4.00	0.486
Tr–Al	0.73	0.90	0.79	0.00	1.67	0.62	1.69	0.86	0.00	1.71	0.806
Tr–Pog’	1.89	1.86	1.36	0.63	2.63	2.00	1.80	1.49	0.65	3.01	0.567
Go–Exo	2.61	2.79	1.98	0.00	3.77	2.71	3.58	0.97	0.00	5.62	0.967
Go–Al	2.48	2.00	2.56	0.82	3.96	4.19	3.10	4.55	1.79	5.71	**0.05**
Go–Pog’	2.42	2.69	2.13	0.97	3.96	3.98	3.33	4.55	1.03	6.80	0.161
Go–Che	5.49	3.84	5.33	2.53	7.79	7.52	4.04	8.14	5.19	9.78	0.116
Tr-Tr	0.51	0.74	0.35	0.00	0.70	0.72	0.72	0.40	0.35	1.12	0.217
168 h											
Trismus	-9.79	14.95	-7.02	-22.41	2.04	-10.27	14.42	-6.56	-19.15	0.00	0.87
Tr–Che	0.72	1.25	0.00	0.00	1.79	0.57	1.27	0.00	0.00	0.87	0.624
Tr–Al	-0.17	0.55	0.00	-0.79	0.00	-0.11	0.85	0.00	0.00	0.00	0.461
Tr–Pog’	0.18	0.58	0.00	0.00	0.65	0.34	1.00	0.00	0.00	1.20	0.775
Go–Exo	0.44	1.59	0.00	-0.88	1.79	1.18	2.92	0.00	0.00	2.11	0.624
Go–Al	0.46	1.02	0.81	0.00	0.97	0.31	1.58	0.00	-0.80	0.95	0.539
Go–Pog’	0.89	2.47	0.83	-0.89	3.00	0.98	2.74	0.00	-1.77	1.98	0.87
Go–Che	1.71	2.25	0.00	0.00	3.53	1.87	2.99	1.19	0.00	3.53	0.87
Tr-Tr	0.00	0.30	0.00	-0.35	0.00	0.16	0.52	0.00	0.00	0.37	0.305

Tr–Che= tragus to the labial commissure; Tr–Al =tragus to the nasal border, Tr–Pog’= tragus to the soft pogonion, Go–Exo =angle of the mandible to the external corner of the eye, Go–Al =angle of the mandible to the nasal border, Go–Pog’=angle of the mandible to the soft pogonion, Go–Che =angle of the mandible to the labial commissure, and Tr-Tr=tragus to tragus. SD=standard deviation; MD=median.

**P*=P value for Mann-Whitney test, α=0.05

OHIP-14 evaluation

The total OHIP-14 score was significantly lower in the ibuprofen group at 48 h, where the domains functional limitation (P=0.018), physical pain (P=0.010) and physical disability (P=0.046) significantly differed between the groups (Fig. 1B, Table 2). No significant differences were observed at the other times evaluated and for the other domains of OHIP-14 (Mann-Whitney test, α=0.05).

VAS evaluation for pain and swelling

The scores for pain VAS were significantly lower in the ibuprofen than celecoxib group at postoperative times of 4, 8, 24, 48 and 72 h (Fig. 1D, Table 3). VAS swelling was significantly lower in the ibuprofen group at postoperative time of 2, 6, 12, 72 and 96 h (Table 3, Fig. 1C).

