

GUSTAVO HENRIQUE DE MATTOS PEREIRA

**ANALGESIA PREEMPTIVA EM CIRURGIAS DE IMPLANTES
DENTAIS: *(i) REVISÃO SISTEMÁTICA E META-ANÁLISE; (ii)*
ENSAIO CLÍNICO TRIPLO-CEGO, PARALELO, RANDOMIZADO E
*CONTROLADO POR PLACEBO***

**Faculdade de Odontologia
Universidade Federal de Minas Gerais
Belo Horizonte
2022**

Gustavo Henrique de Mattos Pereira

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Orientador: Prof. Dr. Fernando de Oliveira Costa
Coorientador: Prof. Dr. Rafael Paschoal Esteves Lima

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ANALGESIA PREEMPTIVA EM CIRURGIAS DE IMPLANTES DENTAIS: (i) REVISÃO SISTEMÁTICA E META-ANÁLISE; (ii) ENSAIO CLÍNICO TRIPLO-CEGO, PARALELO, RANDOMIZADO E CONTROLADO POR PLACEBO

GUSTAVO HENRIQUE DE MATTOS PEREIRA

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alimento para a minha fé. Meus queridos
pais, meus filhos amados e minha adorada
esposa Rachel, a vocês, eu dedico minha
vida e este trabalho.

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“O sucesso não é definitivo, o fracasso não é fatal: o que importa é a coragem para seguir em frente.”

Winston Churchill

RESUMO

Não existem evidências suficientes, para recomendar um regime analgésico específico, para o controle da dor em analgesia preemptiva, após cirurgia de implante dentário. Isto sinaliza a necessidade de estudos adicionais. Esta pesquisa apresenta dois estudos com objetivos distintos: (1) avaliar a eficácia da analgesia preemptiva em cirurgias de implantes dentais por meio de uma revisão sistemática e meta-análise de ensaios clínicos randomizados. (2) avaliar e comparar por meio de um ensaio clínico randomizado (ECR), paralelo, controlado por placebo, a efetividade da analgesia preemptiva em cirurgias de implantes dentais unitários, buscando identificar dentre os analgésicos e anti-inflamatórios não esteroidais (AINES) [eterocoxibe (ETERO), ibuprofeno (IBU), nimesulida (NIME) e acetaminofeno (ACETA)], qual possui maior eficácia no alívio da dor pós-operatória e na redução do uso da medicação de resgate comparados ao uso do placebo. Esta revisão sistemática com meta-análise seguiu as diretrizes PRISMA e foi registrada no PROSPERO (CRD42020168757). Cinco estudos foram incluídos na revisão e quatro foram incorporados à meta-análise. Uma meta-análise de efeito randômico comparou a eficácia da medicação preventiva em comparação ao placebo. Para a interpretação dos resultados utilizamos a certeza da evidência usando a abordagem Grading of Recommendations, Assessment, Development and Evaluation (GRADE) e a magnitude do efeito, de acordo com as diretrizes do GRADE. Todos os estudos demonstraram que a medicação preemptiva contribuiu para uma melhora significativa da dor pós-operatória. No entanto, o desvio médio padrão (DMP) geral agrupado mostrou, que, a medicação preventiva teve um efeito pequeno em comparação com o placebo, na redução da dor (DMP: -0,43; IC: -0,71; -0,15), com baixa certeza da evidência. Essa metanálise mostrou que a magnitude do efeito foi maior seis a oito horas após a cirurgia (efeito grande), comparada ao tempo de uma a duas horas, após a cirurgia (efeito pequeno). Concluiu-se que a analgesia preventiva pode ter um efeito positivo na redução da dor em comparação ao não uso de medicação preemptiva. No entanto, as evidências são ainda insuficientes. O ECR com inserção de implante dental unitário envolveu 135 indivíduos, com média de idade de 57,1 ($\pm 11,2$), de ambos os gêneros alocados em 5 grupos (ETERO, IBU, NIME, ACETA e placebo). A ocorrência, tempo e a intensidade da dor foram analisados por meio testes de teste Qui-quadrado, Exato de Fisher, ANOVA e modelos de equações de estimativas generalizadas quando adequados. Todos os medicamentos testados proporcionaram um efeito benéfico da analgesia preemptiva. Isso foi demonstrado pela redução da dor pós-operatória e do menor uso de medicação de resgate. O grupo IBU apresentou significativamente maiores escores de dor que os outros três grupos testes (IBU>ETERO=NIME=ACETA), que foram equivalentes entre si. Apesar da ocorrência de significância estatística, do ponto de vista da relevância clínica, a diferença entre os grupos foi pequena e todos os grupos apresentaram baixos escores de dor. Assim, sugerimos que a tomada de decisão em relação à escolha do medicamento deve considerar, também, a relação de custo-benefício, efeitos adversos e características individuais dos pacientes. Em

adição, estudos futuros em cirurgias implantodônticas extensas (maior número de implantes inseridos e com enxertos ósseos/gengivais) apresentando alto rigor metodológico, ainda se faz necessário. (CAEE 83534618.5.0000.5149)

Palavras-chave: Analgesia preemptiva. Dor pós-operatória. Cirurgia de implante dental. Revisão sistemática. Ensaio clínico randomizado.

ABSTRACT

Preemptive analgesia in dental implant surgery: (i) systematic review and meta-analysis; (ii) triple-blind, parallel, randomized and placebo-controlled clinical trial

There is insufficient evidence to recommend a specific analgesic regimen for pain management in preemptive analgesia after dental implant surgery, signaling the need for further studies. This research presents two studies with different objectives: (1) to evaluate the effectiveness of preemptive analgesia in dental implant surgeries through a systematic review and meta-analysis of randomized clinical trials. (2) to evaluate and compare, through a randomized clinical trial (RCT), parallel, controlled by placebo, the effectiveness of preemptive analgesia in single dental implant surgeries, seeking to identify among analgesics and non-steroidal anti-inflammatory drugs (NSAIDs) [etorocoxib (ETERO), ibuprofen (IBU), nimesulide (NIME) and acetaminophen (ACETA)], which is more effective in relieving postoperative pain and reducing the use of rescue medication compared to the use of placebo. The systematic review with meta-analysis was conducted by PRISMA guidelines and registered in PROSPERO (CRD42020168757). Five studies were included in the review and four were incorporated into the meta-analysis. A random-effect meta-analysis compared the effectiveness of preventive medication compared to placebo. The interpretation of the results followed the certainty of the evidence using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach together with the magnitude of the effect according to the GRADE guidelines. All studies demonstrated that preemptive medication contributed to a significant improvement in postoperative pain. However, the pooled overall mean standard deviation (SMD) showed that preventive medication had a small effect compared with placebo in reducing pain (SMD: -0.43; CI: -0.71; -0.15) with low certainty of evidence. Our meta-analysis showed that the magnitude of the effect was greater six to eight hours after surgery (large effect), compared to one to two hours after surgery (small effect). It was concluded that preventive analgesia can have a positive effect in reducing pain compared to not using preemptive medication, but the evidence is still insufficient. The RCT with single dental implant insertion involved 135 individuals, with a mean age of 57.1 (± 11.2), of both genders allocated into 5 groups (ETERO, IBU, NIME, ACETA and placebo). The occurrence, duration and intensity of pain were analyzed using Chi-square, Fisher's Exact, ANOVA and generalized estimating equation models when appropriate. All drugs tested provided a beneficial effect of preemptive analgesia demonstrated by reduced postoperative pain and reduced use of rescue medication. The IBU group had significantly higher pain scores than the other three test groups (ETERO, NIME and ACETA), which were equivalent to each other. Despite the occurrence of statistical significance, from the point of view of clinical relevance, the difference between the groups was small and all had low pain scores. Thus, we suggest that the decision

making regarding the choice of medication should also consider the cost-benefit ratio, adverse effects and individual characteristics of patients. In addition, future studies in extensive implant dentistry surgeries (greater number of implants inserted and with bone/gingival grafts) presenting high methodological rigor are still necessary. (CAEE 83534618.5.0000.5149)

Keywords: Preemptive analgesia. Postoperative pain. Dental implant surgery. Systematic review. Randomized clinical trial.

LISTA DE TABELAS E FIGURAS

ARTIGO CIENTÍFICO I

PREEMPTIVE ANALGESIA IN DENTAL IMPLANT SURGERY: A SYSTEMATIC REVIEW AND META-ANALYSIS OF RANDOMIZED CONTROLLED TRIALS.

Table 1. Terms used in the search -----	39
Table 2. Characteristics of the included studies -----	40
Table 3. Risk of bias -----	41
Figure 1. Flowchart (PRISMA) -----	42
Figure 2. Forest plot for primary outcome 1-2 hours -----	43
Figure 3. Forest plot for primary outcome 6-8 hours -----	44
Figure 4. Summary of Finding (SoF) table -----	45

ARTIGO CIENTÍFICO II

PREEMPTIVE EFFECTS OF ETEROCOXIB, ACETAMINOPHEN, NIMESULIDE AND IBUPROFEN ON POSTOPERATIVE PAIN MANAGEMENT AFTER SINGLE-IMPLANT SURGERY: RANDOMIZED CLINICAL TRIAL

Figure 1. Study flowchart. -----	74
Figure 2. Survival curves (Kaplan-Meier) for study drugs -----	75
Table 1. Variables of interest in the study groups -----	76
Table 2. Pain scores by the VAS scale presented by each group at each evaluation time -----	77
Table 3. Comparison among groups for each evaluation time -----	79
Table 4. Pairwise intergroup comparisons of the number of rescue medication -----	80

LISTA DE ABREVIATURAS E SIGLAS

ACETA	Acetaminofeno
AINES	Analgésicos e Anti-Inflamatórios Não Esteroidais
COX	Ciclooxigenase
COX-1	Ciclooxigenase I
COX-2	Ciclooxigenase II
DMP	Desvio de Media Padrão
ECR	Ensaio Clínico Randomizado
ETERO	Eterocoxibe
IBU	Ibuprofeno
NIME	Nimesulida
OMS	Organização Mundial da Saúde
SNC	Sistema Nervoso Central

SUMÁRIO

1	PROBLEMA ABORDADO	16
2	OBJETIVOS	20
2.1	Proposta 1.....	20
2.2	Proposta 2	20
3	HIPÓTESES	21
3.1	Hipótese 1.....	21
3.2	Hipótese 2	21
4	METODOLOGIA	22
4.1	ARTIGO CIENTÍFICO I	23
	Preemptive analgesia in dental implant surgery: a systematic review and meta-analysis of randomized controlled trials	
4.2	ARTIGO CIENTÍFICO II	46
	Preemptive effects of etoricoxib, acetaminophen, nimesulide and ibuprofen on postoperative pain management after single-implant surgery: randomized clinical trial	
5	CONSIDERAÇÕES FINAIS	81
6	PRODUÇÃO ADICIONAL ASSOCIADA AO TEMA DA TESE	83
6.1	Editorial commentary	83
6.2	Book chapter	87
6.3	Premiações	106
	REFERÊNCIAS	107
	ANEXOS	109

1 PROBLEMA ABORDADO

Em todos os procedimentos cirúrgicos odontológicos, a dor é a complicação que mais interfere na adesão dos pacientes ao tratamento, uma vez que está diretamente ligada ao medo e à ansiedade (KYLE *et al.* 2016). Em uma recente meta-análise, Silveira *et al.* (2021), apresentaram dados da prevalência global de medo e ansiedade mediante a tratamentos odontológicos, em torno de 15,3%. De acordo com o Dental Fear Survey, mesmo depois de receber as informações iniciais quanto aos procedimentos, mais de dois terços da população chegam à clínica odontológica com algum nível de ansiedade em relação à dor (CAMACHO-ALONSO *et al.* 2019; LALABONOVA, 2015). Estes dados tornam-se relevantes, para a análise da dor como um ponto de inflexão para o tratamento reabilitador por implantes.

Lopez-Lopez *et al.* (2021), em uma revisão sistemática e meta-análise, apresentaram dados que demonstram que fatores como, cirurgia com retalho, ansiedade, maior tempo de duração do procedimento cirúrgico, e níveis mais altos de dor logo no início do pós-operatório, desempenham um papel fundamental na intensidade da dor aguda após a cirurgia de implante dentário.

A definição de dor dada pela International Association for the Study of Pain mostra a sua individualidade e sua subjetividade, sempre ligada às experiências passadas (RAJA *et al.* 2021). Estas características impedem que a intensidade da dor seja dada de forma generalizada e baseada apenas na extensão da lesão ou do procedimento cirúrgico, pois procedimentos pouco invasivos podem apresentar um nível alto de dor, assim como em cirurgias extensas poderemos observar uma dor de baixa intensidade.

Segundo Rosero e Joshi (2014), a dor pós-operatória está ligada a alterações fisiológicas adversas que eventualmente pode se traduzir em resultados pós-operatórios adversos, incluindo aumento da morbidade. Além disso, a limitação do movimento causada pela dor pode prolongar a reabilitação, reduzir qualidade de vida relacionada à saúde e atrasar o retorno das atividades diárias normais.

De acordo com Kim *et al.* (2013), as cirurgias de implante dentário unitário produzem traumas de grau leve a moderado. Entretanto, o medo e a ansiedade

presentes nos pacientes que irão ser submetidos a algum tipo de intervenção cirúrgica odontológica podem afetar negativamente o padrão de atendimento odontológico e as condições clínicas, como a potencialização da dor.

O uso de analgésicos e anti-inflamatórios é o principal arsenal do cirurgião dentista para minimizar a dor pós-operatória. Como explica Vane (1971), as drogas anti-inflamatórias interrompem a produção de mediadores inflamatórios, através da inibição das enzimas ciclooxigenase (COX) (HEMLER *et al.* 1976).

A COX possui duas isoformas, a COX-1 e a COX-2. A COX-1 é uma enzima constitutiva, com claras funções fisiológicas, exercendo propriedades antitrombogênica no endotélio e citoprotetora na mucosa gástrica. Já a COX-2 é induzida em várias células por estímulos pró-inflamatórios (VANE e BOTTING, 1998). Os níveis de COX-2, normalmente muito baixos nas células, são rigidamente controlados por vários fatores, incluindo citocinas. Deste modo, podemos sugerir que as ações anti-inflamatórias dos AINES são devidas à inibição da COX-2, enquanto os efeitos colaterais indesejados, como irritação do revestimento do estômago e ações tóxicas sobre o rim, são devidos à inibição da enzima constitutiva COX-1 (VANE, 2000).

Na odontologia, os anti-inflamatórios não esteroidais (AINES) são eficazes no tratamento da dor e inflamação agudas relacionadas a procedimentos endodônticos, cirúrgicos, restauradores ou periodontais. Dentre eles, podemos destacar o ibuprofeno (IBU), que segundo a Organização Mundial da Saúde (OMS), deve ser considerado o fármaco de primeira escolha para o manejo da dor inflamatória aguda em pacientes que podem tolerar essa classe de fármacos (HARGREAVES E ABBOTT, 2005).

O acetaminofeno (ACETA) é outro fármaco que é muito utilizado na clínica cirúrgica odontológica para o alívio da dor pós-operatória. Segundo Józwiak-Bebenista e Nowak (2014), atua principalmente no sistema nervoso central (SNC), embora nem o local nem os mecanismos de ação tenham sido claramente estabelecidos. Possui efeitos analgésicos e antipiréticos e é um fraco inibidor das ciclooxigenases COX-1 e COX-2. O ACETA cruza rapidamente para o líquido cefalorraquidiano. No SNC, atua inibindo a síntese de prostaglandinas no hipotálamo, impedindo a liberação de prostaglandina espinhal e inibindo a síntese de óxido nítrico

pelos macrófagos. Em doses terapêuticas, não inibe a prostaglandina nos tecidos periféricos, de modo que há pouca ou nenhuma ação anti-inflamatória.

A busca pela diminuição dos efeitos colaterais induzidos pelos AINES, trouxe o desenvolvimento de novas drogas, com mecanismos de ação diferentes dos demais anti-inflamatórios. Os inibidores seletivos de COX-2, como a Nimesulida (NIME), atuam preferencialmente sobre a COX-2, minimizando os danos causados pela inibição total da COX-1 (VANE, 2000).

O mesmo acontece, com os inibidores preferenciais de COX-2, que por não inibir a COX-1, não provoca o desconforto gastrointestinal, tão recorrente nos anti-inflamatórios não seletivos (MOORE e MAKINSON, 2013). Segundo González-Barnadas, et al. (2019), eventos adversos cardiovasculares foram relatados com inibidores seletivos de COX-2, especialmente com rofecoxibe. No entanto, a segurança cardiovascular de outros inibidores seletivos de COX-2, como celecoxib e o etorocoxib (ETERO), podem ser comparadas à dos AINES tradicionais.

Além da escolha de um medicamento eficiente no tratamento da dor pós-operatória, é necessária a compreensão por parte dos cirurgiões-dentistas sobre os mecanismos básicos da dor pós-cirúrgica e o uso adequado dos métodos para a gestão da dor. Dentre estes métodos podemos destacar a analgesia preemptiva. Esse método é caracterizado pela ministração de um medicamento com efeito analgésico antes que haja a injúria tecidual (CRILLE *et al.* 2001).

Este conceito foi revisto por Kissin e Weiskopf (2000), que o redefiniram como um tratamento antinociceptivo que previne o estabelecimento do processamento central da lesão, contendo pelo menos dois requisitos essenciais. O primeiro é que o estabelecimento de um nível eficaz de analgesia é primordial. A utilização de um antinociceptivo inadequado como intervenção pré-operatória não deve ser considerada como analgesia preemptiva. Portanto, “preemptivo” não significa simplesmente “antes da incisão”. Uma analgesia insuficiente estabelecida antes da incisão não pode ser considerada como tratamento preemptivo. O segundo requisito fornece o conceito-chave de que mediadores inflamatórios devem ser mantidos inibidos, ou os receptores nociceptivos devem permanecer bloqueados durante o período de lesão tecidual associada à inflamação pós-operatória, de modo a prevenir a sensibilização central.

A sensibilização periférica, na qual há um aumento na sensibilidade dos neurônios sensoriais periféricos, é resultante da exposição dos terminais nervosos sensoriais a mediadores liberados no local da lesão. O objetivo do tratamento preemptivo é impedir ou inativar a liberação dos vários neurotransmissores e mediadores inflamatórios, que irão sensibilizar os nociceptores periféricos. Ao reduzir a síntese de prostaglandinas, os inibidores da ciclooxigenase bloqueiam a resposta nociceptiva aos mediadores endógenos da inflamação, sendo o efeito maior nos tecidos que foram submetidos a lesões e traumas. Os tecidos neuronais centrais também sintetizam prostaglandinas, mostrando que os AINES também podem atingir o SNC (CASHMAN, 1996; KELLY *et al.* 2001a; KELLY *et al.* 2001b).

De acordo com Doleman *et al.* (2021), em uma meta-análise sobre a analgesia pré-emptiva em diversos tipos de procedimentos cirúrgicos, foram encontradas evidências que favorecem esta abordagem na redução da dor aguda e no consumo de analgésicos.