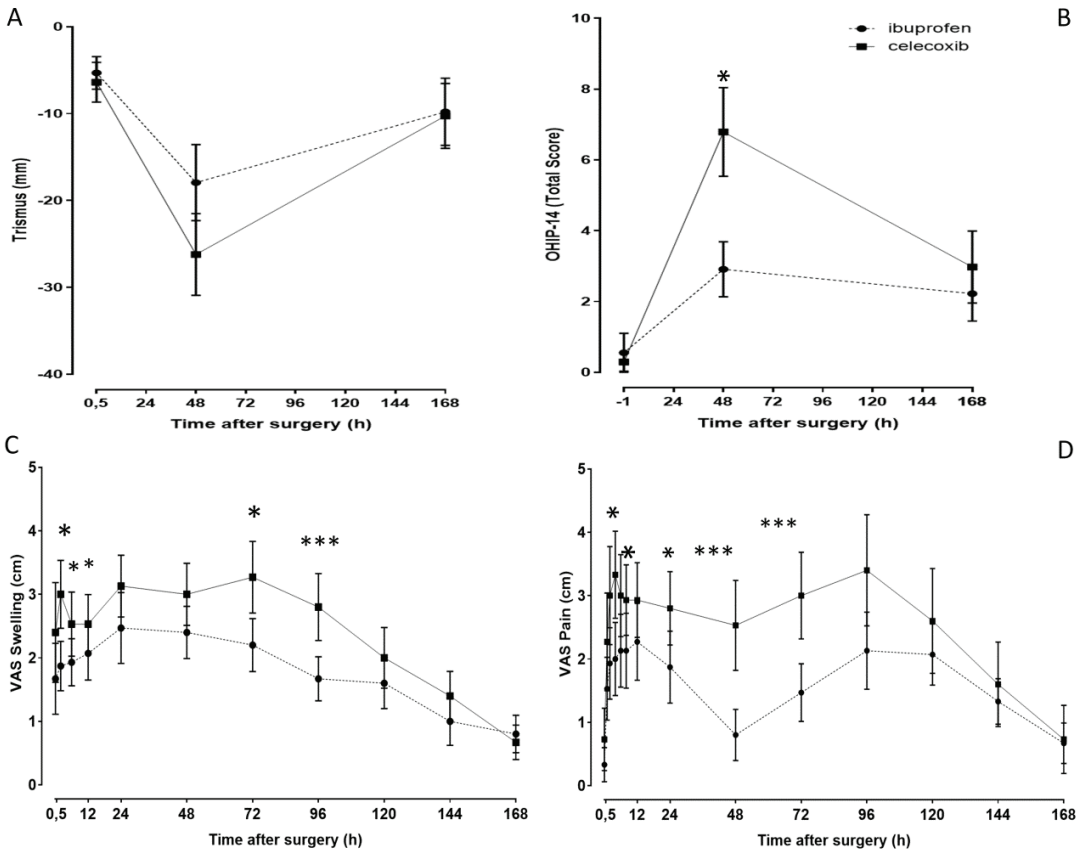

Figure 1. Evaluation of trismus (A), total OHIP-14 score (B), VAS for swelling (C) and VAS for pain (D) in the ibuprofen and celecoxib groups. (A) Mann-Whitney test, P>0.05; (C) and (D) generalized estimating equations (GEE) and Bonferroni test: *P <0.05, ***P <0.01.

Table 2 - OHIP-14 scores in the ibuprofen and celecoxib groups at the different times evaluated

Time/Domain	Group						
	Ibuprofen			Celecoxib			
	Mean	SD	Median	Mean	SD	Median	*P**
Baseline							
Functional limitation	0.00	0.00	0.00	0.00	0.00	0.00	1.00
Physical pain	0.20	0.77	0.00	0.16	0.52	0.00	0.605
Psychological discomfort	0.07	0.28	0.00	0.00	0.00	0.00	0.317
Physical disability	0.06	0.25	0.00	0.00	0.00	0.00	0.317
Psychological disability	0.08	0.31	0.00	0.08	0.31	0.00	1.00
Social disability	0.13	0.52	0.00	0.05	0.20	0.00	0.962
Handicap	0.00	0.00	0.00	0.00	0.00	0.00	1.00
Total score	0.55	0.00	0.00	0.29	0.00	1.00	0.605
48 h							
Functional limitation	0.30	0.45	0.00	0.93	0.82	0.98	**0.018**
Physical pain	0.86	1.12	0.66	1.93	1.25	1.66	**0.010**
Psychological discomfort	0.33	0.48	0.00	0.76	1.05	0.45	0.332
Physycal disability	0.26	0.49	0.00	0.87	0.99	0.52	**0.046**
Psychological disability	0.53	0.90	0.00	0.96	0.96	0.60	0.143
Social disability	0.49	0.59	0.38	0.96	1.12	0.62	0.254
Handicap	0.13	0.30	0.00	0.38	0.70	0.00	0.351
Total score	2.91	0.00	0.00	6.79	0.00	1.00	**0.013**
168 h							
Functional limitation	0.10	0.27	0.00	0.27	0.59	0.00	0.544
Physical pain	0.75	0.93	0.34	0.93	1.19	0.66	0.878
Psychological discomfort	0.21	0.38	0.00	0.30	0.69	0.00	0.845
Physycal disability	0.20	0.41	0.00	0.36	0.51	0.00	0.331
Psychological disability	0.39	0.52	0.00	0.48	0.69	0.00	0.945
Social disability	0.41	0.80	0.00	0.56	0.67	0.38	0.260
Handicap	0.16	0.37	0.00	0.11	0.22	0.00	0.905
Total score	2.22	0.00	0.00	3.00	0.00	1.00	0.483

SD=standard deviation
**P*= P value for Mann-Whitney test, α=0.05

Table 3 - Visual analogue scale (VAS) score for pain and swelling in the postoperative period

Time (hours)	Pain VAS					Swelling VAS				
	Group					Group				
	Ibuprofen		Celecoxib			Ibuprofen		Celecoxib		
	Mean	SD	Mean	SD	*P*	Mean	SD	Mean	SD	*P*
0.5	0.33	1.05	0.73	1.91	0.394	1.67	2.16	2.40	3.04	0.185
1	1.53	1.92	2.27	2.99	0.123	-	-	-	-	-
2	1.93	2.19	3.00	3.00	0.129	1.87	1.51	3.00	2.07	0.060
4	2.00	2.24	3.33	2.66	**0.013**	-	-	-	-	-
6	2.13	2.23	3.00	2.51	0.065	1.93	1.44	2.53	1.96	**0.042**
8	2.13	2.30	2.93	2.15	**0.047**	-	-	-	-	-
12	2.27	2.35	2.93	2.28	0.129	2.07	1.62	2.53	1.81	**0.012**
24	1.87	2.20	2.80	2.24	0.029	2.47	2.17	3.13	1.89	0.194
48	0.80	1.57	2.53	2.75	**0.000**	2.40	1.60	3.00	1.89	0.236
72	1.47	1.77	3.00	2.65	**0.001**	2.20	1.61	3.27	2.19	**0.034**
96	2.13	2.36	3.40	3.40	0.074	1.67	1.35	2.80	2.04	**0.009**
120	2.07	1.87	2.60	3.20	0.486	1.60	1.55	2.00	1.85	0.328
144	1.33	1.40	1.60	2.59	0.664	1.00	1.46	1.40	1.50	0.315
168	0.67	1.23	0.73	2.09	0.881	0.80	1.15	0.67	1.05	0.635

SD=standard deviation
P=*P* value for generalized estimating equations (GEE) and Bonferroni test, α=0.05
Bold printed values showed significant difference

Rescue medication

The frequency of rescue medication use was higher in the celecoxib group (Fisher exact test, *P*=0.025, Table 4), but there was no significant difference between the groups considering the number of tablets of rescue medication consumed (Student *t*-test, *P*=0.93, Table 5). Frequency of infection and duration of surgical procedure did not differ substantially between the groups (Fisher exact test, Student *t*-test, α=0.05; Tables 4 and 5). On the fourth postoperative day, one patient in the celecoxib group presented with fever and mild dental alveolus abscess. Therefore, the patient received 500 mg amoxicillin every 8 h for five days and 0.12% chlorhexidine mouthwash every 12 h for 3 days (Table 4).

Table 4 - Frequency of rescue medication use and infection

Group	Rescue medication						Infection					
	Present		Absent		Total		Present		Absent		Total	
	n	%	n	%	n	%	n	%	n	%	n	%
Ibuprofen	5	33.3	10	66.7	15	100	-	-	15	100	15	50
Celecoxib	12	80.0	3	20.0	15	100	01	6.7	14	93.3	15	50
Total	17	56.7	13	43.3	30	100	01	3.3	29	96.7	30	100
*P**	**0.025**						1.0					

*P value for Fisher exact test, α=0.05

Table 5- Number of tablets used during rescue medication and duration of the surgical procedure

Group	Rescue medication*			Surgery duration (min)		
	Mean	SD	Median	Mean	SD	Median
Ibuprofen	2.60	1.34	2.00	42.87	12.69	40.00
Celecoxib	2.67	1.43	3.00	43.67	12.60	40.00
*P***	0.93			0.864		

*Considering just the patients who took the medication (n=17)
**P value for Student *t*-test, α=0.05

DISCUSSION

According to our results, both groups, ibuprofen and celecoxib, showed a decrease in maximum mouth opening in the postoperative period at the same extent, suggesting that trismus intensity did not significantly differ between them. Considering that the etiopathogenesis of trismus involves the masticatory muscles being affected by the inflammatory process[32], it seems that these results are in agreement with the face measurement results.

In the facial linear measurements used to express swelling, only Go-Al distance significantly differed between the groups, being greater for celecoxib at 0.5 and 48 h. At 68 h, this variable did not show significance anymore. The lack of significant difference in most swelling measurements might have been due to dexamethasone administered to the

patients 1 h before the surgery, which according to Alcântara *et al*.[12], is capable of reducing swelling intensity and trismus as well, giving comfort to the patient without increasing infection rate[4]. Moreover, we should note that in Go-Al measurement, the Go point is difficult to locate on the patient's face by palpation in the postoperative period because this anatomic region becomes painful after third molar extraction. Such limitation could have been a bias in our analysis, explaining why only this linear measurement significantly differed between the groups.

Despite the probable beneficial effects of dexamethasone on the variables analyzed, it is important to point out that the association of either ibuprofen or celecoxib with this glucocorticoid was not capable of improving mouth opening limitation or changing the facial linear measurements. That is, ibuprofen nor celecoxib showed an advantage regarding these variables. Accordingly, Barbalho *et al*.[33] did not find any significant effect of nimesulide combined with dexamethasone on trismus and swelling compared to dexamethasone alone.

We found that pain was significantly lower in the ibuprofen than celecoxib group at 4, 8, 24, 48 and 72 h postoperative. This finding suggested a better analgesic performance of ibuprofen, whose antiinflammatory properties may be weaker than those of some other NSAIDs, but having substantial analgesic and antipyretic effects. Ibuprofen inhibits the synthesis of prostaglandins, which have an important role in the production of pain, inflammation and fever[16]. Celecoxib also inhibits cyclooxygenase and prostaglandins, but with selectivity for Cox-2 and therefore without interference with Cox-1. It does not display full antiinflammatory properties[34], but is capable of significantly reducing capillary vascular permeability[35]. Considering the similar mechanism of action of ibuprofen and celecoxib, it is possible that a higher dose of the latter would have led to different results, since some studies have used celecoxib at 400 mg/day[17,20] or even 600 mg/day[36]. Anyway,

we chose a 200 mg/day celecoxib dose because it is considered efficacious in controlling acute postoperative pain with the advantage of avoiding adverse effects[37,38]. Nevertheless, unlike our study, Salo *et al*.[38] did not find a significant difference between celecoxib and ibuprofen in controlling acute pain at 5 h postoperative, even using 200 mg/day celecoxib and 600 mg/day ibuprofen. It is important to note that these authors used a VAS questionnaire that patients filled out at home, and the injuries suffered by the patients were emergency musculoskeletal ones. In addition, that study did not concomitantly use dexamethasone.

The peak of pain in the celecoxib group occurred at 4 h and for ibuprofen at 12 h. Drug plasma peak, if in fasting state, is 3 and 11 h, respectively, for celecoxib and ibuprofen. If the patient ate, these can be increased by 2 or 3 h. Patients from our sample were not required to fast. It seems that this finding does not represent a better effect of one or the other drug but it is consequence of their pharmacokinetics, and just demands a correct dosage of the drugs. Both groups showed an increase in pain VAS at 96 h, possibly related to the time of the last administration of the drugs, which was at 72 h.