Em um ensaio clínico randomizado, paralelo e controlado, Pereira *et al.* (2020) demonstraram que o uso de ibuprofeno (IBU) em analgesia preemptiva para inserção de implantes dentais unitários resultou em significativa redução de dor pós-operatória em comparação com o uso de placebo e menor uso de medicamento de resgate [acetaminofeno (ACETA)].

Assim, as principais limitações das evidências disponíveis no tema são o pequeno número de ensaios clínicos avaliando o manejo da dor em cirurgia de implante dentário, a heterogeneidade nas intervenções implementadas, comparações de poucos medicamentos, e os resultados serem avaliados com diferentes tempos de acompanhamento.

Neste cenário, este estudo justifica-se pelas evidências insuficientes para recomendar ou desencorajar um regime preemptivo específico para o controle da dor em analgesia preemptiva após cirurgia de implante dentário, sinalizando a necessidade de estudos adicionais.

2 OBJETIVOS

2.1 Proposta 1

Avaliar a eficácia da analgesia preemptiva em cirurgias de implante dentais por meio de uma revisão sistemática e meta-análise de ensaios clínicos randomizados.

2.2 Proposta 2

Avaliar e comparar por meio de um ensaio clínico randomizado, paralelo, controlado por placebo, a efetividade da analgesia preemptiva em cirurgias de implantes dentais unitários, buscando identificar dentre os AINES (ETERO, IBU e NIME) e o ACETA, qual possui maior eficácia no alívio da dor pós-operatória e na redução do uso da medicação de resgate (ACETA) comparados ao uso do placebo.

3 HIPÓTESES

3.1 Hipótese 1

A analgesia preemptiva aplicada em cirurgias de implante dental unitário possui um efeito positivo na diminuição da dor pós-operatória.

3.2 Hipótese 2

O uso de medicamentos AINES (ETERO, IBU e NIME) induz a um menor escore de dor pós-operatória e a um maior tempo de uso de medicamento de resgate comparado ao uso de acetaminofeno ou placebo, em cirurgia de implantes dentais unitários.

4 METODOLOGIA

Será apresentada no formato de dois artigos científicos intitulados:

ARTIGO I

PREEMPTIVE ANALGESIA IN DENTAL IMPLANT SURGERY: A SYSTEMATIC REVIEW AND META-ANALYSIS OF RANDOMIZED CONTROLLED TRIALS.

ARTIGO PUBLICADO: Med Oral Patol Oral Cir Bucal. 2021 Sep 1;26 (5):e632-41.
doi:10.4317/medoral.24639

ARTIGO II

PREEMPTIVE EFFECTS OF ETEROCOXIB, ACETAMINOPHEN, NIMESULIDE AND IBUPROFEN ON POSTOPERATIVE PAIN MANAGEMENT AFTER SINGLE-IMPLANT SURGERY: RANDOMIZED CLINICAL TRIAL

ARTIGO CIENTÍFICO I

PREEMPTIVE ANALGESIA IN DENTAL IMPLANT SURGERY: A SYSTEMATIC REVIEW AND META-ANALYSIS OF RANDOMIZED CONTROLLED TRIALS

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Running title: Preemptive analgesia and dental implant

Keywords: preemptive analgesia, postoperative pain, dental implant surgery, systematic review.

Abstract

Background: To assess the effectiveness of preemptive analgesia in dental implant surgery in randomized controlled trials (RCTs).

Materials and Methods: The present study was conducted in accordance with the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement and registered in PROSPERO database (CRD42020168757). A search without restrictions regarding language or date of publication was conducted in six databases and gray literature. A random effect meta-analysis compared the efficacy of preemptive analgesia to placebo through pooled OR and 95%CI. The interpretation of results followed the certainty of evidence using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach together with the magnitude of the effect according to GRADE guidelines.

Results: Four studies were included in the review and four were incorporated into the meta-analysis. All studies demonstrated that preemptive analgesia contributed to a significant improvement in the postoperative pain control. However, the overall pooled standard mean difference (SMD) showed that preemptive analgesia had small effects compared to placebo in reducing pain (SMD: -0.45; IC: -0.83; -0.08) with low certainty of the evidence. Our meta-analysis showed that the magnitude of the effect was bigger six to eight hours after the surgery (large effect), compared to the time of one to two hours after the surgery (small effect).

Conclusions: Preemptive analgesia may have a positive effect in reducing pain compared to not using preemptive medication, but the evidence is very uncertain.

Introduction

Acute postoperative pain is a normal response to surgical interventions. It is one of the causes of late recovery and post-operative analgesic medication use, often indiscriminate (1).

Among the alternatives for improving postoperative pain control, preemptive analgesia has stood out. Preemptive analgesia consists of administering analgesic medication before tissue injury, that is, before the reception, transmission, modulation, and nociception of the aggressive stimulus, aiming to prevent hyperalgesia and the consequent stimulus that amplifies pain (2). Preemptive analgesia has been used as an effective for pain control method in third molar surgeries (3), also presenting itself as a viable protocol for dental implant surgeries (4).

In implant dentistry, the installation of dental implants comprises a surgical procedure that can generate mild to moderate pain sensations, but which may exceed the normal thresholds in some moments (2). In order to establish an efficient preemptive analgesic effect, it is necessary that an ideal level of antinociceptive medication is administered before the injury and that it remains in the postoperative phase, thus preventing sensitization during the inflammatory phase (5).

There are several groups of analgesic agents used in dentistry, as well as different dosages to be implemented. Therefore, defining which one has the best therapeutic efficacy remains a challenge for dental surgeons (1,3,6).

Therefore, due to the conflicting results in the literature, this systematic review and meta-analysis aims to evaluate the effectiveness of preemptive analgesia in dental implant surgeries.

Materials and methods

Protocols and Records

These systematic review and meta-analysis were conducted in accordance with the recommendations of the Preferring Reporting Items for Systematic Reviews and Meta-analyzes (PRISMA) (7). A study protocol was registered with the International Prospective Register of Systematic Reviews PROSPERO, under the number CRD42020168757.

Eligibility criteria

The clinical question (PICO question) was as follows: "Does preemptive analgesia decrease postoperative pain in patients undergoing dental implant surgery?"

Patient (P): patients undergoing dental implant surgery; Intervention (I): preemptive analgesia using any medication evaluated in clinical trials; Comparison (C): patients who used a placebo as preemptive medication or no treatment; Outcome (O): postoperative pain.

Inclusion criteria

We included parallel arm randomized placebo-controlled trials (RCTs), with healthy patients above 18 years old, and who had undergone surgery to insert dental implants (single or multiple), who received any type of preemptive medication (analgesic or anti-inflammatories), considering that the medication administration time was not established. No minimum follow-up time of the studies was determined.

The exclusion criteria were non-randomized trials and observational studies, studies without placebo or no treatment as a control group, animal studies, systematic reviews, literature reviews, conference proceedings, editorials, and studies that were not written in the English language.

Information sources

An electronic search was conducted from the intersection up to January 2020 and updated in December 2020 in the following databases: MedLine through PubMed, Scopus (Elsevier), Web of Science, Latin American and Caribbean Health Sciences Literature (Lilacs) through Virtual Health Library (Bireme), Cochrane Central Register of Controlled Trials (CENTRAL) and Cochrane Database of Systematic Reviews. We searched gray literature in OpenGrey and Google Scholar, limiting this last one in the last 200 studies. A manual search was conducted on the included studies and reviews. No restrictions were imposed on the year of publication. The research strategies used in each database are displayed in Table 1.

Selection of studies

All the retrieved articles were organized in the EndNote Web program.

The selection of the studies took place in two phases and was conducted by two independent reviewers (GHMP and RPEL). First, the reviewers screened titles and abstracts for eligibility. Studies without enough information to make a decision were

selected for full-text screening. Full texts were obtained and analyzed for further selection. In the case of disagreement, the reviewers discussed the eligibility criteria until a consensus was reached.

Data extraction

Two independent reviewers extracted data (GHMP and RPEL). The following data were extracted from each study in an excel spreadsheet previously created: name of the author (s) and year of publication, country, sample size, sex, age, duration of surgery, anesthetic drug used, drop-outs, tested medication, rescue medication, time when preemptive medication was administered, methods for assessing pain and adverse effects.

Risk of Bias Assessment

The risk of bias was assessed using the Cochrane Bias Risk Tool for Randomized Trials (RoB 2.0) and judged as "low", "some concerns" or "high" (8).

Outcomes

The primary outcomes were pain from one to two hours after surgery and from six to eight hours after surgery. For each outcome we extracted mean or median scores of pain and respective standard deviation (SD), standard error (SE) or 95% CI, when reported by authors. We used the software Review Manager version 5.4 for meta-analysis for these two primary outcomes. The mean and standard deviation were used to calculate the pooled standard mean difference (SMD) and its 95%CI. We used random effect model considering uncertainty in I^2 test for heterogeneity when few studies are used. Moreover, the diversity may occur in meta-analysis with inevitable heterogeneity (8). We subgrouped each outcome for the type of drug comparing to placebo or no medication as the comparison group.

Summary of results and the certainty of the evidence

The certainty of the evidence was assessed through Grading of Recommendations, Assessment, Development and Evaluation tool (GRADE) (9).

RCTs start with high certainty of evidence and it can be rated down due to problems as risk of bias, inconsistency, indirectness, imprecision, and publication bias. Each outcome was tabulated in a Summary of Finding (SoF) table using GRADEpro. For the magnitude of the effect, we used the Cohen's effect sizes for SMD: from -0.2

to 0.2 representing a trivial or no effect; -0.5 to -0.2 or 0.2 to 0.5 representing a small effect; -0.8 to -0.5 or 0.5 to 0.8 representing a moderate effect; and < -0.8 or > 0.8 representing a large effect (10). The interpretation of the results was based on an integrated approach of the magnitude of the effect based on Cohen's effect size and the certainty of the evidence (11).

Results

Selection of studies

One thousand two hundred and thirty five studies were retrieved in the electronic search. After analyzing titles and abstracts, twenty three studies were selected for evaluation through full reading. The main reasons for exclusion after full texts evaluation were studies that: did not use preemptive medication or placebo as a control group, studies that were not clinical trials, and those not written in English. Four studies were included (4,12- 14) in the review and three in the meta-analysis (12-14). Flowchart 1 shows the screening process (Fig. 1). Three (4,13,14) of the four selected studies reported having been registered prior to patient recruitment.

Characteristics of studies

The characteristics of the four included studies are shown in Table 2. The studies were conducted in four different countries. The randomized trials included 326 patients, and 294 patients completed the trials with a drop-out rate of 9.8% of the total number of patients. The number of patients varied from 40 to 117. In the four included studies, a single-implant surgery was performed. Regarding the area of implant placement, only one trial has reported its location that was the posterior region of the mandible (12).

The preemptive medication used were: 4mg dexamethasone (4), 600mg ibuprofen (4,14), 25mg dexketoprofen trometamol (13), and 40mg piroxicam (12), with placebo as control in all studies. In all trials, the participants were allowed to have analgesic rescue medication in any time they needed. There was no restriction regarding minimum time for taking the rescue medication neither for pain score, in a way that patients were free to decide whether to use it or not (4,15). In two studies (12,13), analgesic and anti-inflammatory medication were prescribed to be taken regardless of the level of pain.

Assessment of preemptive medication

The time for administering preemptive medication in most of the included studies was 1 hour before the procedure (4,12,14). In one study (13), preemptive medication was administered 15 min before surgical intervention. All studies used the Visual Analogic Scale (VAS) for pain assessment, one study also used the Numeric Rate Scale (NRS) (4) and one trial also used the Verbal Rating Scale (VRS) (4), thus, the comparative analysis of the level of pain between the studies, took into account the scores obtained by the VAS scale, common to all studies. Pain assessment times varied from the immediate postoperative period (13) to 07 days after the surgical procedure (4). The follow-up time of the included studies varied from 1 to 168 hours (mean time 78.4 hours).

Side effects

All studies collected data on side effects (12-14). The most common reported side effects were edema (12) that presented a significant decrease in the test group but not in the control group. In another study (13), significant differences between the test group and the control group for inflammation and bleeding were noted. The control group had a lower degree of inflammation; however, it obtained a higher degree of bleeding than the test group. No side effects like infections, major edema and bleeding were observed (14).

Bias Risk Assessment

We contacted authors for risk of bias and data extraction when the information was unclear in the text, with only two (14,15) of the five authors responding. Table 3 presents the results for the assessment of risk of bias. All the studies that were analyzed showed "some concerns" on the final judgment.

Meta-analysis of postoperative pain

Figure 2 shows the comparison between preemptive medication versus placebo 1-2 hours after the surgical procedure, divided in subgroups according to the type of drug.

Overall pooled SMD showed that preemptive medication had a small effect in reducing pain (SMD: -0.45; IC:-0.83; -0.08) when compared to placebo, with low cer-

tainty of the evidence. However, only Ibuprofen had large effect compared to placebo (SMD: -0.74; CI: -1.29; -0.19).

Fig. 3 shows the comparison between preemptive medication versus placebo 6-8 hours after the surgical procedure. Preemptive medication had a large effect (SMD= -2.10; 95%CI: -4.24; 0.04) when compared to placebo, with very low certainty of the evidence. Subgroup analysis showed that both ibuprofen (SMD = -1.09; 95%CI: -1.66; -0.51) and piroxicam (MD = -5.80; 95%CI: -7.28;-4.33) had a large effect when compared to placebo.

Certainty of the evidence

The certainty of the evidence was rated down due to problems of risk of bias and imprecision for pain 1-2 hours after surgery. For 6-8 hours after surgery, the certainty of the evidence was rated down due to serious problems of risk of bias, inconsistency, and imprecision (Figure 4).

Discussion

The control of postoperative pain, edema and trismus has been the subject of continuous research in the area of oral and maxillofacial surgery, since pain can significantly reduce the patient's quality of life (3,15).

Tissue damage caused by the insertion of dental implants promotes the onset of an inflammatory process and, consequently, the release of several mediators such as prostaglandins (PGE) and bradykinins that sensitizes nociceptors (16). Anti-inflammatory drugs and local anesthetics inhibit the synthesis of mediators by inactivating the cyclooxygenase (COX) and phospholipase enzymes, altering nociception, and reducing peripheral sensitization. The decrease in the levels of inflammatory mediators at the site of tissue injury is strongly associated with these effects (17-19).

Our results showed that preemptive analgesia can slightly reduce pain 1-2 hours after implant surgery when compared to placebo. When assessing pain 6-8 hours after surgery, preventive analgesia proved to be effective, but the evidence was determined to be uncertain. Preemptive analgesia has been shown to be effective in reducing postoperative pain in the surgical removal of third molars (3,20), despite some studies (21,22) did not demonstrate a significant preemptive effect. Methodological differences may have an impact on these results, with divergence in the perception of postoperative pain. In dental implant placement, the preemptive analgesia protocol has

considerably reduced the average pain scores, especially in the first 6 hours after the surgical procedure (3). A peak in prostaglandin E2 (PGE2) levels was observed approximately 3 hours after periodontal surgery and surgical removal of third molars (23,24). The peak of maximum pain at sites of acute inflammation usually occurs around 3-4 hours, coinciding with the maximum concentration of prostaglandins (22).

Our meta-analysis showed that the magnitude of the effect was bigger for 6-8 hours after surgery (large effect) compared to 1-2 hours after surgery (small effect). Among the drugs used in the evaluated RCTs, two studies (4,13) used Ibuprofen 600mg as preoperative medication. This non-steroidal anti-inflammatory drug (NSAID) inhibits the action of the COX enzyme, blocking the production of inflammatory mediators. It has a plasma half-life of 1 to 3 hours (25). The minimum plasma concentration of 26µg/ml of ibuprofen is capable of producing analgesic effect, and a dose of Ibuprofen of 600 mg has a maximum plasma level close to 69 µg / ml, on average, between 2 and 3 hours after the initial dose (26). Our subgroup analysis showed that ibuprofen had large effect 1-2 hours after surgery, when compared to placebo. Significant differences in pain level were observed in the first 4 hours between the ibuprofen group compared to the placebo group, emphasizing the beneficial effect of preemptive analgesia with ibuprofen (4). Unfavorable results were obtained with 25 mg of dexketoprofen trometamol (13), administered 15 min before the procedure for the period of 1-2 hours and 6-8 hours.

In a recent overview (27), it was shown that Ibuprofen 600mg had the highest proportion of patients (77%) who achieved at least 50% of maximum pain relief for 4-6 hours, followed by combinations of 400 mg of ibuprofen with 1,000 mg of acetaminophen (72%), 200 mg ibuprofen with 500 mg acetaminophen (69%). The evaluation of the duration of pain relief showed that 1000 mg of diflunisal, 650 mg of acetaminophen, 500 mg of diflunisal and 500 to 550 mg of naproxen, had the longest duration of action. The doses of 600 to 650 mg of acetaminophen, 25 mg of potassium diclofenac, 60 mg of codeine and 250 mg of gabapentin, were those that obtained the shortest duration of the analgesic effect.

The 25 mg dexketoprofen trometamol also obtained positive results for postoperative pain relief in third molar surgeries (28). In our meta-analysis, piroxican was effective 6-8 hours postoperative, when compared to placebo.

There was inconsistency for pain control after 6-8 hours due to the high I², lack of overlap of the CIs and different individual effect estimates among studies (29). The heterogeneity may be explained by the different drugs used in the final pooled effect estimate. Moreover, there was serious imprecision for pain control after 1-2 hours and after 6-8 hours. In fact, the amplitude of CI showed that, for 1-2 hours, preemptive analgesia can have a moderate (lower CI: -0.71) to a trivial effect (upper CI:

-0.15) compared to placebo. For 6-8 hours, preemptive analgesia can have a large (lower CI: -3.14) to a trivial effect (upper CI: -0.14) compared to placebo. Although in both cases the preemptive medication has a beneficial effect compared to placebo, the magnitude of the effect in reducing pain is too imprecise. In fact, pain is very subjective and can vary from patient to patient. Preemptive analgesia can have more benefits than harm compared to placebo, as pain after oral and maxillo-facial surgery can affect the patient's quality of life (3,15). However, for implant surgery, the evidence is uncertain due to the variation of the magnitude of the effect. There were also serious problems due to the risk of bias. The clinical trials had some concerns due to randomization process (13,14), missing outcome data (4,13), and selection of reported outcome, as no study reported a registered protocol previously to conducting the trials (4,12-14). In addition, one study had some concerns regarding blinding of the outcome assessor (12), while other study was at high risk of bias (4).

Strengths and limitations:

This meta-analysis is limited due to the small number of included trials, which inputted imprecision on data. Furthermore, there was a variety of treatment protocols and methods for evaluating the results. One of the four selected studies could not be included in the meta-analysis as its data was provided in median values with non-normal distribution and not in mean values.

The present study has strengths as it uses the Cohen's classification for the magnitude of the effect together with GRADE guidelines to interpret data for the clinical practice (11). The small important effect of preemptive analgesia within 1-2 hours leads us to question some protocols, such as the standardization of the anesthetic

drug, the number of implants and the area where they will be placed, since the surgical trauma can influence the results of preemptive analgesia (3,15,27). The 4 studies included in this systematic review, (4,12,13,14) included only cases of single-implant surgery and only one study (12) reported the region where the implants were placed. It is important to note that this can impact the bias risk assessment of studies without this information. Two meta-analyses (30,31) showed a better anesthetic effect of articaine 4% with epinephrine 1:100,000 compared to lidocaine 2% with epinephrine 1: 100,000. In addition, the anesthetic technique used can also influence the perception of postoperative pain and mask the effects of preemptive analgesia. The alveolar nerve block, for example, presents a greater residual postoperative analgesia, when compared to the infiltrative techniques (32). Studies evaluating preemptive analgesia should consider this data during methodological planning and results interpretation and discussion. Ideally, the test and control groups should be comparable in relation to the surgical sites, consequently, in relation to the anesthetic techniques used. These findings lead us to question whether the use of a more potent anesthetic base can mask the effects of preemptive medication. For pain after 6-8 hours, we observed that preemptive medication may have little effect on the expected result, but the evidence is very uncertain.

The study with the largest sample (13) did not demonstrate significant effects of preemptive analgesia in the evaluated postoperative periods. In the qualitative analysis, it demonstrated limitations in relation to bias due to deviation from intended intervention and missing outcome data. Meta-analyses allow gathering the results of several studies with a common objective and, therefore, their results have greater power than results from individual studies.

Preemptive analgesia remains a very controversial, but a timely topic. There are several preventive analgesia protocols in surgical procedures for dental implant placement, with great methodological differences between clinical trials. Among these main differences, the following ones stand out: periods of postoperative pain assessment, methods of drug administration and differences in local anesthetics and vasoconstrictors. The preemptive analgesia is effective for pain control. However, the magnitude of the effect is imprecise and can vary from large to trivial effect. For the clinical practice, there are two factors that can influence pain control: the time of drug administration and the time length of the surgery. When the drug is administered closer

to the surgery, the drug effect can be extended for longer periods. Also, shorter surgeries can influence the perceived pain by the patient when compared to longer surgeries with longer intra-oral manipulation and more implants placement.

For future studies, RCTs should properly randomize patients and provide the blinding of the outcome assessor (the patient) with standardized pills for the intervention and control groups. Moreover, for more transparency in the research protocol, authors should register the trial before starting the study.

Conclusion

The preemptive analgesia may slightly reduce pain from one to two hours after surgery when compared to patients who did not use preemptive medication. After six to eight hours, the preemptive analgesia may have a large effect in reducing pain compared to not using preemptive medication. However, the evidence is very uncertain.

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Author contribution:

Gustavo Henrique de Matos-Pereira: Concept/design, data analysis/interpretation, drafting the article, data extraction, critical revision of article, approval of article. Carolina Castro Martins: data analysis/interpretation, statistics, drafting article, critical revision of article, approval of article. Rafael Paschoal Esteves-Lima: concept/design, data analysis/interpretation, data extraction, drafting article, critical revision of article, approval of article. Rachel Alvarenga Brant: data analysis/interpretation, data extraction, critical revision of article, approval of article. Luís Otávio Miranda Cota: concept/design, data analysis/interpretation, critical revision of article, approval of article. Fernando Oliveira Costa: concept/design, data analysis/interpretation, critical revision of article, approval of article.

Table 1 - Terms used in the search.

Medline through PubMed ((preemptive analgesia OR preoperative administration OR pain measurement OR postoperative pain OR cyclooxygenase inhibitors OR acute inflammation) AND (dental implant surgery OR dental implants OR dental implant))
Scopus TITLE-ABS-KEY ("preemptive analgesia" OR "preoperative administration" OR "pain measurement" OR "postoperative pain" OR "cyclooxygenase inhibitors" OR "acute inflammation") AND TITLE-ABS-KEY ("dental implant surgery" OR "dental implant*")
Cochrane (for Cochrane Reviews and CENTRAL) #1 "preemptive analgesia" #2 "preoperative administration" #3 "pain measurement" #4 "postoperative pain" #5 MeSH descriptor: [Pain, Postoperative] explode all trees #6 "cyclooxygenase inhibitors" #7 MeSH descriptor: [Cyclooxygenase Inhibitors] explode all trees #8 "acute inflammation" #9 #1 OR #2 OR #3 #4 OR #5 OR #6 OR #7 OR #8 #10 "dental implant surgery" #11 dental implant* #12 #10 OR #11 #13 #9 AND #12
Web of Science TS= (("preemptive analgesia" OR "preoperative administration" OR "pain measurement" OR "postoperative pain" OR "cyclooxygenase inhibitors" OR "acute inflammation") AND ("dental implant surgery" OR "dental implant*"))
LILACS ("preemptive analgesia" OR "preoperative administration" OR "pain measurement" OR "postoperative pain" OR "cyclooxygenase inhibitors" OR "acute inflammation") [Palavras] and (dental implant surgery" OR "dental implant*") [Palavras]

Table 2 - Characteristics of the included studies.

Authors	Country	Intervention	Sample size (n)	Gender	Age (years)	Rescue Drug	Pain Assessment	Anesthetic used	Duration of surgery	Side effects
Bahammam et al. 2017	Saudi Arabia	Preemptive medication with Dexamethasone/Ibuprofen 01h before	117 patients	71(M) 46(F)	38,4 ± 10,5	1G Acetaminophen	VAS, VRS and NRS	Lidocaine 2% 1:100.000	30-45 min	Not related
Sánchez-Pérez et al. 2018	Spain	Preemptive medication with Dexcetoprophenol Trometamol 15 min before	83 patients	29(M) 53(F)	52,7	600mg de Ibuprofen	VAS	Lidocaine	40-60 min	Inflammation
Pereira et al. 2020	Brazil	Preemptive medication with Ibuprofen 01h before	54 patients	21(M) 33(F)	37-74	750 mg de Paracetamol	VAS	Prilocaine	60 min	Not related
Bhutani et al. 2019	India	Preemptive medication with Piroxicam 40mg sub lingual	40 patients	UI	16-40	Piroxicam 20 mg	VAS	UI	UI	Swelling
Kose et al. 2015	Turkey	Preemptive medication with Etodolac 600mg	32 patients	17(M) 15(F)	43± 5	Naproxen 550mg	VAS and VRS	Articaína 4% 1:100.000	UI	Not related

M, male; F, female; UI: uninformed; VAS: visual analogic scale; VRS: verbal rating scale; NRS: numeric rating scale

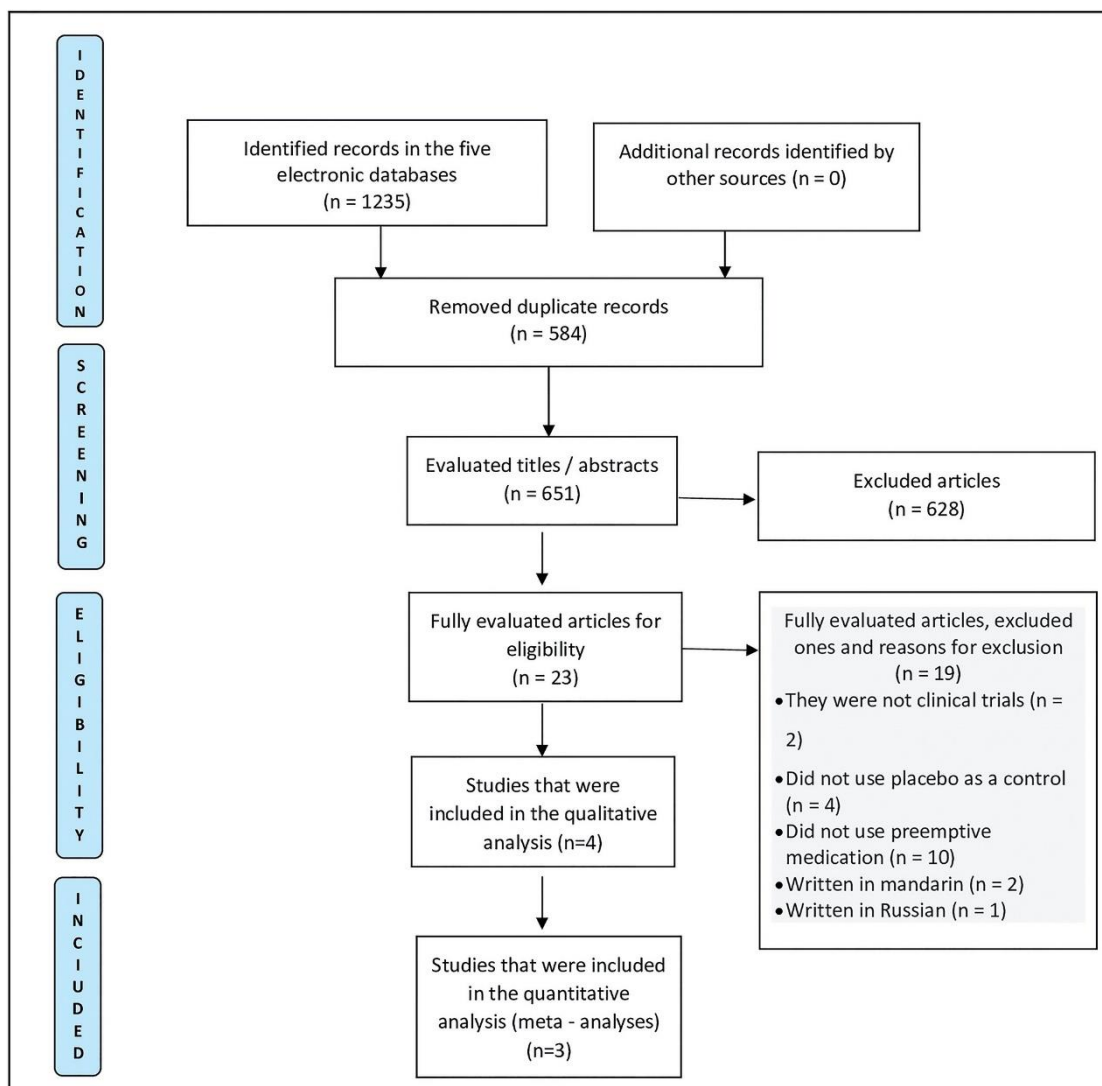
Study	1.1	1.2	1.3	RoB	2.1	2.2	2.3	2.4	2.5	2.6	2.7	RoB	3.1	3.2	3.3	3.4	RoB	4.1	4.2	4.3	4.4	4.5	RoB	5.1	5.2	5.3	RoB	Final RoB
Bahamman et al. 2017	Low	Low	Low	Low	High	High	Low	Uninformed	Uninformed	Uninformed	Uninformed	Low	High	High	Uninformed	Uninformed	Some	Low	Low	Uninformed	Uninformed	High	High	Uninformed	Uninformed	Uninformed	Some	High
Sanchez-Perez et al. 2018	Low	Uninformed	Low	Some	Low	High	Low	Uninformed	Uninformed	Uninformed	Uninformed	Low	High	High	High	Low	Some	Low	Low	Low	High	Low	Low	Uninformed	Low	Uninformed	Some	High
Mattos-Pereira et al. 2020	Low	Low	High	Some	Low	Low	Low	Uninformed	Uninformed	Uninformed	Uninformed	Low	Low	Uninformed	Uninformed	Uninformed	Low	Low	Low	Low	High	Low	Low	Uninformed	Low	Uninformed	Some	High
Bhutani et al. 2019	Low	Low	Uninformed	Low	Low	Low	Low	Uninformed	Uninformed	Uninformed	Uninformed	Low	Low	Uninformed	Uninformed	Uninformed	Low	Low	Low	Low	High	Uninformed	Some	Uninformed	Uninformed	Uninformed	Some	High
Kose et al. 2015	Low	Low	Uninformed	Low	Low	Low	Low	Uninformed	Uninformed	Uninformed	Uninformed	Low	Low	Uninformed	Uninformed	Uninformed	Low	Low	Low	Low	High	Uninformed	Some	Uninformed	Uninformed	Uninformed	Some	High

Table 3 - Risk of bias

Items 1.1 to 1.3 correspond to randomization process; 2.1 to 2.7 correspond to bias due deviation from intended intervention; 3.1 to 3.4 correspond to missing outcome data; 4.1 to 4.5 correspond to measurement of the outcome; 5.1 to 5.3 correspond to selection of reporting bias. Full description is on Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ. 2003;327: 557-60.

 Low risk of bias
  Some concerns
  High risk of bias
  Uninformed

Figure 1 - Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart of study screening selection.



Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med. 2009; 6:e1000097.

Figure 2 - Forest plot for primary outcome 1-2 hours.

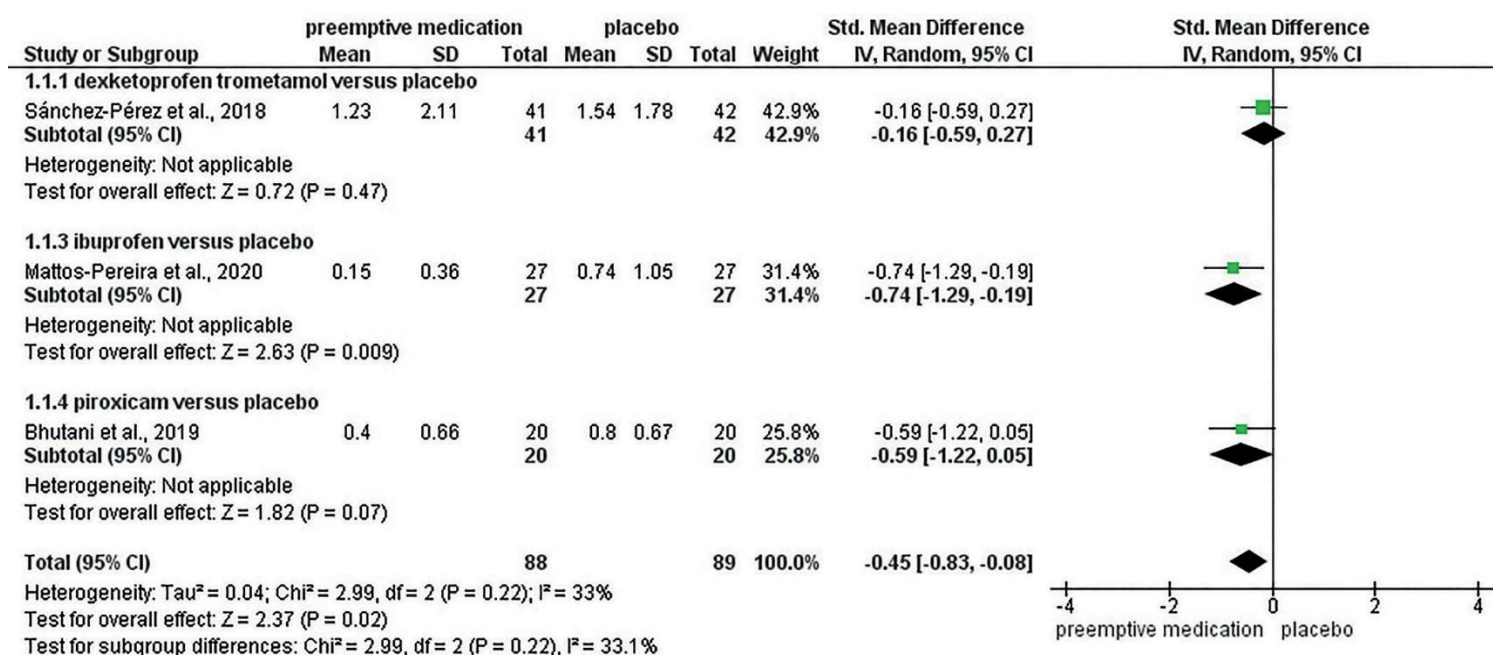


Figure 3 - Forest plot for primary outcome 6-8 hours.

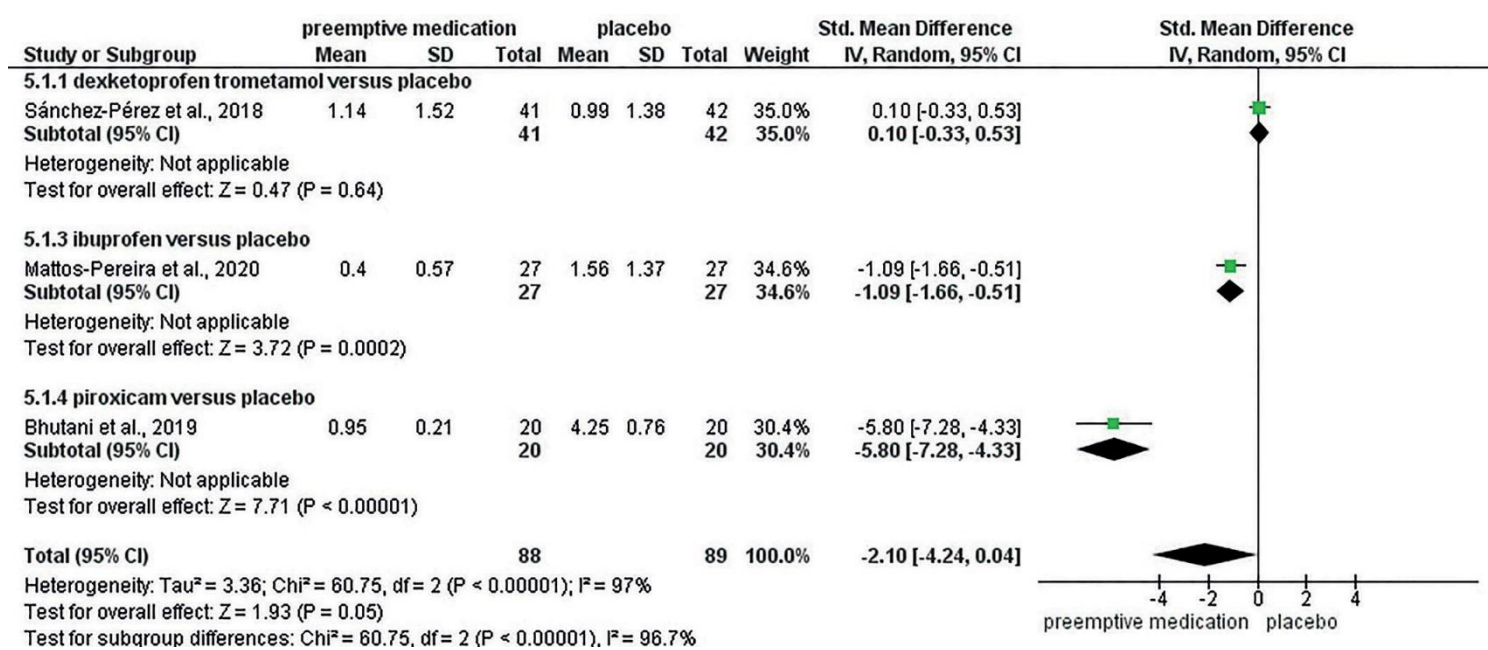


Figure 4 - Summary of Finding (SoF) table showing the effect estimate together with the certainty of the evidence for pain 1-2 or 6-8 hours after the surgery

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Preemptive medication	placebo	Relative (95% CI)	Absolute (95% CI)		
Pain 1 to 2 hours after surgery												
3	randomised trials	serious ^a	not serious	not serious	serious ^b	none	88	89	-	SMD 0.45 SD lower (0.83 lower to 0.08 lower)	⊕⊕○○ LOW	CRITICAL
Pain 6 to 8 hours after surgery												
3	randomised trials	serious ^a	serious ^a	not serious	serious ^b	none	88	89	-	SMD 2.1 SD lower (4.24 lower to 0.04 lower)	⊕○○○ VERY LOW	CRITICAL

CI: Confidence interval; SMD: Standardised mean difference

a. There are some concerns due to randomization process, missing outcome data, measurement of the outcome (blinding of the outcome assessor), and selection of the reported result.

b. The sample size was not sufficient according to the optimal information size (OIS); the CI cross the threshold of the magnitude of the effect. c. The effect estimates of individual studies were not similar, 95%CI did not overlap, there was statistically significant heterogeneity showed by high I².