According to our results, the ibuprofen group showed that VAS for swelling was lower than that for celecoxib at 6, 12, 72 and 96 h, suggesting that ibuprofen was more efficacious in controlling swelling even after withdrawal of the drug, which occurred at 72 h. Regarding pain and swelling VAS, there was a one-off decrease of the indices at 48 h in both groups. Maybe this was related to the face-to-face encounter with the surgeon, suggesting that the psychological factor of being cared for could interfere with pain and swelling perception by the patient. Therefore another point to consider is the subjectivity of pain evaluation and the great variation of its threshold from patient to patient.

The total OHIP-14 score was significantly lower in the ibuprofen group for functional limitation, physical pain and physical disability at 48 h. No significant

differences were observed for the other domains and times evaluated. In addition, when taking celecoxib, patients felt more pain and had more physical disability compared to ibuprofen, expressed by complaints such as unsatisfactory diet, worsening of taste and persistent pain. The results of celecoxib for pain VAS and edema VAS are correlated to the quality of life results in the postoperative period of 48 h. However, at seven days the two groups again did not differ from each other for these variables.

The extraction of third molars, upper and lower, at the same time under local anesthesia, is a common practice in oral surgery. However, the classical design of studies evaluating postoperative complications in third molar extraction applies only the mandibular third molar extraction. In the present study, we tried to simulate what really occurs in the clinical routine, performing the extraction of both upper and lower third molars in the same procedure. Nevertheless, there is no consensus for scoring of difficulty in surgical technique for the extraction of upper third molars as there is for mandibular ones[21], which can work as a bias/limitation during sample selection.

Considering that the use of non-selective NSAIDs in patients who already have gastric problems is restricted, and that these agents can have a deleterious effect on renal function, platelet aggregation, and the mucosal barrier of the gastrointestinal tract, leading to avascular necrosis of renal tubules and gastrointestinal bleeding[37], celecoxib, which is a selective NSAID for Cox-2, may be a lower-risk alternative for postoperative treatment of third molar extraction patients. Meanwhile, further studies with higher doses of celecoxib than those used in the present study and administering just dexamethasone to a group without ibuprofen or celecoxib would be of help to clarify some obscure points.

CONCLUSION

Celecoxib (200 mg/day) performance was similar to ibuprofen for trismus control but was not as effective as ibuprofen to control swelling and pain and to improve quality of life scores in OHIP-14 evaluation.

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ETHICAL APPROVAL

This work was approved by the Research Ethics Committee of Pontifical Catholic University of Rio Grande do Sul (CEP-PUCRS, protocol #62935716.9.0000.5336).

CONFLICT OF INTEREST

Author declare there is no conflict of interest related to this work.

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DISCUSSÃO GERAL

4 DISCUSSÃO GERAL

O desafio que o manejo pós-operatório da extração de terceiros molares representa para o cirurgião-dentista é fato notório (Cho *et al.*, 2017). Isso se deve, em especial, ao quadro de dor, edema, trismo, dificuldade à alimentação e comprometimento da qualidade de vida que afeta o paciente em decorrência desse procedimento cirúrgico (Chugh *et al.*, 2017). Apesar de ser esse um tema intensamente investigado, ainda não se tem estabelecida uma terapia ou posologia padrão-ouro para o manejo da sintomatologia pós-operatória do procedimento cirúrgico em questão, havendo dados conflitantes relatados na literatura científica a esse respeito (Al-Sukhun *et al.*, 2012; Aoki *et al.*, 2012; Au *et al.*, 2015; Christensen *et al.*, 2017; Gönül *et al.*, 2015; Isiordia-Espinoza *et al.*, 2014). Tais controvérsias motivaram a realização do presente estudo, com o objetivo de contribuir com o conhecimento e elucidar alguns pontos relativos aos reais benefícios do uso do celecoxibe em doses moderadas no pós-operatório de terceiros molares inclusos.

No presente estudo, de modo geral, o ibuprofeno (1.800 mg/dia) teve melhor desempenho que o celecoxibe (200 mg/dia) nos parâmetros avaliados. As escalas VAS de dor e edema e os escores do OHIP, métodos subjetivos de aferição, exibiram diferença significativa entre os grupos com melhor *performance* do ibuprofeno. Entretanto, nas análises objetivas como máxima abertura de boca e medidas faciais lineares, não foi encontrada diferença significativa, exceto para a distância Go-Al. Nesse contexto, se poderia inferir que a subjetividade inerente aos métodos de avaliação empregados tenha interferido nos resultados obtidos. Contudo, também é preciso considerar que, independentemente da subjetividade envolvida pelo método, sobressai-se a importância de se avaliar e valorizar a percepção do paciente acerca de sua sintomatologia e qualidade de vida que, por si só, são aspectos subjetivos e

multifatoriais, que variam não apenas de paciente para paciente, mas também de um momento para outro em um mesmo paciente. Quanto às medidas faciais, embora constituam dados objetivos, seu processo de obtenção também envolve a subjetividade do operador. Seria interessante aplicar, em futuros estudos, *softwares* específicos que permitam a reprodução digital tridimensional da face e a aferição automatizada dessas variáveis (Bormann *et al.*, 2016). Em resumo, a subjetividade ocorreu como viés no presente estudo, assim como ocorre em boa parte das pesquisas clínicas que avaliam as variáveis em questão (Koepke *et al.*, 2017).

A avaliação dos grupos ibuprofeno e celecoxibe sem um grupo placebo permitiu estabelecer conclusões relativas à *performance* comparada das duas drogas, entretanto, a sua eficácia independente não pôde ser estimada. Isso equivale a dizer que, embora o desempenho do celecoxibe tenha sido, à primeira vista, inferior ao do ibuprofeno, tal achado não significa que o primeiro não tenha um desempenho satisfatório na situação testada, até porque o mesmo é indicado para controle da dor aguda pós-operatória (Aoki *et al.*, 2014; Moghaddamnia *et al.*, 2013; Yamashita *et al.*, 2013). Entretanto, do ponto de vista ético e humano, não seria razoável submeter o paciente à extração de um terceiro molar sem administração de terapia analgésica.