ARTIGO CIENTÍFICO II

PREEMPTIVE EFFECTS OF ETEROCOXIB, ACETAMINOPHEN, NIMESULIDE AND IBUPROFEN ON POSTOPERATIVE PAIN MANAGEMENT AFTER SINGLE-IMPLANT SURGERY: A RANDOMIZED CLINICAL TRIAL

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Author Contributions

G.H. Mattos-Pereira contributed to conception, design, analysis, and interpretation, drafted and critically revised the manuscript. R.P. Esteves-Lima, L.O.M. Cota, R. Alvarenga-Brant contributed to interpretation, drafted and critically revised the manuscript. F.O. Costa contributed to conception, design, data acquisition, analysis and interpretation of data, drafted and critically revised the manuscript. All authors gave final approval and agree to be accountable for all aspects of the work.

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Abstract

Background: There is insufficient evidence for pain control in preemptive analgesia (PA) after dental implant surgery, signaling the need for further studies. The objective of this study was to evaluate the efficacy of PA in single dental

implant surgeries (SDIS), seeking to identify among the etorocoxib (ETERO), ibuprofen (IBU), nimesulide (NIME) and acetaminophen (ACETA)], which one has the higher efficacy effectiveness in relieving postoperative pain and reducing the use of rescue medication compared to placebo.

Methods: In this triple-blind, parallel, randomized controlled clinical trial, 135 individuals with a mean age of 57.6 years (± 11.7), both genders, were randomly divided into 5 groups according to the test drug: I- PLACEBO; II - 600mg IBU; III – NIME 100mg; IV - ACETA 750mg and V - ETERO 90 mg. The occurrence, duration and intensity of pain were analyzed using the Chi-square, Fisher's Exact and ANOVA tests and the Generalized Estimating Equation models, when appropriate.

Results: Test drugs provided a reduction in postoperative pain scores and lower use of rescue medication when compared to placebo. The ETERO group presented significantly lower pain scores. The IBU group showed the highest mean number of rescue medication used.

Conclusions: All test drugs provided a beneficial preemptive effect demonstrated by the reduced postoperative pain and reduced use of rescue medication. The ETERO group presented lower pain scores and the IBU group showed the highest mean number of rescue medication used among the test groups.

Keywords: preemptive analgesia, postoperative pain, dental implant surgery.

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Total number of figures: 2

Introduction

Postoperative pain is one of the main adverse effects of dental surgeries that contributes to non-adherence to treatment, (Nogueira, et al., 2019). The definition of pain given by the International Association for the Study of Pain shows its individuality and subjectivity, always linked to past experiences. These characteristics prevent pain intensity from being given in a generalized way and based only on the extent of the injury or surgical procedure, (Raja, et al., 2020; Rosero & Joshi, 2014)

The cyclooxygenase (COX) is the key enzyme in the synthesis of prostaglandins (PGs) and, thus, it is closely associated with inflammation and pain (Hemler & Lands, 1976; Gilroy, Tomlinson & Willoughby, 1998; Morita, 2002; Khan, Iadarola, Yang & Dionne, 2007). Evidence-based animal and human studies support the role of COX-2 in the development of inflammation (Morita, 2002; Kan, et al.; O'Banion, 1999). The contribution of COX-2 to inflammation is further supported by the demonstration that COX-2 expression and PG production can be inhibited by anti-inflammatory cytokines and glucocorticoids. It is also believed that COX-1 is responsible for the initial response of prostanoids to inflammatory stimuli, while COX-2 becomes the main contributor to prostanoid synthesis as inflammation progresses (Kan, et al.; O'Banion, 1999).

Some analgesics and anti-inflammatory drugs have COX inhibition as their main mechanism of action. Consequently, they reduce the effects from this enzyme, providing relief and prevention of postoperative pain. They are widely used in particular in implant dentistry (Ong, Lirk, Seymour & Jenkins, 2005; Bahammam, et al., 2017; Sánchez-Pérez, Muñoz-Peñalver, Moya-Villaescusa & Sánchez-

Matás, 2018; Ramires, et al., 2021; Santos, et al., 2021; Santos, Costa, Vasconcelos, Cyrino & Cota, 2022).

In single dental implant surgeries (SDIS), where there is a lower intensity of surgical trauma, non-steroidal anti-inflammatory drugs (NSAIDs) are gaining ground due to their effectiveness in controlling pain and edema and low adverse effects (Khouly, et al., 2021). As important as the drug to be used, the methods of administering the medication must also be taken into account in the analgesia procedure.

Among the available methods, the preemptive analgesia is gaining space in the surgical clinic. It can be defined as the analgesia procedure that begins before surgery and prevents the establishment of central sensitization caused by incisional and inflammatory lesions (Kissin, 2000). In a meta-analysis on preemptive analgesia in different types of surgical procedures, some evidence was found in the reduction of acute pain and analgesic consumption (Doleman, et al., 2021).

In a randomized, parallel, controlled clinical trial, it was demonstrated that the preemptive use of ibuprofen (IBU) in single dental implant surgeries (SDIS), resulted in a significant reduction in postoperative pain compared to placebo (Pereira, Cota, Lima, Costa, 2020).

In a meta-analysis, it was demonstrated that preemptive analgesia in surgeries for the insertion of dental implants can have a positive effect in reducing pain compared to placebo. However, uncertain evidence signals the need for new studies, including different drugs (Mattos-Pereira, et al., 2021).

In this sense, it was hypothesized that the use of NSAIDs [Eterocoxib (ETERO), IBU, Nimesulide (NIME)] provide lower postoperative pain scores and longer rescue time compared to the use of acetaminophen (ACETA) or placebo, in SDIS. The objective of this present clinical trial was to evaluate the effectiveness of preemptive analgesia in SDIS, seeking to identify among the NSAIDs (ETERO, IBU, NIME) and ACETA, which one has greater postoperative pain control and greater reduction in rescue medication use compared to placebo.

Materials and methods

Study design and ethical considerations

The present parallel, triple-blind, randomized controlled clinical trial was conducted in a private implant dentistry clinic in the city of Belo Horizonte, Brazil, from November 2019 to August 2021. One hundred thirty-five non-smoking subjects of both genders, mean age of 57.6 years (± 11.7), were included.

Following the Declaration of Helsinki and the CONSORT guidelines, this study was approved by the Research Ethics Committee from the Federal University of Minas Gerais, Brazil (protocol #83534618.5.0000.5149) and registered in the Brazilian Registry of Clinical Trials (ReBEC) under the number RBR-4b5ddg (www.ensaiosclinicos.gov.br).

The following inclusion criteria were adopted: 1) good systemic general health status (ASA I or II); 2) absence of complaints of pain or presence of any oral inflammatory process; 3) not having used analgesics in the 3 weeks before the study; 4) not making continuous use of steroidal and non-steroidal anti-inflammatory drugs; 5) need to install single-unit dental implants not concomitant with maxillary and/or mandibular tooth extraction; 6) presence of compatible bone

width and height determined by tomographic examination (cone-beam computed tomography). Individuals with a history of kidney, liver, respiratory or cardiovascular problems, smokers, history of abusive use of alcohol or illicit drugs, pregnant or lactating women, those who used any type of medication that could affect the perception of pain, history of allergy or intolerance to the test drugs were excluded from the study.

Sample calculation and study outcomes

A sample size calculation was performed based on a previous study (Pereira, et al.) and a reduction in pain scores by the VAS scale as the primary outcome, assuming: 1) mild to moderate changes in pain scores 24 hours after surgery; 2) differences of at least 15% between test and control groups; 3) non-normally distributed data. Assuming a 5% significance level and 80% study power, 25 individuals were determined to be needed in each group. However, considering a probability of sample loss of up to 10%, the final sample comprised 27 individuals per group. The secondary outcome was defined as the number of rescue medications used in each group.

Study groups and drug testing protocols

Participants were randomly divided by simple drawing into 05 groups according to the test drug used: 1) group I - PLACEBO (corn starch); 2) group II – 600mg IBU (Alivium® - MANTECORP Indústria Química e Farmacêutica Ltda, São Paulo, Brazil); 3) group III – NIME 100mg (Cimelide® - CIMED Indústria de Medicamentos Ltda, Minas Gerais, Brazil); 4) group IV - ACETA 750 mg (Tylenol® - Johnson & Johnson, São José dos Campos, Brazil); 5) group V - ETERO 90 mg (Arcoxia® - Merck Sharp and Dohme, Campinas, Brazil) (Fig. 1). The researcher operator (FOC), in all cases blinded to the group allocation, just

checked whether the indicated medication was taken by the patient 1 hour before each surgical intervention. The placebo was provided in capsules and packages similar to the test drugs (Farmácia Manipulatta Leme Barbosa LTDA, Belo Horizonte, Brazil). All drugs used in the present study were packaged in identical white capsules.

Randomization

The allocation of participants to each group was performed using a non-probabilistic sequential method, that is, consecutive cases were drawn for each eligible intervention (from July 2020 to January 2022). For each group, opaque envelopes named groups I, II, III, IV, and V were used randomly selected before surgery by a non-operating researcher (GHMP). Sequential stratified randomization was performed by blocks of 5, using 135 envelopes. The identifications of the treatment groups (I: PLACEBO; II: IBU; III: NIME; IV: ACETA; and V: ETERO) were placed inside them. The envelopes were sealed and shuffled and then numbered in sequential order. For each new study participant, a subsequently numbered envelope was opened (strategy to control for the ordering effect). Once randomization was performed, the researcher (GHMP) delivered the eligible drug to each individual.

Surgical procedures

All surgical procedures were performed by one single operator (FOC), blinded to the medication used. The surgery was performed using a mucoperiosteal flap, with the insertion of single implants (Titamax®, external hexagon, Neodent, Paraná, Brazil), following the manufacturer's protocols. Patients were anesthetized using an infiltrative local anesthetic (30 mg/ml prilocaine hydrochloride solution). The amount of anesthetic used did not exceed the limit

of 5.4 ml (03 tubes). The duration of the surgical procedure was recorded, being the beginning of the surgery the moment of anesthetic administration, and the completion of the last suture as the end. The mean duration of the surgeries was 40.1 min. (± 9.8).

At the end of each intervention, all patients received standardized verbal and written postoperative instructions (oral hygiene, local use of external ice, food restriction, and physical exertion). In addition, acetaminophen 750 mg tablets were made available to each patient as rescue medication, to be taken whenever necessary in case of pain (Cetira Filho, et al., 2020). Patients were instructed to avoid the use of any other medication that was not provided in the study protocol and, if it occurs, they should report it to the researchers.

Pain assessment

The occurrence and intensity of pain were assessed using a visual analogical scale (VAS) (Moore, Moore, McQuay & Gavaghan, 1997; Huskisson, 1972). This scale is 10 cm long, subdivided into ten equal parts, and numbered from 0 to 10, where the left extremity corresponded to no pain (0) and the right extremity “worst imaginable pain” (10). Participants were instructed to record their perception of pain on the scale for 3 days, at predetermined evaluation times (T1=01h after, T2=06h after, T3=12h after, T4=24h after, T5=48h after, and T6= 72 hours after the surgical procedure), as well as the need, amount and time of rescue medication use in specific forms.

A flowchart with the study strategy is shown in supplementary figure 1.

Statistical analysis

The analyzes were performed without identifying the test or control groups (groups I to V). Initially, descriptive analyzes were performed providing mean

values and absolute/relative frequencies of reported outcomes. To assess the homogeneity of the co-variables between the different groups, the Chi-square or Fisher's Exact test was applied for categorical variables and the ANOVA test for quantitative variables. The assumptions of normality and homoscedasticity were checked.

Subsequently, differences between groups of variables without the temporal dimension (i.e. use and amount of rescue medications) were tested. For this, generalized linear models were fitted with the most adequate probability distribution for each variable.

For the use or not use of rescue medication, we used the binomial distribution, suitable for analyzing dichotomous data, and modeling the probability of occurrence of the event. The number of rescue medications was evaluated using the Poisson distribution. For variables measured over time, generalized estimating equation models were fitted.

The mean values and 95%CI of the predictor variables (groups, time, sex, age, duration of surgery, income, quadrant, and implant position) were included in the regression models and non-significant variables were excluded step by step (backward selection). Subsequently, the main effects and possible interactions were tested. Multiple comparison tests (pairwise) were performed by applying Tukey's correction.

Survival curves were performed using the meantime to rescue medication in all groups. Differences between survival curves were tested by the Mantel-Cox test and multiple comparisons were analyzed by Bonferroni correction.

All statistical analyzes were performed using R software version 3.6.1 (R Core Team, 2019), with a significance level of 5%.

Results

Of the 135 selected patients, 77 were women and 58 were men. All participants completed the study. The mean age was 57.6 years (± 11.7). There were no significant differences among groups regarding the mean duration of surgery ($p=0.74$), mean age ($p=0.061$), family income ($p=0.139$) and sex ($p=0.353$) (Table 1). There were also no significant differences in relation to the operated quadrant ($p=0.277$) and implant insertion sites (corresponding to the position of the teeth) ($p=0.151$) (Table 1).

The mean VAS score remained below the score of 2 for all groups throughout the evaluated period (Table 2). The p-values for group comparisons at different evaluation times are shown in Table 3.

When observing the pain level of each group for the same hour, we noticed that the PLACEBO group did not present a significant difference in the first hour, when compared to the test drugs. It is important to emphasize that in this first hour, the ACETA group presented an absolute mean pain score above all other groups, including the PLACEBO group (Table 2 and 3).

The IBU group was the only one that did not show significant differences among the different times evaluated. From the 6th hour, pain scores became significantly relevant among the PLACEBO group and the test drugs, except for the ACETA group ($p=0.960$), which had a significant difference from the 12th hour. Then, in the PLACEBO group, there was an increase in the mean VAS score up to 12 hours followed by a reduction until 72 hours, but always showing significant differences among all the test groups (Table 3).

In the intergroup evaluation, we observed the first significant difference at the 12th hour among the IBU ($p=0.003$), ACETA ($p<0.001$) and NIME ($p=0.048$) groups when compared to the ETERO group (Table 3).

It is important to point out that the pain scores in the ACETA and ETERO groups started to significantly reduce from the 12th hour onwards, remaining stable 24 hours after the end of the procedure. The NIME group, on the other hand, started to present a significant reduction at 24 hours after surgery ($p=0.000$) (Table 2).

Regarding the number of rescue medications, the PLACEBO group had the highest average number of all the other groups (Table 4). Furthermore, in the pairwise comparisons, the IBU group also had a significantly higher number of rescue medication than the NIME group ($p=0.032$). Among the other groups, there were no significant differences (Table 4).

Regarding the survival curves, the one for the PLACEBO group was the only that crossed the 50% cumulative survival, and thus the median survival could be estimated only for this group (median time = 11.5 hours; 95% CI 6.8 – 13.5 hours). Additionally, multiple comparisons demonstrated differences in survival curves only among PLACEBO and NIME, ACETA, and ETERO (Figure 2).

All participants did not report any adverse effects from the use of the medications.

Discussion

This clinical trial sought to evaluate the efficacy of preemptive analgesia by comparing the effects of 04 types of drugs [(3 NSAIDs: IBU vs NIME vs ETERO) and 1 analgesic (ACETA)], for the prevention and control of postoperative pain in the surgery of single-unit dental implants. All test drugs provided a reduction in

both postoperative pain and use of rescue medication when compared to placebo.

Specifically, when comparing the mean pain score among the groups in the first hour, we observed that there were no significant differences among them. This finding may be linked to residual anesthetic effect and should not be considered in the overall analysis of the preemptive efficacy, even though long-acting anesthetics were not used to minimize these confounding effects (Bridgman, Gillgrass, Zacharias, 1996; Liporaci, 2012; Costa, et al., 2015). In the sixth hour, there was a significant difference between the IBU and ACETA groups and between the ETERO and ACETA groups. The ACETA group presented the highest pain score among the test groups, until the 12th hour, not presenting statistical differences between the PLACEBO group, until the 6th hour (Table 3). The ETERO group reached the lowest pain scores among all other groups, from the 12th hour onwards. The clinical efficacy of etoricoxib in relieving postoperative pain can be explained by the potency of this drug in inhibiting the COX-2 enzyme. In vitro human blood tests described the COX-2 - (IC 50 = COX-1/COX-2) selectivity rate of etoricoxib and other NSAIDs as follows: etoricoxib = 106, valdecoxib = 30, celecoxib = 7.6, nimesulide = 7.3, ibuprofen = 0.2, diclofenac = 3, meloxicam = 2, piroxicam = 0.08 and indomethacin = 0.4 (Riendeau, et al., 2001). An animal study confirmed a superior analgesic potency of etoricoxib compared to other coxibs or NSAIDs (Franco de la-Torre, et al., 2021). Moreover, the study groups were homogeneous for important variables that could directly affect pain scores. Therefore, no significant difference was observed among the groups in terms of mean duration of surgery, mean age, family income, sex, quadrant, and insertion site of the implants in the arch.

Preemptive analgesia is mainly focused on minimizing adverse effects such as pain caused by the surgical trauma. Due to the release of at least two known isoforms of COX (COX-1 and COX-2), which occur after tissue injury, there is a production of pro-inflammatory mediators such as endotoxins, cytokines and growth factors. These mediators will be responsible for the onset of inflammation. They can induce a 10- to 80-fold increase in the level of COX-2 expression in monocytes, macrophages, chondrocytes, fibroblasts, and endothelial cells. The pharmacological effects of NSAIDs occur through the inhibition of COX synthesis, causing a reduction in the synthesis of these mediators, leading to a decrease in the entire inflammatory process and, consequently, pain (Bacchi, Palumbo, Sponta & Coppolino, 2012; Atkinson & Fudin, 2020).

Several studies on preemptive analgesia have been published in recent years focusing on different dental procedures, such as endodontics (Teja, Ramesh, & Vasundhara, 2022), surgeries for the removal of third molars (Santos, et al., 2021; Avelar, et al., 2012; da Costa Araújo, et al., 2012; Pouchain, Costa, Bezerra & Soares, 2015; Barbalho, et al., 2017; Lima, Bagordakis, Falci, Dos Santos & Pinheiro, 2018; Gately, Ali, & Burns, 2022), periodontal surgeries (Santos, et al., 2022; Pilatti, Santos, Bianchi, Cavassim & Tozetto, 2006; Steffens, Santos, Sartori & Pilatti, 2010; Steffens, Santos & Pilatti, 2011; Konuganti, Rangaraj & Elizabeth, 2019), and relatively few studies on surgeries for the placement of dental implants (Bahammam, et al., 2017; Sánchez-Pérez, et al., 2018; Pereira, et al., 2020; Bhutani, Sangolikar, Bhutani, Tapashetti & Pushpalatha, 2019).

Several drugs have also been tested to verify their potential as a preemptive medication in different dental surgeries: nimesulide (Santos, et al., 2022; da Costa Araújo, et al., 2012; Pouchain, et al.; Barbalho, et al. 2017),

dexamethasone (Bahammam, et al., 2017; Ramires, et al., 2021; Santos, et al., 2021; Barbalho, et al., 2017; Lima, et al., 2018; Pilatti, et al. 2006; Steffens, et al., 2010; Konuganti, et al., 2019), eterocoxibe (Steffens, et al., 2010; Steffens, et al., 2011; Konuganti, et al., 2019), celecoxib (Pilatti, et al., 2006; Steffens, et al., 2011), ibuprofen (Bahammam, et al., 2017; Santos, et al., 2022; Pereira, et al. 2020; Vogel, Desjardins & Major, 1992) and acetaminophen (Santos, et al., 2021), which is widely used in most clinical trials as rescue medication (Bahammam, et al., 2017; Ramires, et al., 2021; Santos, et al., 2021; Santos, et al., 2022; Pereira, et al., 2020; da Costa Araújo, et al., 2012; Pouchain, et al., 2015; Lima, et al., 2018; Pilatti, et al., 2006; Steffens, et al., 2010; Steffens, et al. 2011; Konuganti, et al., 2019). In general, studies have shown the superiority of test drugs over placebo (Bahammam, et al., 2017; Ramires, et al., 2021; Santos, et al., 2021; Santos, et al., 2022; Pereira, et al., 2020; da Costa Araújo, et al., 2012; Pouchain, et al., 2015; Barbalho, et al., 2017; Lima, et al., 2018; Pilatti, et al., 2006; Steffens, et al., 2010; Steffens, et al. 2011; Konuganti, et al., 2019; Vogel, et al., 1992).

However, controversial results were observed in these studies with the use of different medications. Comparative results between dexamethasone and eterocoxib or celecoxib did not show significant differences in postoperative pain control in periodontal flap surgeries (Pilatti, et al., 2006; Steffens, et al., 2010; Steffens, et al. 2011). Differences between eterocoxib and celecoxib were also not observed (Pilatti, et al., 2006).

Regarding the preemptive administration of nimesulide, it was effective in reducing postoperative pain and swelling, as well as in reducing the need for rescue medication in the surgical removal of impacted third molars in different

studies (Santos, et al., 2021; da Costa Araújo, et al., 2012; Pouchain, et al., 2015; Barbalho, et al., 2017).

In a split-mouth randomized controlled clinical trial aiming at evaluating and comparing the preemptive effect of the preventive administration of ibuprofen and NIME in periodontal open flap surgery, it was observed that both drugs had similar and significant preemptive effects on postoperative pain control in the first 1 hour (Santos, et al., 2022). However, the NIME regained this effect on pain control after 24 hours, extending up to 72 hours postoperatively and showing an overall preemptive effect superior to ibuprofen. Similar results were found in another study when they evaluated preemptive analgesia in third molar surgeries (Santos, et al., 2021). Our findings also showed no differences in mean pain score between the NIME and IBU groups at 1h, 6h, and 12h intervals, with statistical significance only at the 24th hour.

In this present study, the PLACEBO group had the highest mean number of rescue medications used, followed by the IBU group. In multiple comparisons, we can observe a significant difference between the IBU and NIME groups, with a slight advantage for the latter. The same does not occur when comparing the other drug groups. The NIME group presented the lowest average for the number of rescue medications, but without significant differences among the others. A possible explanation for this occurrence may be related to the maximum time for the 600 mg ibuprofen dose to reach its maximum concentration, which may vary from 0.93h to 1.95h in young adults (Davies, 1998). These findings were confirmed by other studies (Mehlisch & Sykes, 2013; Moore, Derry, Straube, Ireson-Paine & Wiffen, 2014; Varrassi, Pergolizzi, Dowling & Paladini, 2020). On the other hand, the NIME presents its maximum concentration from 1.22 to 2.75

hs (Singla, Chawla & Singh, 2000), reaching 3hs (Hanif, et al., 2017). Similar findings were described by other studies (Costa, et al., 2015; la Torre, et al., 2021). In a meta-analysis of clinical trials on preemptive analgesia of third molar surgeries, no significant difference in the amount of rescue medication was observed (Moore, et al., 1997).

Mean pain scores were ascending in the first 12h for the PLACEBO group. The test groups had an average score below the 1.5 level at all times evaluated. It also observed a substantial decrease in pain scores after 48 hours for all groups. This result may be related to the low trauma caused by the SDIS. There are reports that the duration of pain for implant surgeries is around one day, with score intensity varying around 2 on the numerical scale (NRS) (Mei, Lee & Yeh, 2016). Thus, we can conclude that the first 24 hours are, from a statistical point of view, the critical zone for preemptive analgesia. In this sense, we can draw attention to the ACETA, NIME, and ETERO groups which obtained significant mean differences between the 6th and 24th hours. The ETERO group, a Cox 2 inhibitor, presented the lowest mean pain scores. These findings demonstrated that preemptive medication was effective in reducing postoperative pain, in line with other studies (Bahammam, et al., 2017; Sánchez-Pérez, et al., 2018; Lima, et al., 2018). Our findings presented ACETA as the only drug that surpassed an average above 1 in the first 6h. Some studies have shown that ACETA does not have significant anti-inflammatory activity, nor does it inhibit the production of pro-coagulant thromboxane A. It does not seem to have a great effect peripherally, and its action seems to be mainly central through the inhibition of prostaglandins in the central nervous system (CNS). It seems reasonable to assume that,

although there may be some effect on COX enzymes, this effect is different from that observed with NSAIDs (Anderson, 2008).

In a systematic review, ACETA was evaluated for pain relief after the removal of lower third molars and it was found that groups with a dose of 1000 mg were more effective than doses below 1000 mg (Weil, et al., 2007).

Some limitations of the present study should be pointed out, such as the single-unit implant placement surgery (short duration surgeries may influence the patient's pain threshold when compared to long surgeries with greater intra-oral manipulation and those with the placement of a greater number of implants), the specific pain assessment times and the pain score metrics. Therefore, the generalization of the study results must be done with caution and restrictions. Although there is evidence of the beneficial effect of preemptive analgesia in single-unit implant placement surgeries, it remains a controversial topic and there is no standardized protocol for each type of dental surgery.

Overall, a beneficial effect of preemptive analgesia was observed in all test groups compared to placebo. The ETERO and NIME groups obtained a significant difference in pain scores in relation to the PLACEBO group, from the 6th to the 48th hour, thus presenting a greater preemptive effect than the other groups from a statistical point of view. The ETERO group showed a slight advantage over the NIME group at the 12th and 24th hours.

Thus, through the interpretation of the VAS scale, this study showed that the pain complaints of study participants in all test groups were within the mild pain level. From the point of view of clinical relevance, this difference was small and it was not enough to define which drug has the greatest analgesic efficacy. Analyzing clinical versus statistical relevance, all tested drugs were effective in reducing

postoperative pain, with a slight statistical advantage for the ETERO group. Regarding the use of rescue medication, the IBU group presented a worse performance compared to the others. However, the decision-making on drug indication must still consider the cost-benefit relationship, adverse effects, and individual characteristics of the patients.

In this sense, this study can be considered a starting point for the use of preemptive medication in future trials that should include the insertion of multiple implants and complementary surgeries, such as bone and gingival grafts (where higher postoperative pain scores can be expected), and the evaluation of patient-centered outcomes and quality of life. An interesting evaluation would be the quantification of inflammatory mediators through specific biomarkers to clarify the presence of relevant clinical differences between the different drugs for an eligible indication of the best drug for preemptive analgesia based on scientific evidence. In conclusion, all test drugs provided a beneficial preemptive effect demonstrated by the reduced postoperative pain and reduced use of rescue medication when compared to placebo. However, the ETERO group presented significantly lower pain scores at the different evaluation times. On the other hand, the IBU group presented the highest mean number of rescue medication used among the test groups.

Conflict of interest

The authors declare no potential conflicts of interest with respect to the authorship and/or publication of this article.

Data Availability Statement

Data that support the findings of this study are available from the corresponding author upon reasonable request.

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Figure and Tables Legends

Figure 1. Study flowchart.

Figure 2. Survival curves (Kaplan-Meier) for study drugs.

Table 1. Variables of interest in the study groups.

Table 2. Pain scores by the VAS scale presented by each group at each evaluation time.

Table 3. Comparison among groups for each evaluation time.

Table 4. Pairwise intergroup comparisons of the number of rescue medication.

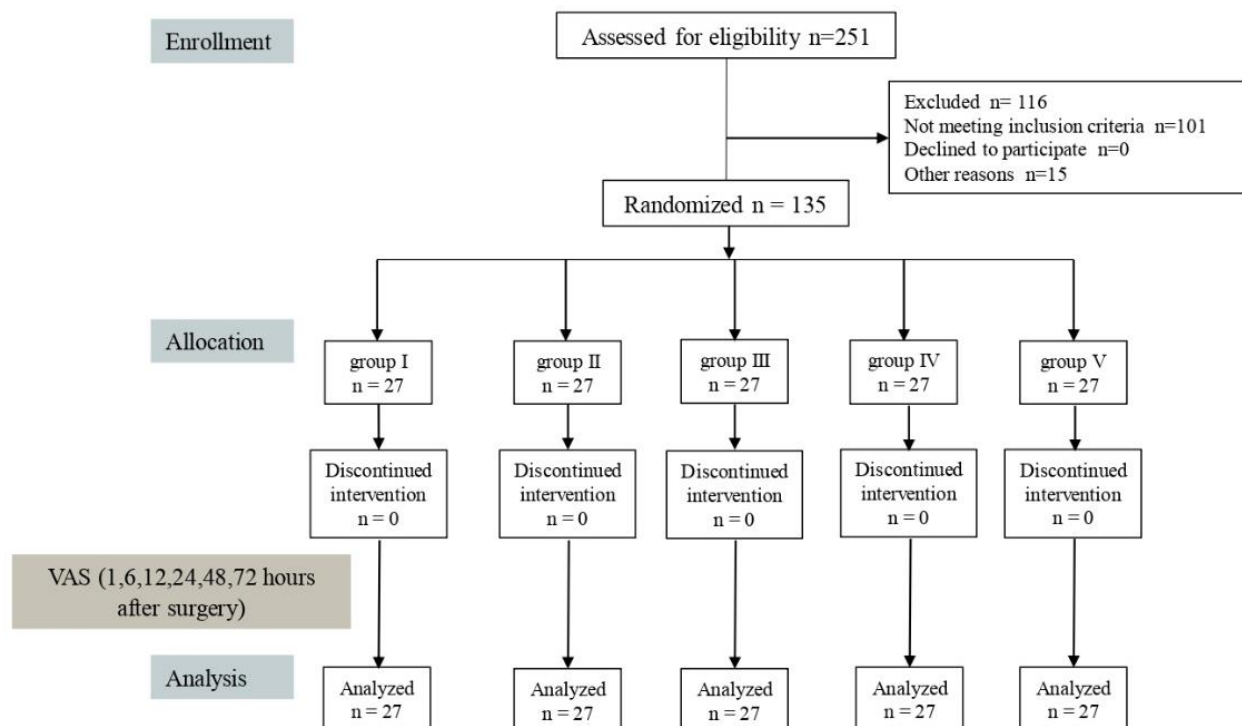
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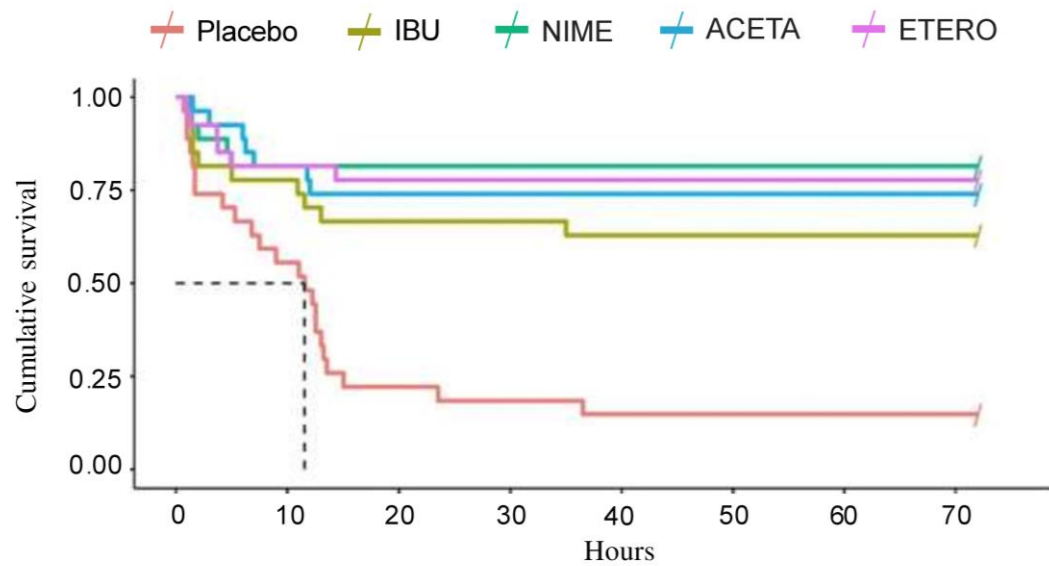


Table 1. Variables of interest in the study groups.

Study groups	Variables of interest					
	Sex ^a		Family income ^b		Age ^c mean (SD)	Duration of surgery ^c mean (SD)
	Male n (%)	Female n (%)	<5 BS n (%)	>5 BS n (%)		
PB	7 (25.9%)	20 (74.1%)	3 (11.1%)	24 (88.9%)	56.6 (11.0)	38.9 (7.4)
IBU	13 (48.1%)	14 (51.9%)	5 (18.5%)	22 (81.5%)	62.6 (8.3)	37.6 (9.8)
NIME	12 (44.4%)	15 (55.6%)	8 (29.6%)	19 (70.4%)	53.6 (13.4)	40.4 (9.9)
ACETA	14 (51.9%)	13 (48.1%)	4 (14.8%)	23 (85.2%)	56.4 (10.0)	41.7 (11.6)
ETERO	12 (44.4%)	15 (55.6%)	1 (3.7%)	26 (96.3%)	58.9 (13.6)	41.9 (10.1)
Total	58 (43.0%)	77 (57.0%)	21 (15.6%)	114 (84.4%)	57.6 (11.7)	40.1 (9.8)

Abbreviations – BS: basic salary; SD: standard deviation; PB: PLACEBO group; IBU: ibuprofen group; NIME: nimesulide group; ACETA: acetaminophen group; ETERO: eterocoxib group; ^a Chi-square test; ^b Fisher's exact test; ^c ANOVA test.

Table 2. Pain scores by the VAS scale presented by each group at each evaluation time.

Inter-hours comparisons		PB	IBU	NIM	ACETA	ETERO
Mean α (IL-UL); p-values						
1H vs. 6H		0.89 (0.41-1.74); 1.59 (0.90-2.62); 0.161	0.05 (0.15-1.37); 0.56 (0.21-1.10); 1.000	0.78 (0.48-1.18); 0.67 (0.37-1.14); 0.976	1.22 (0.68-1.87); 1.30 (0.72-2.31); 0.960	0.56 (0.24-1.19); 0.59 (0.24-1.02); 0.998
1H vs. 12H		0.89 (0.41-1.74); 1.96 (1.17-2.99); 0.044	0.05 (0.15-1.37); 0.41 (0.18-0.92); 0.998	0.78 (0.48-1.18); 0.41 (0.09-0.94); 0.248	1.22 (0.68-1.87); 0.81 (0.34-1.56); 0.431	0.56 (0.24-1.19); 0.07 (0.00-0.28); 0.002
1H vs. 24H		0.89 (0.41-1.74); 1.26 (0.72-2.07); 0.898	0.05 (0.15-1.37); 0.41 (0.11-1.00); 0.990	0.78 (0.48-1.18); 0.04 (0.00-0.26); <0.001	1.22 (0.68-1.87); 0.22 (0.00-0.97); 0.001	0.56 (0.24-1.19); 0.00 (0.00-0.01); <0.001
1H vs. 48H		0.89 (0.41-1.74); 0.37 (0.06-1.13) 0.325	0.05 (0.15-1.37); 0.19 (0.00-1.27); 0.774	0.78 (0.48-1.18); 0.00 (0.00-0.00); <0.001	1.22 (0.68-1.87); 0.07 (0.00-0.50); <0.001	0.56 (0.24-1.19); 0.00 (0.00-0.00); <0.001
1H vs. 72H		0.89 (0.41-1.74); 0.22 (0.00-0.97); 0.029	0.05 (0.15-1.37); 0.16 (0.00-0.62); 0.269	0.78 (0.48-1.18); 0.00 (0.00-0.00); <0.001	1.22 (0.68-1.87); 0.07 (0.00-0.47); <0.001	0.56 (0.24-1.19); 0.00 (0.00-0.00); <0.001
6H vs. 12H		1.59 (0.90-2.62); 1.96 (1.17-2.99); 0.667	0.56 (0.21-1.10); 0.41 (0.18-0.92); 0.996	0.67 (0.37-1.14); 0.41 (0.09-0.94); 0.123	1.30 (0.72-2.31); 0.81 (0.34-1.56); 0.008	0.59 (0.24-1.02); 0.07 (0.00-0.28); 0.001
6H vs. 24H		1.59 (0.90-2.62); 1.26 (0.72-2.07); 0.843	0.56 (0.21-1.10); 0.41 (0.11-1.00); 0.972	0.67 (0.37-1.14); 0.04 (0.00-0.26); <0.001	1.30 (0.72-2.31); 0.22 (0.00-0.97); <0.001	0.59 (0.24-1.02); 0.00 (0.00-0.01); <0.001
6H vs. 48H		1.59 (0.90-2.62); 0.37 (0.06-1.13); <0.001	0.56 (0.21-1.10); 0.19 (0.00-1.27); 0.490	0.67 (0.37-1.14); 0.00 (0.00-0.00); <0.001	1.30 (0.72-2.31); 0.07 (0.00-0.50); <0.001	0.59 (0.24-1.02); 0.00 (0.00-0.00); <0.001
6H vs. 72H		1.59 (0.90-2.62); 0.22 (0.00-0.97); <0.001	0.56 (0.21-1.10); 0.16 (0.00-0.62); 0.046	0.67 (0.37-1.14); 0.00 (0.00-0.00); <0.001	1.30 (0.72-2.31); 0.07 (0.00-0.47); <0.001	0.59 (0.24-1.02); 0.00 (0.00-0.00); <0.001

12H vs. 24H	1.96 (1.17-2.99); 1.26 (0.72-2.07); 0.024	0.41 (0.18-0.92); 0.41 (0.11-1.00); 1.000	0.41 (0.09-0.94); 0.04 (0.00-0.26); 0.041	0.81 (0.34-1.56); 0.22 (0.00-0.97); 0.007	0.07 (0.00-0.28); 0.00 (0.00-0.01); 0.105
12H vs. 48H	1.96 (1.17-2.99); 0.37 (0.06-1.13); <0.001	0.41 (0.18-0.92); 0.19 (0.00-1.27); 0.848	0.41 (0.09-0.94); 0.00 (0.00-0.00); <0.001	0.81 (0.34-1.56); 0.07 (0.00-0.50); <0.001	0.07 (0.00-0.28); 0.00 (0.00-0.00); 0.990
12H vs. 72H	1.96 (1.17-2.99); 0.22 (0.00-0.97); <0.001	0.41 (0.18-0.92); 0.16 (0.00-0.62); 0.339	0.41 (0.09-0.94); 0.00 (0.00-0.00); <0.001	0.81 (0.34-1.56); 0.07 (0.00-0.47); <0.001	0.07 (0.00-0.28); 0.00 (0.00-0.00); 0.222
24H vs. 48H	1.26 (0.72-2.07); 0.37 (0.06-1.13); <0.001	0.41 (0.11-1.00); 0.19 (0.00-1.27); 0.785	0.04 (0.00-0.26); 0.00 (0.00-0.00); 0.073	0.22 (0.00-0.97); 0.07 (0.00-0.50); 0.319	0.00 (0.00-0.01); 0.00 (0.00-0.00); 0.090
24H vs. 72H	1.26 (0.72-2.07); 0.22 (0.00-0.97); 0.007	0.41 (0.11-1.00); 0.16 (0.00-0.62); 0.081	0.04 (0.00-0.26); 0.00 (0.00-0.00); 0.162	0.22 (0.00-0.97); 0.07 (0.00-0.47); 0.891	0.00 (0.00-0.01); 0.00 (0.00-0.00); 0.601
48H vs. 72H	0.37 (0.06-1.13); 0.22 (0.00-0.97); 0.856	0.19 (0.00-1.27); 0.16 (0.00-0.62); 0.894	0.00 (0.00-0.00); 0.00 (0.00-0.00); 0.751	0.07 (0.00-0.50); 0.07 (0.00-0.47); 0.607	0.00 (0.00-0.00); 0.00 (0.00-0.00); 0.078

Abbreviations – IL: inferior limit; UL: upper limit; PB: PLACEBO group; IBU: ibuprofen group; NIME: nimesulide group; ACETA: acetaminophen group; ETERO: eterocoxib group; ^a Tukey's post-hoc test. Significant p-values in bold.