Considerando-se o fator econômico, o ibuprofeno apresenta-se como um fármaco mais acessível, com menor custo, se comparado ao celecoxibe. Por outro lado, pacientes com doença gastrointestinal como, por exemplo, úlcera gástrica, têm contraindicação de uso do ibuprofeno; assim como o uso deste fármaco deve ser criteriosamente avaliado em caso de pacientes trombocitopênicos (Curtis, 2014). Em contrapartida, o celecoxibe, que apresenta risco de eventos cardiovasculares em doses elevadas, é considerado seguro e com risco comparável ao dos demais AINEs, se administrado na dose de 200 mg/dia (Nissen *et al.*, 2016). Ainda, o risco de efeitos

adversos cardiovasculares está associado ao uso crônico desse fármaco (Bally *et al.*, 2017), o que não acontece no pós-operatório de extração de terceiros molares. A dose de 200 mg/dia de celecoxibe foi estabelecida para uso no presente estudo partindo-se do pressuposto de que é uma dose eficaz e segura do ponto de vista cardiovascular (Nissen *et al.*, 2016). Talvez doses maiores, já empregadas em outros estudos, tivessem originado resultados mais favoráveis para esse fármaco. Entretanto, o objetivo foi verificar a eficácia dessa posologia em específico, em função da já atestada segurança de seu uso.

A dexametasona administrada no pré-operatório de cirurgia de terceiros molares exibe eficácia na redução do edema e da dor e tem sido associada rotineiramente ao uso de analgésicos (Bamgbose *et al.*, 2006; Moghaddamnia *et al.*, 2013). Por esse motivo, o presente estudo associou o uso da dexametasona a ambos os fármacos, celecoxibe e ibuprofeno. Contudo, se o desenho do trabalho não fosse do tipo *split-mouth*, seria pertinente a amostra contemplar mais três grupos distintos, cada um empregando exclusivamente cada uma das drogas, dexametasona, ibuprofeno e celecoxibe.

O manejo pós-operatório da extração de terceiros molares mantém-se alvo de pesquisas. Cho *et al.* (2017) relatam que o paracetamol e o ibuprofeno são eficazes no tratamento da dor pós-operatória de extração de terceiros molares, enquanto a clorexidina é capaz de prevenir a osteíte alveolar. Por outro lado, defendem que corticosteroides e antibióticos só devem ser usados em casos selecionados. Já os benefícios da crioterapia, irrigação pós-operatória e gel de ozônio, segundo esses autores, ainda não foram estabelecidos. Outros estudos têm sugerido que o uso da cafeína (Weiser *et al.*, 2018) e da antibioticoterapia podem favorecer significativamente a evolução do paciente no pós-operatório da cirurgia de extração de terceiro molar

(Marchionni *et al.*, 2017; Ramos *et al.*, 2016). Os pontos controversos entre os resultados dos diversos estudos persistem, provavelmente associados a fatores metodológicos. Novos estudos seguindo método padronizado no que concerne à seleção da amostra, técnica cirúrgica, drogas testadas, bem como sua dosagem e tempo de uso, devem ser encorajados.

Considerando-se a situação clínica e variáveis avaliadas, o presente estudo sugere que o celecoxibe não traz maiores benefícios que o ibuprofeno, uma vez que este exibiu, de modo geral, melhores resultados. Entretanto, na rotina clínica, essa comparação deve ser feita de forma individualizada, tendo-se em conta fatores específicos de cada paciente. Sendo assim, o celecoxibe permanece como opção terapêutica para a sintomatologia pós-operatória, especialmente em indivíduos com contraindicação de uso do ibuprofeno ou de outros AINEs não-seletivos. Mais uma vez a eleição do melhor fármaco vai depender da ponderação de critérios clínicos e farmacológicos, quais sejam: condições clínicas do paciente e a relação destas com eficácia, mecanismo de ação e efeitos adversos da droga. Novas pesquisas direcionadas tanto ao uso de novos fármacos, quanto a novas posologias e associações das drogas já existentes podem contribuir para a otimização do pós-operatório do paciente submetido à extração de terceiro molar.

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ANEXOS

ANEXO A

Comprovante de submissão do artigo *Celecoxib versus ibuprofen in controlling postoperative symptomatology of third molar extraction: a randomized double-blind clinical trial* ao periódico *International Journal of Oral & Maxillofacial Surgery*

Submission Confirmation for Celecoxib versus ibuprofen in controlling postoperative symptomatology of third molar extraction: a randomized double-blind clinical trial

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Responder a todos

Hoje, 12:25

Karen Cherubini; karencherubibi66@gmail.com; Karen Cherubini

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ANEXO B

Normas para submissão de manuscritos ao periódico *International Journal of Oral and Maxillofacial Surgery*

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Would authors please note that the reference style for the journal has now changed. Please pay special attention to the guidelines under the heading "References" below

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• based on a sound hypothesis and an adequate investigation method analysing a statistically relevant series, leading to relevant results that back the conclusion
• well written in simple, scientific English grammar and style
• presented with a clear message and containing new information that is relevant for the readership of the journal
• Note the comment above relating to case reports. • Please include a paragraph in your cover letter where you explain what is new about your study and why it will have an impact on your field of research.

Following peer-review, authors are required to resubmit their revised paper within **3 months;** in exceptional circumstances, this timeline may be extended at the editor's discretion.

Presentation of Manuscripts

General points

Papers should be submitted in journal style. Failure to do so will result in the paper being immediately returned to the author and may lead to significant delays in publication. Spelling may follow British or American usage, but not a mixture of the two. Papers should be double-spaced with a margin of at least 3 cm all round. Each line must be numbered.

Format

Observational or Case Cohort Studies, as well as Case Series must be presented in conformance with STROBE guidelines: http://www.strobe-statement.org

Randomized Controlled Trials must be presented in conformance with CONSORT guidelines: http://www.consort-statement.org

Systematic Reviews and Meta-Analyses must be presented according to PRISMA guidelines: http://www.prisma-statement.org

Papers should be set out as follows, with each section beginning on a separate page: • title page• abstract• text• acknowledgements• references• tables• captions to illustrations.Please note that the qualifications of the authors will not be included in the published paper and should not be listed anywhere on the manuscript.

*Title page*The title page should give the following information: • title of the article• full name of each author• name and address of the department or institution to which the work should be attributed•

name, address, telephone and fax numbers, and e-mail address of the authorresponsible for correspondence and to whom requests for offprints should be sent• sources of support in the form of grants• key words.If the title is longer than 40 characters (including spaces), a short title should be supplied for use in the running heads.

Abstract

200 words maximum. Do not use subheadings or abbreviations; write as a continuous paragraph. Must contain all relevant information, including results and conclusion.

Text

Please ensure that the text of your paper conforms to the following structure: Introduction, Materials and Methods, Results, Discussion. There is no separate Conclusion section.

Introduction

• Present first the nature and scope of the problem investigated
• Review briefly the pertinent literature
• State the rationale for the study
• Explain the purpose in writing the paper
• State the method of investigation and the reasons for the choice of a particular method
•; Should be written in the present tense

Materials and Methods

• Give the full details, limit references• Should be written in the past tense• Include exact technical specifications, quantities and generic names• Limit the number of subheadings, and use the same in the results section• Mention statistical method• Do not include results in this section

Results

• Do not describe methods
• Present results in the past tense
• Present representations rather than endlessly repetitive data
• Use tables where appropriate, and do not repeat information in the text

Discussion

• Discuss - do not recapitulate results• Point out exceptions and lack of correlations. Do not try to cover up or 'fudge' data• Show how results agree/contrast with previous work• Discuss the implications of your findings• State your conclusions very clearly

Headings: Headings enhance readability but should be appropriate to the nature of the paper. They should be kept to a minimum and may be removed by the Editors. Normally only two categories of headings should be used: major ones should be typed in capital letters; minor ones should be typed in lower case (with an initial capital letter) at the left hand margin.

Quantitative analysis: If any statistical methods are used, the text should state the test or other analytical method applied, basic descriptive statistics, critical value obtained, degrees of freedom, and significance level, e.g. (ANOVA, $F=2.34$; $df=3,46$; $P<0.001$). If a computer data analysis was involved, the software package should be mentioned. Descriptive statistics may be presented in the form of a table, or included in the text.

Abbreviations, symbols, and nomenclature: Only standardized terms, which have been generally accepted, should be used. Unfamiliar abbreviations must be defined when first used. For further details concerning abbreviations, see Baron DN, ed. Units, symbols, and abbreviations. A guide for biological and medical editors and authors, London, Royal Society of Medicine, 1988 (available from The Royal Society of Medicine Services, 1 Wimpole Street, London W1M 8AE, UK).

The minus sign should be -.

If a special designation for teeth is used, a note should explain the symbols. Scientific names of organisms should be binomials, the generic name only with a capital, and should be italicised in the typescript. Microorganisms should be named according to the latest edition of the Manual of Clinical Microbiology, American Society of Microbiology.

Drugs: use only generic (non-proprietary) names in the text. Suppliers of drugs used may be named in the Acknowledgments section. Do not use 'he', 'his' etc where the sex of the person is unknown; say 'the patient' etc. Avoid inelegant alternatives such as 'he/she'. Patients should not be automatically designated as 'she', and doctors as 'he'.

References

The journal's reference style has changed. References should be numbered consecutively throughout the article, beginning with 1 for the first-cited reference. References should be listed at the end of the

paper in the order in which they appear in the text (not listed alphabetically by author and numbered as previously).

The accuracy of references is the responsibility of the author. References in the text should be numbered with superscript numerals inside punctuation: for example "Kenneth and Cohen[14] showed..."; "each technique has advantages and disadvantages[5-13]." Citations in the text to papers with more than two authors should give the name of the first author followed by "*et al.*"; for example: "Wang et al[37] identified..."

All references cited in the text must be included in the list of references at the end of the paper. Each reference listed must include the names of all authors. Please see section "Article Types" for guidance on the maximum number of reference for each type of article.

Titles of journals should be abbreviated according to Index Medicus (see www.nlm.nih.gov.uk) . When citing papers from monographs and books, give the author, title of chapter, editor of book, title of book, publisher, place and year of publication, first and last page numbers. Internet pages and online resources may be included within the text and should state as a minimum the author(s), title and full URL. The date of access should be supplied and all URLs should be checked again at proof stage.

Data References This journal encourages you to cite underlying or relevant datasets in your manuscript by citing them in your text and including a data reference in your Reference List. Data references should include the following elements: author name(s), dataset title, data repository, version (where available), year, and global persistent identifier. Add [dataset] immediately before the reference so we can properly identify it as a data reference. The [dataset] identifier will not appear in your published article.

Examples:

Journal article: Halsband ER, Hirshberg YA, Berg LI. Ketamine hydrochloride in outpatient oral surgery. J Oral Surg 1971: 29: 472-476.

When citing a paper which has a Digital Object Identifier (DOI), use the following style: Toschka H, Feifel H. Aesthetic and functional results of harvesting radial forearm flap. Int J Oral Maxillofac Surg 2001: 30: 45-51. doi: 10.1054/ijom.2000.0005

Book/monograph: Costich ER, White RP. Fundamentals of oral surgery. Philadelphia: WB Saunders, 1971: 201-220.

Book chapter: Hodge HC, Smith FA. Biological properties of inorganic fluorides. In: Simons JH, ed.: Fluorine chemistry. New York: Academic Press, 1965: 135.

Internet resource: International Committee of Medical Journal Editors. Uniform requirements for manuscripts submitted to biomedical journals. http://www.icmje.org [Accessibility verified March 21, 2008]

Please note you can only include up to a maximum of 6 tables and/ or figures within your article.

Tables

Tables should be used only to clarify important points. Double documentation in the form of tables and figures is not acceptable. Tables should be numbered consecutively with Arabic numerals. They should be double spaced on separate pages and contain only horizontal rules. Do not submit tables as photographs. A short descriptive title should appear above each table, with any footnotes suitably identified below. Care must be taken to ensure that all units are included. Ensure that each table is cited in the text.

Figures

All illustrations (e.g. graphs, drawings or photographs) are considered to be figures, and should be numbered in sequence with Arabic numerals. Each figure should have a caption, typed double-spaced on a separate page and numbered correspondingly. **The minimum resolution for electronically generated figures is 300 dpi.**

Line illustrations: All line illustrations should present a crisp black image on an even white background (127 x 178 mm (5 x 7 in), or no larger than 203 x 254 mm (8 x 10 in). The size of the lettering should be appropriate, taking into account the necessary size reduction.

Photographs and radiographs: Photomicrographs should show magnification and details of any staining techniques used. **The area(s) of interest must be clearly indicated with arrows or other symbols.**

Colour images are encouraged, but the decision whether an illustration is accepted for reproduction in colour in the printed journal lies with the editor-in-chief. Figures supplied in colour will appear in colour in the online version of the journal.

Size of photographs: The final size of photographs will be: (a) single column width (53 mm), (b) double column width (110 mm), (c) full page width (170 mm). Photographs should ideally be submitted at the final reproduction size based on the above figures.

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Instructions for Letters to the Editor

The IJOMS welcomes Letters to the Editor. To facilitate submission of the highest quality of Letters to the Editor, the following guidelines should be followed:

1. Letters are meant to be focus pieces and, therefore, are limited to no more than 600 words, 6 references and a maximum of 2 figures. One reference should include a reference to the IJOMS article being addressed.
2. It is recommended that you limit your letter to one or two important and critical points to which you wish to provide a clear and precise discussion regarding the previously published article.
3. One should support all assertion by peer review literature which should be a primary research or large clinical studies rather than a case report.
4. Please include any financial disclosures at the end of the letter. This would include the potential conflicts of interest not just related to the specific content of your letter but also the content of the IJOMS article and other related areas.
5. Please recognize that letters that are essentially in agreement with the author's findings and offer no additional insights provide little new information for publication. Likewise, letters that highlight the writer's own research or are otherwise self promotional will receive a low publication priority.
6. There may be a need for additional editing. Should editing be required the letter will be sent back to the author for final approval of the edited version.

7. It is important to use civil and professional discourse. It is not advisable that one adopt a tone that may be misconstrued to be in anyway insulting.
8. Finally, it is not advisable to provide a letter that is anecdotal. While personal experiences can have great value in patient care, it is generally not strong evidence to be placed in a letter to the editor.

ANEXO C

SIPESQ

Sistema de Pesquisas da PUCRS

Código SIPESQ: 7639 Porto Alegre, 28 de setembro de 2016.

Prezado(a) Pesquisador(a),

A Comissão Científica da FACULDADE DE ODONTOLOGIA da PUCRS apreciou e aprovou o Projeto de Pesquisa "CELECOXIBE VERSUS IBUPROFENO NA EXTRAÇÃO DE TERCEIROS MOLARES". Este projeto necessita da apreciação do Comitê de Ética em Pesquisa (CEP). Toda a documentação anexa deve ser idêntica à documentação enviada ao CEP, juntamente com o Documento Unificado gerado pelo SIPESQ.

Atenciosamente,

Comissão Científica da FACULDADE DE ODONTOLOGIA

ANEXO D

PONTIFÍCIA UNIVERSIDADE CATÓLICA DO RIO GRANDE DO SUL - PUC/RS

PARECER CONSUBSTANCIADO DO CEP

DADOS DO PROJETO DE PESQUISA

Título da Pesquisa: CELECOXIBE VERSUS IBUPROFENO NA EXTRAÇÃO DE TERCEIROS MOLARES
Pesquisador: Claiton Heitz
Área Temática:
Versão: 2
CAAE: 62935716.9.0000.5336
Instituição Proponente: UNIAO BRASILEIRA DE EDUCACAO E ASSISTENCIA
Patrocinador Principal: Financiamento Próprio

DADOS DO PARECER

Número do Parecer: 1.970.388

Apresentação do Projeto:
A cirurgia de terceiros molares acarreta desconforto ao paciente, motivo pelo qual o controle dos sinais e dos sintomas de dor, edema e trismo é de suma importância, tratando-se de relevante problemática para pesquisas científicas. O uso de fármacos é o método mais utilizado para o controle dos sinais e dos sintomas inflamatórios da região da face. Nesse sentido, celecoxibe é uma medicação que possui boa eficácia para analgesia pós-operatória, porém ainda não há relatos na literatura sobre existência de testes para controle do edema9. Por outro lado, a dexametasona é um medicamento reconhecidamente eficaz no controle da dor e do edema pós-operatório, embora não tenha sido testada em associação ao Celecoxibe.

Objetivo da Pesquisa:
Comparar a eficácia da administração pós-operatória de 100 mg de celecoxib (grupo experimental) versus 600 mg de Ibuprofeno (grupo controle), no pós-operatório de terceiros molares impactados, avaliando a qualidade de vida, dor, edema e trismo (no pré-operatória todos paciente utilizarão 8 mg de dexametasona).

Avaliação dos Riscos e Benefícios:
Segundo os pesquisadores, como os dois medicamentos (ibuprofeno e celecoxib) já são usados no

Endereço: Av.Ipiranga, 6681, prédio 50, sala 703
Bairro: Partenon **CEP:** 90.619-900
UF: RS **Município:** PORTO ALEGRE
Telefone: (51)3320-3345 **Fax:** (51)3320-3345 **E-mail:** cep@pucrs.br

pós operatório de extração de terceiros molares e liberados pela ANVISA, os riscos são iguais a qualquer outra extração de terceiro molar.
Quantos aos benefícios da pesquisa, os pesquisadores consideram a extração de terceiros molares, que tenham indicação de remoção, além do uso de medicamentos seguros e eficazes no controle e alívio da dor pós operatória.

Comentários e Considerações sobre a Pesquisa:
Será realizado um ensaio clínico randomizado, de boca dividida (Split-mouth), duplo cego, comparando a eficácia da administração, via oral, pós-operatória de celecoxibe 100 mg de seis em seis horas versus ibuprofeno 600 mg de oito em oito horas. Os 32 pacientes serão selecionados na Faculdade de Odontologia da Pontifícia Universidade Católica do Rio Grande do Sul. Nas extrações dos terceiros molares inferiores será avaliado dor, edema, trismo e qualidade de vida. A análise estatística prevista é o t de Student para comparação entre os dois grupos. O teste estatístico ANOVA de medidas repetidas e o teste de Bonferroni também serão utilizados para o edema, trismo e dor. O nível de insignificância máxima assumido será de 5% e o software a ser utilizado para análise estatística será o SPSS versão 22.0.

Considerações sobre os Termos de apresentação obrigatória:
O projeto apresenta as cartas necessárias a sua execução, bem como todos os documentos necessários para a sua aprovação, assim como os Termos de Consentimento Livre e Esclarecido.

Conclusões ou Pendências e Lista de Inadequações:
Considero que os aspectos científicos e metodológicos estão bem detalhados e fundamentados, assim como foram apresentados todos os Termos obrigatórios, portanto o projeto possui mérito para ser executado.

Considerações Finais a critério do CEP:
Diante do exposto, o CEP-PUCRS, de acordo com suas atribuições definidas nas Resoluções CNS n°466 de 2012, n°510 de 2016 e da Norma Operacional n° 001 de 2013 do Conselho Nacional de Saúde, manifesta-se pela aprovação do projeto de pesquisa proposto.

Este parecer foi elaborado baseado nos documentos abaixo relacionados:

Tipo Documento	Arquivo	Postagem	Autor	Situação
Informações Básicas do Projeto	PB_INFORMAÇÕES_BÁSICAS_DO_PROJETO_818666.pdf	09/03/2017 18:54:49		Aceito

PONTIFÍCIA UNIVERSIDADE CATÓLICA DO RIO GRANDE DO SUL - PUC/RS

Continuação do Parecer: 1.970.388

TCLE / Termos de Assentimento / Justificativa de Ausência	TCLEmodificado.docx	09/03/2017 18:54:25	Claiton Heitz	Aceito
TCLE / Termos de Assentimento / Justificativa de Ausência	termoconsentimentoVelho.docx	09/03/2017 18:53:50	Claiton Heitz	Aceito
Outros	cartarespostapendencias1.pdf	09/03/2017 18:52:28	Claiton Heitz	Aceito
TCLE / Termos de Assentimento / Justificativa de Ausência	TCLEmodificado.pdf	24/01/2017 19:43:38	Claiton Heitz	Aceito
Declaração de Instituição e Infraestrutura	laboassinado.pdf	12/12/2016 11:51:58	Claiton Heitz	Aceito
Projeto Detalhado / Brochura Investigador	dissertacao.pdf	08/11/2016 09:39:04	Claiton Heitz	Aceito
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Declaração de Pesquisadores	compromissodados.pdf	08/11/2016 09:32:39	Claiton Heitz	Aceito
TCLE / Termos de Assentimento / Justificativa de Ausência	termoconsentimento.pdf	08/11/2016 09:32:13	Claiton Heitz	Aceito
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Folha de Rosto	folhaderostoassinada.pdf	31/10/2016 17:01:52	Claiton Heitz	Aceito

Situação do Parecer:
Aprovado

Necessita Apreciação da CONEP:
Não

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PORTO ALEGRE, 17 de Março de 2017

Assinado por:
Denise Cantarelli Machado
(Coordenador)