Table 3. Comparison among groups for each evaluation time.

Intergroup comparisons (p-values)	1h	6h	12h	24h	48h	72h
PB X IBU	0.693	0.002	0.000	0.007	0.891	0.978
PB X NIM	0.983	0.005	0.000	0.000	0.000	0.140
PB X ACETA	0.872	0.960	0.009	0.005	0.245	0.994
PB X ETERO	0.713	0.000	0.000	0.000	0.002	0.058
IBU X NIM	0.839	0.937	0.985	0.020	0.139	0.483
IBU X ACETA	0.176	0.023	0.505	0.834	0.947	0.999
IBU X ETERO	1.000	1.000	0.003	0.000	0.731	0.271
NIM X ACETA	0.308	0.066	0.322	0.782	0.387	0.069
NIM X ETERO	0.865	0.927	0.048	0.016	0.059	0.859
ACETA X ETERO	0.115	0.013	0.000	0.009	0.994	0.013

Abbreviations - PB: PLACEBO group; IBU ibuprofen group; NIME, nimesulide group; ACETA, acetaminophen group; ETERO, etorocoxib group. Significant p-values in bold.

Table 4. Pairwise intergroup comparisons of the number of rescue medication.

Intergroup comparisons	Mean α (IL-UL)	p- values
PB vs IBU	1.6 (1.1-2.4); 0.8 (0.4-1.4)	0.055
PB vs NIME	1.6 (1.1-2.4); 0.2 (0.1-0.6)	<0.001
PB vs ACETA	1.6 (1.1-2.4); 0.4 (0.2-0.9)	0.001
PB vs ETERO	1.6 (1.1-2.4); 0.3 (0.1-0.7)	<0.001
IBU vs NIME	0.8 (0.4-1.4); 0.2 (0.1-0.6)	0.032
IBU vs ACETA	0.8 (0.4-1.4); 0.4 (0.2-0.9)	0.411
IBU vs ETERO	0.8 (0.4-1.4); 0.3 (0.1-0.7)	0.087
NIME vs ACETA	0.2 (0.1-0.6); 0.4 (0.2-0.9)	0.587
NIME vs ETERO	0.2 (0.1-0.6); 0.3 (0.1-0.7)	0.979
ACETA vs ETERO	0.4 (0.2-0.9); 0.3 (0.1-0.7)	0.883

Abbreviations - IL: inferior limit; UL: upper limit; PB: PLACEBO group; IBU: ibuprofen group; NIME: nimesulide group; ACETA: acetaminophen group; ETERO: etorocoxib group. Significant p-values in bold

5 CONSIDERAÇÕES FINAIS

Esta pesquisa demonstrou por meio da revisão sistemática e meta-análise que:

(1) A analgesia preemptiva é eficaz para o controle da dor. No entanto, a magnitude do efeito é imprecisa e pode variar de grande a um efeito insignificante. Para a prática clínica, existem dois fatores que podem influenciar no controle da dor: o tempo de administração do medicamento e o tempo de duração da cirurgia. Quando o fármaco é administrado mais próximo da cirurgia, o efeito do fármaco pode ser prolongado por períodos mais longos. Além disso, cirurgias mais curtas podem influenciar na percepção da dor pelo paciente quando comparadas a cirurgias com manipulação intra-oral mais longa e maior número de implantes inseridos; (2) Para estudos futuros, os ensaios clínicos devem randomizar adequadamente os pacientes e fornecer o cegamento do paciente e operador com pílulas padronizadas para os grupos de intervenção e controle. Além disso, para maior transparência no protocolo de pesquisa, os autores devem antes de iniciar o estudo registrar o mesmo; (3) A analgesia preemptiva pode reduzir discretamente a dor de uma a duas horas após a cirurgia quando comparada com pacientes que não fizeram uso de medicação preemptiva. Após seis a oito horas, a analgesia preventiva pode ter um grande efeito na redução da dor em comparação ao uso de placebo.

No ensaio clínico, todos os medicamentos testados proporcionaram um efeito benéfico da analgesia preemptiva demonstrados pela redução da dor pós-operatória e do menor uso de medicação de resgate quando comparados ao placebo. Entretanto, o grupo IBU apresentou significativamente maiores escores de dor que os outros três grupos testes (ETERO, NIME e ACETA), que foram equivalentes entre si.

Em adição, observou-se que por meio da interpretação da escala VAS, que a queixa de dor dos participantes da pesquisa em todos os grupos testes estiveram dentro do nível de dor leve. Do ponto de vista de relevância clínica, esta diferença foi pequena e não é suficiente para definirmos qual droga possui a maior efetividade analgésica. Analisando relevância clínica versus estatística, os leves escores de dor no geral e o pior desempenho do IBU, determinam uma elegibilidade do ETERO, NIME e ACETA em cirurgias para implantes dentários unitários. Entretanto a tomada de

decisão de qual a ser indicado deve ainda considerar relação de custo-benefício, efeitos adversos e características individuais dos pacientes.

Neste cenário, observa-se a necessidade de estudos adicionais que devem incluir a inserção de implantes múltiplos e de cirurgias complementares, como enxertos ósseos e gengivais (onde existe uma probabilidade de maiores escores de dor pós-operatória), e uma avaliação interessante seria realizar a quantificação dos mediadores inflamatórios através de biomarcadores. A implementação destas questões em pesquisas futuras pode auxiliar a esclarecer a presença de uma diferença clínica relevante entre os diferentes medicamentos para uma indicação elegível do melhor medicamento para analgesia preemptiva baseada em evidências científicas.

6 PRODUÇÃO ADICIONAL ASSOCIADA AO TEMA DA TESE

6.1 Editorial commentary

Editorial Commentary published on *Journal of Oral and Maxillofacial Anesthesia*, entitled "Post-operative pain: what are the ways we can find to minimize it".

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Understanding pain in attempt to try to control it has always been among the main goals of science. According to the International Association for the Study of Pain, pain can be defined as "an unpleasant sensory and affected experience associated with or similar to that associated with actual or potential tissue damage". Furthermore, pain is a personal experience that can be influenced differently by social, biological and psychological factors, showing that individuals learn its meaning through life experiences (1).

The comprehension of pain mechanisms through its physiology and the discovery of the main ways to its prevention and mitigation are essential points and the focus of clinical research in this area. The pain caused by tissue damage is derived from the inflammatory process. Its purpose, through increased sensitivity, is to minimize the risk of further damage. In this manner, it helps to promote wound recovery. However, even with the need to adapt to this pain, it requires to be reduced in order to minimize the adverse effects on the individual (2).

Despite being a procedure that tends to generate low levels of pain, dental implant insertion surgeries still cause pain as one of its main complications. Seeking to find the most appropriate therapy to decrease postoperative pain after dental implant surgeries, a systematic review of the literature assessing the clinical efficacy of various analgesic drugs used in clinical trials around the world (3). The authors presented a

statistically significant level of pain on the first postoperative day, with a gradual decline from the fourth postoperative day. Furthermore, no significant differences were found in the level of postoperative pain between the different groups of analgesics (NSAIDs, glucocorticoids and codeine adjuvants). Through these findings, this study drives its focus to other directions. The dosage regimen becomes an important point in the attempt to minimize post-surgical algesia. When conducting a meta-analysis between two studies whose main difference was the dosage of NSAIDs (preoperative vs. postoperative), this study corroborated the theory of preemptive analgesia, first described by Crile in 1913 (4).

Preemptive analgesia is characterized by a treatment that starts before the surgical procedure, preventing the establishment of central sensitization caused by incisional and inflammatory lesions, embracing the period of surgery and the initial postoperative period (5). This mechanism may be behind some of the answers to these questions. Perhaps, the first question should be "What is the best dosage regimen for analgesics and anti-inflammatory drugs that should be used to mitigate post-surgery pain?" After getting this answer, we could think about finding the best analgesic drug available for use in implant dentistry.

In a meta-analysis (6) evaluating studies that addressed the use of preemptive medication, it was demonstrated that there is a risk of bias classified as "some concerns" according to the Cochrane Bias Risk Tool for Randomized Trials (RoB 2.0) (7). According to the Classification of Recommendations, Assessment, Development and Assessment Tool (GRADE) (8), the certainty of the evidence was reduced due to issues related to risk of bias and imprecision for pain 1-2 hours after surgery. By 6-8 hours after surgery, certainty of evidence was reduced due to serious issues of risk of bias, inconsistency and imprecision.

These findings, added to those by Kouly et al. (2021), support the need to future clinical trials with more rigid designs, seeking to reduce potential bias. It is also important to focus on to the type and quantity of anesthetic drugs used. Two studies showed a better anesthetic effect of 4% articaine with 1:100,000 epinephrine compared to 2% lidocaine with 1:100,000 epinephrine (9-10). The anesthetic technique used can also play an important role in the perception of postoperative pain, masking the effects of preemptive analgesia. As an example, we can mention the alveolar nerve block, which has greater postoperative residual analgesia when compared to infiltrative techniques (11). Studies evaluating preemptive analgesia should consider these data

in its methodological planning and in the interpretation and discussion of the results. Ideally, the test and control groups should be comparable in terms of surgical sites and, consequently, in terms of the anesthetic techniques used.

In this sense, according to Kouly et al. (2021), the main limitation of the available evidence is the small number of clinical trials evaluating pain management in dental implant surgery, the heterogeneity of the implemented interventions, the way the results were evaluated and the different follow-up periods.

Thus, there is no sufficient evidence to recommend or discourage the use of an analgesic regimen for pain control after dental implant surgery in clinical practice. Ultimately, analgesic prescription should be guided by the patient's medical history in order to increase pain management success in a short period of time and decrease potential adverse effects.

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6.2 Book chapter

Book Title: Advances in Health and Disease. Volume 54, 2022. Nova Science Publishers, Inc. NY, USA (ID: 23147).

Chapter:

IBUPROFEN: USES, MECHANISMS OF ACTION AND CLINICAL OUTCOMES

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a. Abstract

The Ibuprofen is a derivative of 2-phenylpropionic acid, belonging to a group of phenylalcanic acids. It was introduced in England in 1969 and in the United States in 1974 as an anti-inflammatory drug. Available in more than 80 countries, the ibuprofen is one of the most widely used over-the-counter painkillers and its effectiveness has been widely evaluated. Along with paracetamol and aspirin, it is included in the WHO list of essential medicines. It emerged as a new option for the symptomatic treatment of rheumatoid arthritis and osteoarthritis, presenting results like those of aspirin, but with considerably lower adverse effect on the gastrointestinal tract. Ibuprofen has been shown to be effective in many clinical conditions such as dysmenorrhea, pain, headache and migraine, soft tissue pain and fever. It also showed promising effect as part of the treatment regimen in children with cystic fibrosis. The primary mechanism of ibuprofen is through the inhibition of prostaglandin precursors. Upon a physiological or pathological stimulus, membrane phospholipids release arachidonic acid that passes through one of three enzymatic pathways. Ibuprofen, as a non-steroidal anti-inflammatory drug (NSAID), acts on the cyclooxygenase (COX) pathway. COX-2, in addition to its well-known roles in inflammation, is also constitutively expressed during early carcinogenesis. It has been observed that higher levels of COX-2 have been demonstrated in several human tumors, including breast, colorectal, esophagus, lung and pancreas.

Current findings on COX-2 and its various effects on cells suggest that the anticancer effects of NSAIDs such as ibuprofen are due to COX-2 inhibition.

Keywords: ibuprofen, nonsteroidal anti-Inflammatory

b. Introduction

Ibuprofen, or 2-(4-isobutylphenyl) propionic acid, is a non-steroidal agent with anti-inflammatory action and analgesic and antipyretic characteristics. It is a stable colorless crystalline solid, which has a low aqueous solubility in acidic media, but is easily soluble in most organic solvents. It was introduced in England in 1969 and in the United States in 1974 as an anti-inflammatory drug in humans (Piper et al., 1977; Kantor, 1979). Its development has brought a new option for the symptomatic treatment of rheumatoid arthritis (RA) and osteoarthritis (OA), with results similar to those of aspirin, but with a minimization of adverse effects on the gastrointestinal tract (GIT). Its analgesic property is probably related to its anti-inflammatory effect, since its mechanism of action occurs through the inhibition of prostaglandin synthesis (Rainsford, 2009; Moore et al., 2014).

c. Analytical Framework

i. Literature Review

According to Ha and Paek (2021), ibuprofen was valued at around US\$300 million in 2020. In addition, it was prescribed more than 2.4 million times in the US in 2018, being the most prescribed NSAID that year.

The large increase in the number of severe cases and also of studies in which participants had severe bleeding due to peptic ulcer were the main problems associated with the consumption of aspirin and other NSAIDs (Piper et al., 1977).

In this context, a search for an effective drug for the improvement of rheumatoid arthritis (RA) symptoms was initiated.

Some compounds derived from phenoxyphenyl and phenylalkanoic acids were tested. Stewart Adams started tracking phenylalkanoic acids, including phenylacetic and then phenylpropanoic acids. Several types of assays were used to evaluate the analgesic and antipyretic activity of ibuprofen. It was through these in vivo tests that it was possible to track all three major therapeutic requirements for the control of the classic cardinal and pathognomonic signs of inflammation described by Celsus: tumor, flushing, heat, pain, and loss of function (Rainsford, 1999).

According to Rainsford (2004) and Dieppe and Blake (1986), some studies led to the selection of a series of drugs to be tested in patients with RA. Some compounds were shown to be clinically active, but they produced a rash in about a fifth of RA patients and had to be withdrawn.

The progenitor of ibuprofen, ibufenac, one of these active compounds, has produced liver toxicity in patients with RA. Therefore, its withdrawal was required in the United Kingdom. The occurrence of liver toxicity required an investigation of the pharmacokinetics of this drug, where the result presented identified the accumulation of this drug in the liver as the main factor of this side effect. The subsequent identification of ibuprofen as a drug candidate was supported by observations of low GIT intolerance and low liver toxicity, associated with low systemic drug accumulation, particularly in the liver (Adams, 1987).

Rainsford (2012) showed that the initial clinical effects in RA and osteoarthritis (OA) showed that ibuprofen had modest actions in relieving joint pain and symptoms when given in dosages of 600-1200 mg/day. Regarding gastric tolerance, it was better than aspirin, thus fulfilling one of the requirements for the development of the new drug. In later clinical studies, there was improvement in therapeutic responses after increasing the dose to 2400 mg/day, without modifying the good gastric tolerance.

Since the introduction of ibuprofen on the market to the present time, other classes of drugs, such as selective inhibitors of cyclooxygenase-2 (COX-2) or coxib, have emerged. The main claim was the improved tolerance of the gastrointestinal (GI) tract in relation to traditional non-steroidal anti-inflammatory drugs (tNSAIDs). Several randomized, double-blind, controlled trials (placebo or NSAID reference) were performed in patients with RA and OA. These showed that ibuprofen had better effects on pain control and joint symptoms when compared with placebo. Effects were similar

when compared to established reference tNSAIDs (e.g., indomethacin, fenamates, phenylbutazone) or newer drugs. Ibuprofen has also been shown to be effective in relieving toothache, migraine and non-migraine headaches, dysmenorrhea, cold and 'flu' symptoms and a variety of acute painful conditions, including those in children (Kean, Buchanan and Rainsford, 1999).

According to Adatia, Rainsford and Kean (2012), in an evaluation of the effectiveness of ibuprofen in randomized clinical trials comparing its effectiveness in the therapy of hand and hip OA showed that at anti-rheumatic doses, it results in an improvement of 50 to 60% in the Ontario McMaster (WOMAC) scores for pain and joint function disability comparable to tNSAIDs and coxibs. Ibuprofen has been shown to be relatively well tolerated and effective for short-term treatment although serious gastrointestinal reactions may be observed. Another point worth noting is the short plasma elimination half-life ($t_{1/2}$), giving ibuprofen safety advantages in the treatment of OA, while showing clinically relevant anti-inflammatory effects in the joints.

In endoscopic examinations and through observation of blood loss, it was observed that ibuprofen had a low level of ulceration or bleeding in the GI tract. In trials with coxibs, ibuprofen had comparable effects in relieving joint pain and symptoms in arthritic conditions (Muncie and Nasrallah, 1989; Lanza et al. 2008; Lanza, Collaku and Liu, 2018).

The discovery of ibuprofen was initially based on a very limited understanding of what was already known about the therapeutic targets, the inflammatory effects of prostaglandins (PGs), and the actions of aspirin and other NSAIDs. Enzymes that control the production of pro-inflammatory PGs have become important biochemical targets for understanding the actions of these drugs. Thus, through several experiments, careful planning and management, ibuprofen was developed and has been successfully applied in clinical practice.

ii. Ibuprofen Applications

According to Irvine et al. (2017), ibuprofen has been shown to be effective in many clinical conditions such as dysmenorrhea, pain, headache and migraine, soft tissue pain, and fever. It also showed promising effect as part of the treatment regimen in children with cystic fibrosis.

Dysmenorrhea: There are two types of dysmenorrhea, namely primary dysmenorrhea that has no demonstrable pathology and the pain usually starts before or shortly after the period starts, usually lasting 8 to 72 hours; and secondary dysmenorrhea is associated with pelvic pathology (e.g., endometriosis or fibrosis), and usually occurs later in life. Prostaglandins (prostaglandin F₂ α and prostaglandin E₂) are responsible for smooth muscle spasms and local inflammation presents dysmenorrhea and therefore ibuprofen appears to be a suitable therapeutic agent.

Toothache: Ibuprofen has been shown to be effective for pain associated with third molars and their surgical removal. Standard doses of 800-1200 mg/day have been shown to be superior in providing postsurgical analgesia after third molar removal compared to placebo and equal or better compared to acetaminophen; however, this high dose can cause serious unwanted adverse effects. The use of ibuprofen as a preemptive medication in dental surgeries has shown promise (Pereira et al. 2020; Santos et al. 2021; Santos et al. 2022).

Headache and Migraine: Studies show that ibuprofen is an effective medication for relieving headaches and migraines in children and young adults. The therapeutic effects are believed to be due to the action of ibuprofen on platelet activation, thromboxane A₂ production and local vascular effects. Efficacy is aided by the drug's ability to enter the central nervous system, resulting in local accumulation and central analgesia (Kokki et al. 2007).

Soft Tissue Pain: Ibuprofen has been shown to be superior compared to placebo and other non-narcotic analgesics for the relief of pain associated with sports injuries and other minor soft tissue injuries. Doses of up to 1200 mg/day are adequate for most soft tissue pain, but occasionally higher antiarthritic doses of up to 2400 mg/day are used for therapeutic benefit.

Fever in Children: Fever is a common complaint in children and the goal of treatment is to reduce the child's temperature. Ibuprofen has proven superior to placebo and

acetaminophen and is as effective as the ibuprofen-paracetamol combination (Tan et al. 2020).

Cystic Fibrosis: Although ibuprofen is not primarily used for cystic fibrosis therapy, it does play a potential role in reducing inflammation during the treatment of infections due to its synergistic action with antibiotics. A slower rate of respiratory decline compared to placebo was observed in children younger than 13 years of age who were given ibuprofen orally for four years. More recent studies such as the one by Shah et al. (2018) demonstrated a possible antimicrobial action of ibuprofen against Gram - pathogens associated with cystic fibrosis.

iii. Mechanism of Action

According to Hiřovská, Jendřelovský and Fedoročko (2015), the primary mechanism of ibuprofen, an NSAID, is through the inhibition of prostaglandin precursors. Upon a physiological or pathological stimulus, membrane phospholipids release arachidonic acid due to the enzyme phospholipase A2. The arachidonic acid then passes through one of three different enzymatic pathways: cyclooxygenase (COX), lipoxygenase (LOX), and cytochrome P450 (CYP450). The cyclooxygenase pathway converts arachidonic acid into prostaglandins, prostacyclins, and thromboxanes: the lipoxygenase pathway produces hydroxyeicosatetranoic acids (HETEs), leukotrienes, and lipoxins from arachidonic acid metabolism. Finally, arachidonic acid is converted to HETEs and epoxyeicosatrienoic acids (EET) via the cytochrome P450 pathway.

All these metabolic pathways create products called eicosanoids, which are molecules involved in the intercellular and intracellular signaling processes of a variety of physiological processes, acting on transport proteins, platelet aggregation and cell proliferation, on the regulation of smooth muscle tone and vascular permeability. As in the case of products of the cyclooxygenase pathway, eicosanoids are also involved in autoimmunity, angiogenesis, inflammation, and cancer development (Huang et al. 2021; Harizi et al. 2008).

According to Wallace (2008), NSAIDs can initiate or potentiate several potentially toxic effects in the gastrointestinal tract. The property common to all those capable of causing harm is the ability to inhibit prostaglandin synthesis. Prostaglandins play an important role in protecting the gastric mucosa, maintaining mucosal blood flow, and

secreting bicarbonate and mucus. It also acts in the maintenance of a protective waxy hydrophobic surface layer of epithelial and endothelial cells, possibly as a result of the dilution of permeable fluids. In addition, prostaglandins also appear to coordinate the secretion of epithelial cells.

Thus, inhibition of prostaglandin synthesis may predispose to gastric mucosal injury by various agents, including acid, bile salts, and antigens, although probably by different mechanisms. By limiting prostaglandin synthesis, NSAIDs override these reactions to such stimuli (Rainsford, 1999a; Seager and Hawkey, 2001).

Relative to current ibuprofen indications, the cyclooxygenase pathway plays a prominent role. There are three distinct isoforms in the COX pathway: COX-1 (PGH synthase), COX-2 and COX-3. COX-1 is a constitutionally expressed isoform, with relatively stable levels in reaction to most physiological or pathological stimuli. In contrast, COX-2 expression is highly inducible by mitogenic and inflammatory stimuli such as transforming growth factor, fibroblast growth factor, vascular endothelial growth factor, and tumor necrosis factors. In relation to the COX-3 isoform, little is known, requiring further studies on its constitution and action.

According to Ngo and Bajaj (2021), both enzymes contain an active catalytic site that consists of a long hairpin-shaped molecule that is approximately in the shape of a prostaglandin molecule that is responsible for the synthesis of the prostaglandin endoperoxide PGG₂ and PGH₂. When injury occurs, fatty acid precursors, such as arachidonic acid, are positioned in a lipophilic channel, where a tyrosine carries a heme radical. Both COX-1 and COX-2 have a polar arginine molecule in the middle of the channel, and non-selective inhibitors can block both enzymes at this point by simple steric hindrance.

There is a high degree of similarity between COX-1 and COX-2, where 61% of the amino acids are identical. Of particular importance is a substitution at position 523 between isoleucine (in COX-1) and valine (in COX-2). The difference of a single methyl group is enough to create extra space on the active site. It is at this site that rofecoxib, celecoxib and other related tricyclic enzymes appear to act. These drugs are too bulky to access COX-1 easily and therefore selectivity is achieved. Another difference is the substitution of leucine (in COX-2) for phenylalanine (in COX-1), which leads to greater

flexibility of active site coverage in COX-2. It is possible that chemically different drugs such as meloxicam could work here. (Seager and Hawkey, 2001; Nagano et al. 2021).

Hilfovská, Jendželovský and Fedoročko (2015) and Schwier (2016) demonstrated that inhibition of the COX-1 and COX-2 pathways decreases the expression of prostaglandin precursors; this, in turn, decreases the degree of cellular response to pathological or physiological stimuli. It is through this mechanism that non-selective NSAIDs such as ibuprofen derive their analgesic, antipyretic and anti-inflammatory properties. Specifically, for ibuprofen, COX-1 is inhibited approximately 2.5 times more potently than COX-2, which suggests implications for much research on the comparative effectiveness of selective COX-2 inhibitors in treating diseases normally treated with ibuprofen.

iv. Dosages

Rainsford (1999) explains that the initially recommended prescription for the treatment of muscular disorders, skeletal pain and inflammation, as well as other painful conditions was a dose of up to 2400 mg/day. Initially, the drug was used in low doses ranging from 400 to 1,200 mg/day. From there, a cautious scaling of doses was observed, reaching a dosage of 2,400 mg/day. The emphasis on the cautious use of ibuprofen was one of the hallmarks of its early success and the growing confidence that it was a safe drug.

Currently marketed ibuprofen formulations are indicated for dosing between 4-6 hours in various stages of pain. There are times, however, when a prolonged duration of analgesia may be desired, such as in the treatment of pain associated with osteoarthritis, low back pain, or dysmenorrhea. In such cases, an analgesic that provides long-term pain relief may provide more consistent analgesia, helping to prevent re-emerging pain during the time that subsequent doses of standard ibuprofen are administered, absorbed, and exert their therapeutic effect (Legg et al. 2017).

According to Jones, Seymour and Hawkesford (1997), the basic pharmacokinetic properties of ibuprofen have been well studied. It is reported to be rapidly absorbed, with a mean serum peak between 1.5 and 2 hours, the drug being almost completely bound to plasma protein. Dose and serum area under curve (AUC) were found linearly

between 200 and 800 mg after single doses. Apparently, the serum half-life is approximately 2 hours.

In a clinical trial, where ibuprofen at dosages of 400 mg, 600 mg and 800 mg was compared with 400 mg of aluminum ibuprofen and placebo, Laska et al. 1986, found that aluminum ibuprofen produced less analgesia as well as lower serum levels compared to the same dose of ibuprofen. This was particularly apparent in the first 2 hours. It seems likely that the observed differences in analgesia are the result of the observed differences in serum levels. For ibuprofen, mean analgesic scores provide little or no evidence of a dose-response relationship between 400 and 800 mg in terms of clinical efficacy. In addition, a relatively high degree of variability was observed in the serum levels obtained from a dose of the drug. The distributions of serum levels for different doses overlapped considerably.

Another important point highlighted by Laska et al. 1986, is the individuality of each individual, which can lead to the variation of pharmacokinetic parameters, such as absorption metabolism, protein binding, volume of distribution or clearance. This may explain the individual variation in analgesic efficacy for a given dose. Furthermore, differences in formulation can directly influence the rate of absorption and, in turn, the clinical response. There was a clear and substantial linear relationship between serum ibuprofen levels and the degree of pain relief, particularly within the first 2 hours. While this strengthens the evidence for a correlation, one cannot help but wonder why this occurred. One explanation for this lies in the dissolution characteristics of the tablets.

This can be demonstrated by the study by Moghadamnia et al. (2019), who compared the pharmacokinetics of conventional ibuprofen tablet with that of ibuprofen in sodium alginate enteric-coated capsules. A higher concentration was observed in the group that received enteric-coated ibuprofen 4 h after administration. The serum ibuprofen concentration rapidly increased to the maximum level after 1 hour in the group receiving the regular tablet form and increased with enteric coating after 4 hours. Dissolution rates were determined in a phosphate-buffered medium at pH 7.2, with the tablet rotated in a basket at 150 rpm until 50% of the tablet was dissolved. The mean dissolution rate for the 400 mg tablet was 7 minutes at baseline ($n = 6$) and 12 minutes ($n = 2$) for the remaining tablets at the end of the study. The mean dissolution for the 600 mg tablet was 4 minutes ($n = 6$) before the study and 6 minutes ($n = 2$) at the end of the study. Although the difference is small and too few pills were analyzed to draw

a definitive conclusion, the data suggest that the 600 mg dose may have been more bioavailable than the pills used in the 400 and 800 mg groups. This would help explain the serum levels increased by 0.5 hours to 600mg.

Another extremely important point that cannot be overlooked is that ibuprofen, as a weak acid ($pK_a = 4.4$), is able to dissolve in an acidic pH medium. This property may have a key effect on plasma drug concentration. To increase the water solubility, the manufacture of salt forms of acidic drugs has been suggested as a practical method, which does not affect the bioavailability of the drug. Formulation of more soluble drug forms leads to a higher absorption rate, followed by an increased peak plasma concentration and a lower concentration rate, higher C max and lower T max, causing a preservation of the other pharmacokinetic processes. In general, if the objective is to control intense pain more quickly and efficiently, formulations with a faster absorption rate are suggested, where decreasing drug concentration or delaying drug release may fail in the treatment process. Conversely, the use of rapidly absorbed formulations in patients with gastrointestinal problems may exacerbate pain, which may contribute to treatment failure (Moghadamnia et al. 2019).

Lawati and Jamali (2016), in a meta-analysis, compared the onset of action and the efficacy of Ibuprofen Liquigel to Solid Tablets and concluded from the available clinical data that both solid tablets and ibuprofen liquigel are effective in controlling moderate pain. The evidence, although moderate, suggests a faster onset of analgesia for liquigel compared to tablets. This information is timely given the increasing number of softgel products appearing on the market.

Despite advances in pathophysiology, pain management, and the development of new drugs and treatment methods, many patients still suffer from post-surgical pain. Proper management of postoperative pain is an important factor in recovery, decreasing hospital stay and related conditions. The idea that postoperative pain can be controlled preoperatively as preventive analgesia has gained more importance recently. The preemptive administration of intravenous (IV) ibuprofen aims to estimate its effect on postoperative pain, which is hypothesized to reduce postoperative pain and analgesic requirements in various surgical procedures (Ahiskalioglu et al. 2017; Karaaslan et al. 2019; Martínez et al. 2016; Pereira et al. 2020; Silva et al. 20210).

Acute postoperative pain is an almost daily problem for healthcare professionals, reports Doleman et al. (2021). According to these authors, in recent years, complicated surgical interventions have increased and important advances in anesthetic techniques have come to provide a reduction in postoperative pain. Recently, anesthesia management is becoming increasingly important in preoperative, intraoperative and postoperative patient care. Clinicians generally prefer to use conventional anesthetic and analgesic methods as a multimodal approach to analgesia and aim to act at different sites in the pain pathways. Therefore, both preventive and preventive analgesia can be provided where their aim is to decrease and prevent pathological modulation of acute pain centrally and thus inhibit the development of chronic pain. Anesthesiologists and surgeons must work together in the perioperative process to ensure successful patient management and be able to manage postoperative pain.

As an example of the use of NSAIDs in pain prevention, Mattos-Pereira et al. (2021), in a meta-analysis, evaluated the effectiveness of preemptive analgesia in dental implant surgery in randomized clinical trials. A comparison was made between preemptive medication and placebo in the periods of 1-2 h and 6-8 h after the surgical procedure. This meta-analysis divided the studies into subgroups according to drug type. Analysis in the 1-2 h subgroup showed that preemptive medication had a small effect on pain reduction compared to placebo. However, ibuprofen has been shown to have a great effect on preemptive use. When analyzing the period of 6-8 hours, ibuprofen had a similar effect to piroxican, with both having a great effect over placebo.

In another meta-analysis, where the clinical efficacy of several analgesics in minimizing postoperative pain was evaluated, Khouly et al. (2021) showed that NSAIDs have a greater effect on postoperative pain in patients undergoing dental implant surgery than opioid analgesics.

Bahamman et al. (2017) observed that ibuprofen and dexamethasone obtained the same results for pain reduction, relief of edema and in the use of rescue medication, when preemptively administered in implant surgeries.

v. Ibuprofen in Addition to the Anti-Inflammatory Action

As described above, NSAIDs exert their effects by inhibiting the synthesis of prostanoids, particularly prostaglandin E₂ (PGE₂) by cyclooxygenase (COX) enzymes. By altering the balance of pro-inflammatory and anti-inflammatory mediators in the joint, it is hypothesized that they may affect the pathogenesis of OA. These effects, if any, are, however, controversial, as both potential benefits (eg, relief of joint inflammation and reduction of cartilage catabolism) and harm (eg, impairment of cartilage anabolism and radiographic destruction) joint) have been reported. Based on this hypothesis, studies on the effects of ibuprofen on gene expression in chondrocytes from patients with OA have been developed. Pemmari et al. (2021) studied the effects of ibuprofen on gene expression in chondrocytes from OA patients using NB sequencing. It was observed that ibuprofen did not induce statistically significant changes in chondrocyte transcriptome when cells were cultured in the absence of added cytokines. However, under inflammatory conditions (when cells were exposed to the OA-related cytokine interleukin (IL)-1 β), 51 genes were up-regulated and 42 down-regulated by ibuprofen with a fold shift > 1.5 in either direction. The up-regulated genes included anti-inflammatory factors and genes associated with cell adhesion, while several mediators of inflammation were among the down-regulated genes. Ibuprofen has been shown to have modulatory effects on inflammation-related pathways, such as integrin, IL-8, ERK/MAPK, and cAMP-mediated signaling pathways. These findings support the hypothesis that ibuprofen can change the chondrocyte transcriptome to the anti-inflammatory phenotype in environments with inflammation. These findings may pave the way for further research to prove the effects of ibuprofen on the transcriptome of OA primary chondrocytes.

COX-2, in addition to its well-known roles in inflammation, is also constitutively expressed during early carcinogenesis. Liu et al. (2017), observed that higher levels of COX-2 were demonstrated in several human tumors, including breast, colorectal, esophagus, lung, and pancreas. Current findings on COX-2 and its various effects on cells suggest that the anticancer effects of NSAIDs such as ibuprofen are due to COX-2 inhibition. Although the anticancer effects of COX-2 inhibition are well documented, there are still questions about the exact mechanism by which this occurs. Furthermore, there is also evidence that other pathways may be involved in the anticancer and antitumor effects of NSAIDs, due to reduced cell survival by NSAIDs in both COX-2

overexpressing malignant cells and COX-2 deficient malignant cells (Harris, Beebe and Alshafie, 2012).

Another important and very current point, which has undergone several developments, is the relationship of NSAIDs, especially Ibuprofen, with COVID-19. Its use was quite common to minimize the symptoms of the disease, however, it was observed that some effects of the action of these drugs could favor SARS-CoV-2 (Robb et al. 2020).

According to Fang, Karakiulakis and Roth (2020), the coronaviruses that cause severe acute respiratory syndrome (SARS-CoV and SARS-CoV-2) bind to their target cells through the angiotensin-converting enzyme 2 (ACE2), which is expressed by epithelial cells of the lung, intestine, kidney, and blood vessels. ACE2 expression is substantially increased in patients with type 1 or type 2 diabetes who are treated with ACE inhibitors and type I angiotensin II receptor blockers (ARBs). Hypertension is also treated with ACE inhibitors and ARBs, which results in upregulation of ACE2. ACE2 can also be increased by thiazolidinediones and ibuprofen.

According to Chen et al 2021, several hypotheses may associate the use of NSAIDs and the pathogenesis of COVID-19. It has been suggested that the use of NSAIDs may up-regulate angiotensin-converting enzyme 2 (ACE2), the cell entry receptor for SARS-CoV-2 and increase the risk of infection. Second, NSAIDs can directly affect the replication of SARS-CoV-2, as COX signaling has been shown to regulate the replication of other viruses, including the mouse coronavirus. Third, given their anti-inflammatory properties, NSAIDs can impair the immune response to SARS-CoV-2 and delay disease resolution or, alternatively, attenuate the cytokine storm associated with severe disease.

In a systematic review and meta-analysis, where only observational studies were evaluated, Moore et al 2021 did not find an excessive risk of positivity for SARS-CoV-2. In SARS-CoV-2 positive patients, exposure to NSAIDs was not associated with excessive risk of hospital admission, death, or serious outcomes. Of the 19 articles selected for the study, five studied the relationship between ibuprofen exposure and the risk of death, but the analysis did not prove an increased risk of death in patients with COVID-19 who used ibuprofen.

This result was in agreement with a prospective cohort that concluded that acute ibuprofen use was not associated with an increased risk of mortality relative to non-

use. Chronic use of NSAIDs was also not associated with an increased risk of mortality. Use of ibuprofen in acute inflammatory conditions was not associated with an increased risk of admission compared with non-users of NSAIDs. NSAID users did not have a significantly longer time to clinical improvement or length of stay (Esba et al. 2021).

The World Health Organization does not contraindicate the use of ibuprofen in patients with COVID-19 (WHO).

d. Conclusion

The analgesic property of ibuprofen is probably related to its anti-inflammatory effect given that mechanism of action occurs through the inhibition of prostaglandin synthesis. Despite being a drug in continuous use for more than half a century around the world, ibuprofen still arouses strong interest from the scientific community seeking further clarification of its pharmacokinetics. As part of the demonstration of its great pharmacotherapeutic potential, we are currently experiencing the exploration of its anti-inflammatory capacity and its immunomodulatory action as a potential tumor growth inhibition factor. There is no doubt that several lines of research can still be developed with this drug, expanding its potential beyond its anti-inflammatory activity.

e. References

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6.3 Premiações



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ANEXO A – Registro no PROSPERO

To enable PROSPERO to focus on COVID-19 submissions, this registration record has undergone basic automated checks for eligibility and is published exactly as submitted. PROSPERO has never provided peer review, and usual checking by the PROSPERO team does not endorse content. Therefore, automatically published records should be treated as any other PROSPERO registration. Further detail is provided [here](#).

Citation

Gustavo Pereira, Rafael Lima, Rachel Brant, Carolina Martins, Fernando Costa, Luís Otávio Cota.
Preemptive analgesia in dental implant surgery: systematic review and meta-analysis of clinical trials.
PROSPERO 2020 CRD42020168757 Available from:
https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42020168757

Review question

Do patients undergoing dental implant surgery and who received preemptive medication report less pain than patients who received preemptively placebo?

Searches

MEDLINE Ovid, Web of Science, PubMed, Scopus e LILACS

Types of study to be included

Clinical Trials

Condition or domain being studied

There is no well-defined protocol for the use of analgesics in dental implant surgery. One of the alternatives for reducing postoperative pain is the use of preemptive analgesia, which can decrease the amount of analgesics that the patient will take to reduce pain.

Participants/population

The following inclusion criteria were adopted: 1) good

systemic health status (ASA I or II); 2) absence of current pain or presence of any oral inflammatory process;

3) without analgesics in the 3 weeks prior to the study;

4) lack of continuous use of steroid and non-steroidal

anti-inflammatory drugs. The following were

excluded: pregnant or lactating women, use of some

type of medication that could affect the perception of

pain, history of allergy or intolerance to the drugs used in the research; and history of alcohol or drug abuse.

Intervention(s), exposure(s)

To evaluate postoperative pain in patients who have undergone dental implant surgery and who have used preemptive, analgesic or anti-inflammatory medication.

Comparator(s)/control

The control group is made up of patients who used a placebo

Context

Inclusion criteria:

clinical trials

use of preemptive medication

dental implant surgeries

Main outcome(s)

The postoperative pain is the most important result. Pain is measured immediately after completion and at predefined times, 1, 6, 8, 12, 24, 48, 72 hours after.

Measures of effect

None

Additional outcome(s)

Not applicable

Measures of effect

None

Data extraction (selection and coding)

Two independent reviewers (GHMP and RAB) were responsible for the selection of the articles and will be responsible for the analysis of the full text, data extraction and qualitative evaluation. When there is disagreement between the reviewers, the relevance and the possibility of inclusion will be discussed among the two reviewers to establish consensus.

Risk of bias (quality) assessment

The methodological quality of the included studies will be performed for Tools for Evaluating Strength and Quality of Evidence of the University of Ottawa.

Strategy for data synthesis

The average of each study will be evaluated, comparing the same time intervals in which the data were obtained. The averages of pain between each evaluated medication will also be compared.

Analysis of subgroups or subsets

Does not apply in this study

Contact details for further information

Gustavo Pereira
ghmattos75@gmail.com

Organisational affiliation of the review

Universidade Federal de Minas Gerais
<https://www.odonto.ufmg.br>

Review team members and their organisational affiliations

Mr Gustavo Pereira. Universidade Federal de Minas Gerais
Professor Rafael Lima. Universidade Federal de Minas Gerais
Mrs Rachel Brant. Universidade Federal de Minas Gerais
Professor Carolina Martins. Universidade Federal de Minas Gerais
Professor Fernando Costa. Universidade Federal de Minas Gerais
Professor Luís Otávio Cota. Universidade Federal de Minas Gerais

Type and method of review

Meta-analysis, Systematic review

Anticipated or actual start date

10 December 2019

Anticipated completion date

31 March 2020

Funding sources/sponsors

Faculty of Dentistry, Federal University of Minas Gerais

Conflicts of interest
Language

Inglés (there is not an English language summary)

Country

Brazil

Stage of review

Review Ongoing

Subject index terms status

Subject indexing assigned by CRD

Subject index terms

MeSH headings have not been applied to this record

Date of registration in PROSPERO

28 April 2020

Date of first submission

25 February 2020

Stage of review at time of this submission

Stage	Started	Completed
Preliminary searches	Yes	No
Piloting of the study selection process	Yes	No
Formal screening of search results against eligibility criteria	Yes	No
Data extraction	No	No
Risk of bias (quality) assessment	No	No
Data analysis	Yes	No

The record owner confirms that the information they have supplied for this submission is accurate and complete and they understand that deliberate provision of inaccurate information or omission of data may be construed as scientific misconduct.

The record owner confirms that they will update the status of the review when it is completed and will add publication details in due course.

Versions

28 April 2020

ANEXO B – Aprovação do comitê de ética em pesquisa

UNIVERSIDADE FEDERAL DE
MINAS GERAIS



PARECER CONSUBSTANCIADO DO CEP

DADOS DA EMENDA

Título da Pesquisa: Avaliação da Eficácia de Diferentes Protocolos de Analgesia Preemptiva em Cirurgias Odontológicas.

Pesquisador: Luís Otávio de Miranda Cota

Área Temática:

Versão: 3

CAAE: 83534618.5.0000.5149

Instituição Proponente: UNIVERSIDADE FEDERAL DE MINAS GERAIS

Patrocinador Principal: Financiamento Próprio

DADOS DO PARECER

Número do Parecer: 2.793.885

Apresentação do Projeto:

Esta emenda ao projeto de pesquisa solicita inclusão de participantes não previstos no desenho inicial, com inclusão de pacientes em cirurgia para implante dentário.

Objetivo da Pesquisa:

Conforme informado pelos pesquisadores:

"Objetivo Primário:

- Avaliar e comparar a eficácia de diferentes protocolos no controle da dor e em pós-operatórios em cirurgias odontológicas.

Objetivo Secundário:

- Avaliar e comparar a eficácia da administração do paracetamol, ibuprofeno; nimesulida; cetoprofeno e Dexametasona (medicamentos testes) no controle da dor pós-operatória em cirurgias a retalho periodontal e exodontia de 3ºs molares.- Avaliar a presença de edema nos grupos testes".

Avaliação dos Riscos e Benefícios:

Considera-se que os riscos e benefícios de inclusão de outro grupo de participantes (pacientes em cirurgia para implante dentário) são equivalentes aos grupos já previstos anteriormente. Prevalece, portanto, a redação dos riscos e benefícios do parecer de número 2.616.550.

Endereço: Av. Presidente Antônio Carlos, 6627 2º Ad SI 2005

Bairro: Unidade Administrativa II

CEP: 31.270-901

UF: MG

Município: BELO HORIZONTE

Telefone: (31)3409-4592

E-mail: coop@prpq.ufmg.br

**UNIVERSIDADE FEDERAL DE
MINAS GERAIS**



Continuação do Parecer: 2.793.885

Comentários e Considerações sobre a Pesquisa:

Equivalentes ao parecer de número 2.616.550.

Considerações sobre os Termos de apresentação obrigatória:

Considerados adequados no parecer de número 2.616.550.

Recomendações:

Sem maiores recomendações.

Conclusões ou Pendências e Lista de Inadequações:

Aprova-se a emenda ao projeto de pesquisa "Avaliação da Eficácia de Diferentes Protocolos de Analgesia Preemptiva em Cirurgias Odontológicas", do pesquisador responsável Luís Otávio de Miranda Cota.

Considerações Finais a critério do CEP:

Tendo em vista a legislação vigente (Resolução CNS 466/12), o COEP-UFMG recomenda aos Pesquisadores: comunicar toda e qualquer alteração do projeto e do termo de consentimento via emenda na Plataforma Brasil, informar imediatamente qualquer evento adverso ocorrido durante o desenvolvimento da pesquisa (via documental encaminhada em papel), apresentar na forma de notificação relatórios parciais do andamento do mesmo a cada 06 (seis) meses e ao término da pesquisa encaminhar a este Comitê um sumário dos resultados do projeto (relatório final).

Este parecer foi elaborado baseado nos documentos abaixo relacionados:

Tipo Documento	Arquivo	Postagem	Autor	Situação
Informações Básicas do Projeto	PB_INFORMAÇÕES_BÁSICAS_1173321_E1.pdf	14/07/2018 00:58:01		Aceito
Outros	Parecer_Mestrado_Assinado.pdf	13/07/2018 11:49:39	Luís Otávio de Miranda Cota	Aceito
Outros	projeto_mestrado.pdf	13/07/2018 11:46:19	Luís Otávio de Miranda Cota	Aceito
Outros	835346185parecerassinado.pdf	24/04/2018 10:13:32	Vivian Resende	Aceito
Outros	835346185parecerassinado.pdf	24/04/2018 10:13:32	Vivian Resende	Aceito
Outros	835346185aprovacaoassinada.pdf	24/04/2018 10:13:22	Vivian Resende	Aceito
Outros	835346185aprovacaoassinada.pdf	24/04/2018 10:13:22	Vivian Resende	Aceito
Outros	CARTA_RESPOSTA_AS_PENDENCIA S.pdf	16/04/2018 21:44:57	Luís Otávio de Miranda Cota	Aceito

Endereço: Av. Presidente Antônio Carlos, 6627 2º Ad SI 2005

Bairro: Unidade Administrativa II

CEP: 31.270-901

UF: MG

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UNIVERSIDADE FEDERAL DE
MINAS GERAIS



Continuação do Parecer: 2.793.885

TCLE / Termos de Assentimento / Justificativa de Ausência	TCLE.pdf	13/04/2018 16:46:54	Luís Otávio de Miranda Cota	Aceito
Cronograma	Cronograma.odt	19/01/2018 16:46:34	Luís Otávio de Miranda Cota	Aceito
Projeto Detalhado / Brochura Investigador	Projeto_de_doutorado.pdf	19/01/2018 16:34:22	Luís Otávio de Miranda Cota	Aceito
Parecer Anterior	Arquivo.pdf	19/01/2018 16:32:43	Luís Otávio de Miranda Cota	Aceito
Folha de Rosto	Folha_de_rostoassinada.pdf	19/01/2018 16:27:23	Luís Otávio de Miranda Cota	Aceito
Outros	835346185emendaassinad.pdf	01/08/2018 09:37:01	Vivian Resende	Aceito
Outros	835346185pareceremassinado.pdf	01/08/2018 09:37:11	Vivian Resende	Aceito

Situação do Parecer:

Aprovado

Necessita Apreciação da CONEP:

Não

BELO HORIZONTE, 01 de Agosto de 2018

Assinado por:
Vivian Resende
(Coordenador)

Endereço: Av. Presidente Antônio Carlos, 6627 2º Ad SI 2005

Bairro: Unidade Administrativa II **CEP:** 31.270-901

UF: MG **Município:** BELO HORIZONTE

Telefone: (31)3409-4592

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ANEXO C – Registro Brasileiro de Ensaios Clínicos (REBEC)



RBR-4b5dsg Evaluation of the efficiency of different schemes of Pre-operative Analgesia in Oral Surgeries

Data de registro: 21/12/2018 (cc/mm/yyyy)

Última data de aprovação: 22/09/2022 (dd/mm/yyyy)

Tipo de estudo:

Intervenções

Título científico:

en

Evaluation of the efficacy of different protocols of Preemptive Analgesia in Oral Surgeries

pt-br

Avaliação da eficácia de diferentes protocolos de Analgesia Preemptiva em Cirurgias Odontológicas

Identificação do ensaio

- Número do UTN: U1111-1223-0074
- Título público:

en

Evaluation of the efficiency of different schemes of Pre-operative Analgesia in Oral Surgeries

pt-br

Avaliação da eficiência de diferentes esquemas de Analgesia Pré-operatória em Cirurgias Odontológicas

• Identificadores secundários:

- 83534618.5.0000.5149

Orgão emissor: Plataforma Brasil

- 2.793.885

Orgão emissor: Comitê de Ética em Pesquisa da Universidade Federal de Minas Gerais – COEP UFMG

ANEXO D - Termo de consentimento livre e esclarecido

TERMO DE CONSENTIMENTO LIVRE E ESCLARECIDO

Projeto de pesquisa: "Avaliação da Eficácia de Diferentes Protocolos de Analgesia Preemptiva em implantes dentais".

Registro no Comitê de Ética em Pesquisa da UFMG: 83534618.5.0000.5149

Natureza da pesquisa: O Sr(a) está sendo convidado(a) a participar desta pesquisa que tem como finalidade avaliar e comparar a eficácia da administração de diferentes medicamentos pré-operatórios (Usados antes do procedimento) no controle da dor e edema (inchaço) pós-operatórios (Usados após o procedimento) em implantes dentais.

1. **Participantes da pesquisa:** Serão avaliados pacientes que necessitem de cirurgia para inserção de implantes, encaminhados para tratamento na Faculdade de Odontologia da Universidade Federal de Minas Gerais.
2. **Envolvimento na pesquisa:** Ao participar deste estudo, o Sr(a) receberá medicamentos comerciais (Cetoprofeno ou Ibuprofeno ou Paracetamol ou Nimesulida ou Dexametasona) de acordo com um sorteio, para tomar na sua cirurgia e permitirá que os pesquisadores façam um acompanhamento para ver se o Sr(a) está com dor ou apresentou inchaço, em diferentes momentos (1 h, 6 h, 12 h, 24 h, 48 h e 7d) após a cirurgia. O Sr(a) receberá ainda uma escala ilustrativa para que possa assinalar a presença e a intensidade da dor e inchaço, caso esteja presente. Lembramos que o Sr(a) tem liberdade de se recusar a participar em qualquer fase da pesquisa, sem qualquer prejuízo. Sempre que quiser poderá pedir mais informações sobre a pesquisa ao pesquisador e, se necessário, ao Comitê de Ética em Pesquisa - COEP UFMG.
3. **Sobre a coleta de dados:** Serão coletados dados clínicos e informações por meio de fichas padronizadas e escalas específicas. Esta coleta ocorrerá durante o atendimento clínico na Faculdade de Odontologia da UFMG.
4. **Riscos e desconforto:** De acordo com a Resolução 196/96 do Ministério da Saúde a participação nesta pesquisa oferece riscos considerados, maiores que o mínimo, uma vez que serão administrados alguns medicamentos por via oral e como informados na própria bula destes medicamentos, existe a possibilidade de ocorrência de efeitos adversos, desconfortos, hipersensibilidade e alergias. Caso isso ocorra, o Sr(a) deverá relatar ao pesquisador responsável e será suspensa imediatamente a medicação. De qualquer forma, os medicamentos serão escolhidos de acordo com a história de cada participante.
5. **Confidencialidade:** Todas as informações coletadas neste estudo são estritamente confidenciais. Somente os pesquisadores terão conhecimento dos dados pessoais. Na apresentação dos resultados dessa pesquisa, sua identificação será preservada.
6. **Benefícios:** Esperamos que este estudo traga informações relevantes sobre a analgesia preemptiva, principalmente no que diz respeito a um maior conforto para os pacientes frente as necessidade de intervenções cirúrgicas.
7. **Pagamento:** O Sr(a) não terá nenhum tipo de despesa para participar da pesquisa, bem como nada será pago por sua participação.

Após estes esclarecimentos, solicitamos o seu consentimento de forma livre para participar desta pesquisa. Portanto, preencha, por favor, os itens que seguem abaixo.

Nome do participante da pesquisa

Assinatura do participante da pesquisa

ANEXO E - Ficha de anamnese e periodontograma

Identificação do Indivíduo

Nome		Código de Identificação:	
Endereço:			
Telefones:	Idade:	Gênero:	Raça:
Nível socioeconômico (renda familiar em SM)			
Companheiro: () sim () não		Última visita ao dentista:	
Peso-Altura (IMC)		Doença sistêmica: () sim () não Qual?	
Tratamento periodontal nos últimos 12 meses: () não () sim			
Necessita de profilaxia antibiótica antes do tratamento: () não () sim			
Uso de antibiótico ou anti-inflamatório nos últimos 3 meses: () não () sim			
Diabetes: Sim ☐	Não ☐	Hipertensão: Sim ☐	Não ☐
Glicemia:			
Fumo: ☐ ex-fumante	Sim ☐	Não ☐	Quantidade
Halitose: Sim ☐	Não ☐		
Uso de álcool	Sim ☐	Não ☐	Quantidade
Tipo de bebida alcoólica	Frequência:		
Uso de antidepressivo / qual?	Frequência e tempo de uso		
Uso de ansiolítico/ qual?	Frequência e tempo de uso		
Higiene Bucal (escovação/fio dental)	Frequência		
Escovação (Frequência)	Uso de fio Dental () sim () não		
Uso de drogas ilícitas. Se sim quais?			

Índice de placa

FACULDADE DE ODONTOLOGIA DA UFPA

Índice de Placa de Silness & Loe:

Nome: _____ Reg. FOUFG Nº: _____

PESOS PARA EXAME:

0 - Ausência de placa.

0,5 - Presença de placa em pontos espessos, fora da junção dento-gengival.

1 - Presença de placa supra gengival, estendendo-se até 1/3 da superfície exposta do dente.

2 - Presença de placa supra gengival, cobrindo mais de 1/3 e menos de 2/3 da superfície exposta.

3 - Presença de placa supra gengival, cobrindo mais de 2/3 da superfície exposta do dente.

SIGNIFICADOS:

1- ÓTIMO = 0 a 16 %

2- BOM = 16 a 33%

3- MAU = 33 a 66%

4- PÉSSIMO = 66 a 100%

Data: _____

Dentes 18,17,16,15,14	Dentes 13,12,11,21,22,23	Dentes 24,25,26,27,28	Subtotal	Total	Percentual/ Significado
Dentes 48,47,46,45,44	Dentes 43,42,41,31,32,33	Dentes 34,35,36,37,38			

ANEXO F - Escala visual analógica

ESCALA VISUAL ANALÓGICA

NOME:

DATA DA CIRURGIA: / /

Horário do término da cirurgia: : horas



1) De acordo com a escala acima, identifique o seu nível de dor, nos seguintes momentos:

01 hora após o término da cirurgia:

06 horas após o término da cirurgia:

12 horas após o término da cirurgia:

24 horas após o término da cirurgia:

48 horas após o término da cirurgia:

72 horas após o término da cirurgia:

2) Caso seja necessário fazer uso da medicação analgésica de resgate, identifique o dia, a hora e o nível da dor no momento do uso do medicamento.

1º) Data: / / . Horário: : hs. Nível de dor:

2º) Data: / / . Horário: : hs. Nível de dor:

3º) Data: / / . Horário: : hs. Nível de dor:

4º) Data: / / . Horário: : hs. Nível de dor:

5º) Data: / / . Horário: : hs. Nível de dor: