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# PROTOCOLO PARA CONTROLE DE DOR PÓS-OPERATÓRIA EM CIRURGIA PERIODONTAL: REVISÃO SISTEMÁTICA E METANÁLISE

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Dissertação apresentada para obtenção do título de Mestre na Universidade Estadual de Ponta Grossa, Programa de Pós-graduação em Ciências da Saúde, área de concentração: Atenção Interdisciplinar em Saúde.

Orientadora: Profa. Dra. Márcia Thaís Pochapski

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Ponta Grossa, 17 de setembro de 2021.

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## RESUMO

A dor pós-operatória resulta da combinação de fenômenos cognitivos e fisiopatológicos. Dentro desta perspectiva, a percepção da dor é subjetiva, portanto seu controle deve levar em consideração a individualidade de cada paciente. Dentro das opções de manejo da dor, existem técnicas farmacológicas e não farmacológicas a fim de amenizar este desconforto pós-operatório, incluindo pós-operatório de cirurgia periodontal. A literatura apresenta ensaios com tratamentos específicos para controle da dor após cirurgia periodontal em consideração aos níveis leves a moderados de dor frequentemente apresentados pelos pacientes submetidos a este tipo de intervenção. Neste sentido, esta dissertação foi dividida entre dois capítulos. O primeiro capítulo refere-se a uma revisão de literatura, a qual retrata algumas possibilidades de intervenção analgésica, assim como a percepção da dor pós-operatória em cirurgia periodontal diante de fatores sócio-demográficos. O segundo capítulo inclui uma revisão sistemática e metanálise, com a investigação da efetividade dos protocolos de analgesia farmacológica pré e pós-operatória também diante de cirurgias periodontais. É consistente a aplicação de controle farmacológico, tanto via oral como via tópica, uso de laseterapia e também de barreiras mecânicas no pós-operatório de pacientes submetidos a cirurgia periodontal. Além disso, os protocolos de analgesia pré e pós-operatória tem efetividade semelhante se utilizados analgésicos e anti-inflamatórios via oral. Deste modo, este trabalho compila informações de aplicação prática e clínica, a fim de auxiliar o profissional cirurgião-dentista na escolha de métodos de analgesia pós-operatória em cirurgia periodontal.



**Palavras-chave:** Periodontia. Analgesia. Dor Pós-Operatória. Revisão Sistemática. Metanálise.

## ABSTRACT

Postoperative pain results from the combination of cognitive and pathophysiological phenomena. Under this perspective, the perception of pain is subjective so its control must take into account the individuality of each patient. Considering pain management options, there are pharmacological and non-pharmacological techniques to ease this postoperative discomfort, including postoperative pain after periodontal surgeries. Literature presents trials with specific treatments for pain control after periodontal surgery considering mild to moderate levels of pain often presented by patients undergoing this type of intervention. Hence, this dissertation was divided into two chapters. The first chapter refers to a literature review, which depicts some possibilities of analgesic intervention, as well as the perception of postoperative pain in periodontal surgery in the context of socio-demographic factors. The second chapter includes a systematic review and meta-analysis, investigating the effectiveness of preoperative and postoperative pharmacological analgesia protocols in periodontal surgery. The application of pharmacological control, both oral and topical, use of lasotherapy and also mechanical barriers in the postoperative period of patients undergoing periodontal surgery is current. In addition, pre- and postoperative analgesia protocols have similar effectiveness when oral analgesics and anti-inflammatory drugs are used. Thus, this paper compiles information of practical and clinical application in order to assist the dental surgeon in choosing methods of postoperative analgesia in periodontal surgery.



**Keywords:** Periodontics. Analgesia. Postoperative Pain. Systematic Review. Meta-Analysis.

## LISTA DE ILUSTRAÇÕES

## LISTA DE ABREVIATURAS E SIGLAS

| | |
|---|---|
| AAP | American Academy of Periodontology |
| BBO | Bibliografia Brasileira de Odontologia |
| CI | Confidence interval |
| EFP | European Federation of Periodontology |
| GRADE | Grading of Recommendations Assessment, Development and Evaluation |
| GRADEpro GDT | GRADEpro Guideline Development Tool |
| IADR | International Association for Dental Research |
| LILACS | Literatura Latino-Americana e do Caribe em Ciências da Saúde |
| MA | Meta-analysis |
| MEDLINE | Medical Literature Analysis and Retrieval System Online |
| MeSH | Medical Subject Headings |
| MPQ | McGill pain questionnaire |
| NPRS | Numerical pain rating scale |
| NRS | 101-point numerical rating scale |
| NSAID | Non-steroidal anti-inflammatory drug |
| OpenGrey | System for Information on Grey Literature in Europe |
| PRISMA | Preferred Reporting Items for Systematic Reviews and Meta-Analyses |
| RevMan | Review Manager |
| RCT | Randomized controlled trial |
| SAID | Steroidal anti-inflammatory drug |
| SciELO | Scientific Eletronic Library Online |
| SMD | Standardized mean difference |
| SR | Systematic review |
| VRS | Verbal rating scale |
| VRS-4 | Four-category verbal rating scale |
| VAS | Visual analogue scale |

## SUMÁRIO

## INTRODUÇÃO

A intenção do tratamento periodontal é restabelecer a saúde e proporcionar equilíbrio aos tecidos periodontais (ECHEVERRÍA; ECHEVERRÍA; CAFESSE; 2019). Embora a raspagem e o alisamento radicular sejam mais prevalentes, a cirurgia periodontal é um elemento relevante do tratamento periodontal (GRAZIANI *et al*., 2017). Ela permite o acesso à manipulação profissional, e também contribui para a formação de uma anatomia tecidual suscetível ao controle de biofilme através da higiene (GRAZIANI *et al*., 2018).

A cirurgia periodontal consiste em vários tipos de técnicas, que podem variar de acordo com as necessidades terapêuticas, desde o acesso para raspagem, cirurgia regenerativa e cirurgias plásticas, até aumento de coroa clínica e gengivectomia (ECHEVERRÍA; CAFESSE; 2019). Neste sentido, a cirurgia periodontal compreende a correção de tecidos moles e/ou duros, e, deste modo, os indivíduos podem desenvolver dor pós-operatória devido à injúria local. A cirurgia periodontal é uma experiência considerada dolorosa para muitos pacientes, afinal a dor pós-operatória pode ter intensidade agravada conforme tipo de técnica cirúrgica aplicada, idade do paciente e níveis de ansiedade pré-tratamento (CANAKÇI; CANAKÇI, 2007).

De modo geral, a sensação da dor conta com dois componentes: o fisiopatológico e o cognitivo. O componente fisiopatológico da dor pós-operatória pode ser categorizado em dor nociceptiva, inflamatória ou neuropática (HORN; KRAMER, 2018). Todas são mediadas pelas vias neurais aferentes: a dor nociceptiva é mediada por fibras nervosas em resposta a estímulos nocivos, como incisões no tecido operado. A dor inflamatória se apresenta na sensibilização das fibras nervosas através da liberação de mediadores inflamatórios. E a dor neuropática é o resultado da lesão direta de estruturas neuronais, nas quais há o aumento da sensibilidade axonal aos estímulos (HORN; KRAMER, 2018).

Fisiologicamente, os estímulos agressivos são transformados em potenciais de ação pelos receptores específicos da dor (nociceptores) das fibras nervosas aferentes. Desta forma, o estímulo doloroso é transmitido até o sistema nervoso central e interpretado no córtex cerebral (HORN; KRAMER, 2018).

Paralelamente, o componente cognitivo da dor pós-operatória se estabelece a partir da percepção do indivíduo, determinada por suas expectativas e

aprendizagem. Deste modo, as informações de experiências prévias são utilizadas na constituição de expectativas sobre percepção futura e para interpretar a entrada sensorial (WIECH, 2016). Assim sendo, uma avaliação pré-operatória completa aponta fatores -físicos e comportamentais- individuais do paciente que podem impactar na intensidade da dor pós-operatória e também na seleção de intervenções para o seu protocolo de analgesia (HORN; KRAMER, 2018).

Considerando que a dor pós-operatória é uma combinação singular de vias, o protocolo de analgesia pode envolver intervenções terapêuticas para a gestão da dor através de vários mecanismos de ação. Através de métodos farmacológicos, é possível atuar diretamente nos nociceptores ou ainda bloquear a produção de mediadores pró-inflamatórios (HORN; KRAMER, 2018). Além da intervenção farmacológica, reduzir ao máximo o risco de lesões e inflamação teciduais e preparações físicas, emocionais e psicológicas no período pré-operatório pode atenuar a intensidade da dor experienciada (GAN, 2017).

Frentes de ação analgésica diversificadas agem diferentemente diante de procedimentos cirúrgicos distintos. Afinal, cada procedimento cirúrgico não só resulta em diferente estado de dor, como em intensidade e local diferentes. A literatura desenvolveu o conceito de controle da dor pós-operatória específico para cada tipo de procedimento cirúrgico, na qual as evidências sobre a cirurgia correspondente são analisadas e, através de leitura crítica, é formulada uma abordagem de tratamento para o manejo da dor pós-operatória (POGATZKI-ZAHN; SEGELCKE; SCHUG, 2017).

Diante do exposto, o objetivo geral deste estudo foi elencar as intervenções analgésicas farmacológicas e não farmacológicas para controle da dor pós-operatória em cirurgia periodontal.

# 1 REVISÃO DE LITERATURA: INTERVENÇÕES ANALGÉSICAS PARA CONTROLE DA DOR PÓS-OPERATÓRIA EM CIRURGIA PERIODONTAL

A dor pós-operatória é um fenômeno subjetivo e variável, portanto alvo de investigações e questionamentos. No universo das intervenções cirúrgicas periodontais, a dor pós-operatória depende de fatores perioperatórios, porém o controle sobre o acometimento tecidual e a predição de dor são limitados (MEI *et al*., 2016).

Na semana subsequente à cirurgia periodontal, até 73% dos pacientes podem experienciar dor pós-operatória e, ainda na semana subsequente à cirurgia periodontal, até 21% deles podem identificar essa dor como severa (STRAHAN; GLENWRIGHT, 1967). E, mesmo que a maioria dos pacientes reporte dor leve em 51% dos casos (CURTIS; MCLAIN; HUTCHINSON, 1985), a dor pós-operatória pode influenciar a qualidade e a duração do período de recuperação pós-operatória, e, mais tarde, a qualidade de vida (GELMAN *et al*., 2018).

A fim de restabelecer o paciente em suas funções, é possível empregar recursos de analgesia com foco no período pós-operatório. A combinação de intervenções com início nos períodos pré-operatório, intra-operatório e pós-operatório é peça-chave na obtenção de resultados satisfatórios para o controle da dor no momento pós-cirúrgico (GELMAN *et al*., 2018). Os regimes de manejo de dor que incluem componentes multimodais tem eficácia analgésica comprovada, proporcionando ao paciente a oportunidade de receber um tratamento mais individualizado (CHOU *et al.*, 2016; MARIANO; SCHATMAN, 2019). Os componentes multimodais tem como objetivo atuar em diferentes frentes de tratamento, as quais são divididas em técnicas farmacológicas e não farmacológicas (MARIANO; SCHATMAN, 2019). Essas técnicas visam diferentes mecanismos de ação no sistema nervoso periférico e/ou central, e, desta maneira, podem apresentar efeitos sinérgicos e alívio mais eficaz da dor em comparação com intervenções de modalidade única (CHOU *et al*., 2016).

Dentro da área da Saúde, a analgesia multimodal é mais bem estabelecida e conta com uma diversidade de técnicas, como 1) estímulos físicos: estimulação elétrica transcutânea de nervos, acupuntura, massagem, compressas e imobilização; 2) cognitivo-comportamentais: imagens guiadas, relaxamento, hipnose, música e sugestões intra-operatórias sobre o paciente ter a capacidade de gerir e

lidar com o período pós-operatório; e 3) farmacológicos: analgésicos via oral, analgésicos via parenteral, anti-inflamatórios não-esteroidais, anticonvulsivantes, sedativos e infiltrações anestésicas locais (CHOU *et al*., 2016).

Paralelamente a estas técnicas, determinadas intervenções já adotadas para controle da dor na Odontologia podem ser aplicadas para reduzir a dor pós-operatória em cirurgias periodontais e a percepção da dor dentro deste contexto permanece em discussão. Essa percepção é abordada pela literatura através de vários panoramas diferentes e já foi associada a fatores sócio-demográficos, variações entre técnicas cirúrgicas e intervenções farmacológicas e não farmacológicas. Estas associações envolvem a variabilidade na percepção da dor e a resposta do paciente frente a intervenções, as quais culminam em medidas para controle da dor pós-operatória.

## 1.1 FATORES SÓCIO-DEMOGRÁFICOS

A percepção da dor é investigada dentre as variações de fatores sócio-demográficos da população a fim de definir se há predição de dor por alguma especificidade ou característica do sujeito.

A avaliação da relação entre sexo e a predição e memória de dor aguda após cirurgia periodontal apontou que homens esperavam experienciar mais, porém recordaram menos dor pós-operatória. Por conseguinte, o sexo teve efeito sobre a predição e memória de dor e as mulheres apresentaram maiores níveis de dor pós-operatória (ELI *et al.*, 2000). Consonante a isso, a ansiedade e a percepção da dor foram consideradas maiores nas mulheres para cirurgia periodontal com retalho e a ansiedade foi associada à percepção de maiores níveis de dor. No entanto, não houve associação entre idade e dor pós-operatória (AHMADI; KIAKOJORI; MOUDI, 2018).

Dissonante a esses resultados, o sexo não foi correlacionado positivamente à dor pós-operatória em cirurgias periodontais com retalho de Widman modificado. No entanto, o sexo feminino apresentou maiores taxas de ansiedade e não houve diferença estatisticamente significante entre fumantes e não fumantes quanto à dor pós-operatória (FARDAL; MCCULLOCH, 2012).

Comprovadamente, a dor pós-operatória já foi associada a dor pré-operatória, ansiedade, depressão e idade jovem (IP *et al*., 2009; YANG *et al*., 2019), no entanto, o sexo permanece como fator controverso nas evidências científicas.

## 1.2 TÉCNICAS CIRÚRGICAS

A percepção da dor também pode variar no pós-operatório de cirurgias periodontais com aplicações técnicas diferentes.

As cirurgias de retalho com preservação de papila com ou sem aplicação de matriz derivada do esmalte proporcionaram baixos níveis de dor pós-operatória aos pacientes, sem diferenças quanto ao desempenho clínico dessas técnicas (TONETTI *et al*., 2004). Dentre outras técnicas, envolvendo retalho de Widman modificado, retalho com ressecção óssea e gengivectomia, a cirurgia de retalho com ressecção óssea e gengivectomia foram consideradas as mais dolorosas pelos pacientes (CANAKÇI; CANAKÇI, 2007).

Para recobrimento radicular, a técnica do enxerto gengival livre e a da membrana de fibrina rica em plaquetas apresentaram resultados clínicos similares. No entanto, como a técnica com fibrina rica em plaquetas demonstrou menores níveis de dor pos-operatória, esta é uma alternativa para manter o conforto do paciente em comparação ao enxerto gengival livre (MUFTI *et al.*, 2017).

Além das técnicas cirúrgicas em si, a experiência cirúrgica prévia foi associada a ausência de dor ou dor pós-operatória leve. Por outro lado, houve uma relação diretamente proporcional da dor pós-operatória com a extensão cirúrgica, a duração da cirurgia e quantidade de anestesia em cirurgia plástica periodontal (MANHAES, 2018).

Alguns dos achados destes estudos convergem com os resultados da literatura, nos quais as técnicas cirúrgicas que envolvem maiores níveis de dor pós-operatória são cirurgia plástica periodontal, cirurgias mais complexas e extensas, com grande quantidade de anestesia (MEI *et al.*, 2016), curetagem de bolsas periodontais profundas associadas a gengivectomia, retalhos mucogengivais e recontorno ósseo (STRAHAN; GLENWRIGHT, 1967).

## 1.3 CONTROLE FARMACOLÓGICO VIA ORAL

O controle farmacológico é um componente significativo na percepção da dor pós-operatória. É recorrente que estudos ofereçam comparações entre medicamentos comumente utilizados na prática clínica odontológica.

Um deles é o analgésico paracetamol, que, na dose de 500mg, não apresentou diferença significativa entre horário fixo e por demanda quando empregado para controle da dor pós-operatória após cirurgia periodontal com retalho. No entanto, houve menor ingestão de analgésicos pelos pacientes que obedeceram ao horário fixo (PIARDI, 2017). O paracetamol também já foi combinado a outros componentes (325mg de paracetamol, 200mg de ibuprofeno e 40mg de cafeína) e comparado ao anti-inflamatório ibuprofeno, na dose de 400mg, para controle de dor pós-operatória em cirurgia periodontal com retalho. Como resultado, ambos os fármacos foram efetivos para o controle da dor, no entanto a combinação de paracetamol, ibuprofeno e cafeína superou o ibuprofeno isolado a partir do primeiro dia de pós-operatório (BABALOO *et al*., 2017).

Além dos analgésicos e anti-inflamatórios não-esteroidais, outra classe de medicamentos usada para manejo da dor é a de anti-inflamatórios esteroidais. A dexametasona 4mg proporcionou maior alívio da dor a partir de 3h do procedimento cirúrgico em comparação ao ibuprofeno 400mg em pacientes submetidos a recobrimento radicular associado a enxerto gengival livre (CASARIN *et al*., 2018).

Além destes estudos clínicos, uma revisão sistemática de 2020 (CAPOROSSI *et al*., 2020) comparou o efeito farmacológico de diferentes medicamentos no alívio da dor após cirurgia periodontal, considerando analgésicos e anti-inflamatórios. Devido à alta heterogeneidade entre os estudos, nenhum protocolo farmacológico fixo foi proposto. Os autores afirmaram que o paciente pode obter benefícios de vários esquemas farmacológicos para alívio da dor após cirurgias periodontais.

## 1.3 CONTROLE FARMACOLÓGICO ALTERNATIVO À VIA ORAL

Outra possibilidade, além da medicação via oral, é o controle farmacológico via tópica. Os enxaguantes bucais com princípios ativos fazem parte desta forma de administração e entram como coadjuvantes na analgesia pós-operatória.

Durante a comparação entre o enxaguante bucal cloridrato de benzidamina 0,15% e paracetamol 500mg com codeína 30mg via oral, o comprimido teve maior efeito sobre a redução de dor pós-operatória após cirurgia periodontal em sítios com periodontite mais avançada. Para periodontite moderada ou cirurgias sem manipulação óssea, não houve diferença entre o enxaguante e o comprimido. Dessa forma, este enxaguante pode ser recomendado para cirurgias com predição de dor pós-operatória moderada (KHOSHKHOONEJAD; KHORSAND; RASTGAR, 2004).

Outro fármaco utilizado para controle da dor foi o diclofenaco em forma de enxaguante 0,074% e comprimido 50mg via oral em pacientes submetidos a cirurgia periodontal. As duas formas farmacológicas, quando comparadas entre si, obtiveram reduções similares nos níveis da dor. Neste sentido, este enxaguante seria uma melhor alternativa para controle de dor, considerando os efeitos adversos do mesmo medicamento via oral (MISHRA *et al*., 2017).

Quando foi comparado a um enxaguante placebo, para dor pós-operatória em cirurgia similar, o enxaguante diclofenaco 0,074% obteve resultados significativamente melhores (AGARWAL *et al*., 2010). No entanto é importante salientar a importância de um controle positivo para controle da dor (como um medicamento via oral comprovadamente eficaz para tal fim).

Em concentração de 0,01%, o enxaguante bucal diclofenaco também demonstrou reduzir os níveis de dor pós-operatória em cirurgia periodontal quando comparado a um enxaguante placebo, mesmo com o uso de um anti-inflamatório não-esteroidal (ibuprofeno 400mg) via oral em concomitância (YAGHINI et al., 2011).

Outro fator perioperatório de grande significância para predição de dor pós-operatória em cirurgia periodontal é a anestesia local, que depende de fármacos que bloqueiem reversivelmente a condução nervosa, os anestésicos locais. Os anestésicos lidocaína 2% com epinefrina 1:100 000 e mepivacaína 2% com norepinefrina 1:100 000 tiveram ação clínica similar no controle da dor após cirurgia periodontal de acesso para realização de raspagem (STEFFENS *et al*., 2011). Por outro lado, ao se comparar lidocaína 2% com epinefrina 1:100.000 e bupivacaína 0,5% com epinefrina 1:200.000 após cirurgia periodontal, a percepção de dor foi diminuída e os pacientes consumiram uma quantidade menor de analgésicos quando receberam bupivacaína (LINDEN *et al*., 1986).

## 1.4 BARREIRAS MECÂNICAS

Parte da dor pós-operatória ocasionada em cirurgias periodontais são resultado da exposição do tecido conjuntivo.

Para cirurgias de aumento de coroa, o cimento cirúrgico pode atuar como barreira mecânica protegendo o tecido conjuntivo exposto. No entanto, os níveis de dor para o cimento cirúrgico são mais elevados em comparação ao placebo nos dois primeiros dias pós-operatórios (ANTONIAZZI *et al*., 2014). Para feridas após remoção de enxerto gengival livre do palato, o cimento cirúrgico também provoca maior sensação dolorosa mesmo com a associação a placas acrílicas quando comparado a uma membrana de látex natural (SPIN, 2018). No entanto o cimento cirúrgico é recomendado para cirurgias com exposição de tecido conjuntivo ou osso. Isso se deve a outras vantagens do cimento cirúrgico, como a prevenção de recessão gengival. Desta forma, o cimento pode ser empregado junto a um protocolo analgésico (ANTONIAZZI *et al*., 2014).

Outra possibilidade é a utilização de barreiras mecânicas que liberem fármacos ativos na ferida cirúrgica, os quais podem ser incluídos no controle farmacológico via tópica.

Pacientes que receberam o filme adesivo de cetorolaco 30mg após cirurgia periodontal de enxerto gengival livre apresentaram redução da dor em comparação ao filme placebo. Neste sentido, o filme adesivo de cetorolaco foi efetivo no controle da dor sem causar efeitos gastrointestinais, os quais são possíveis com a ingestão de anti-inflamatórios não-esteroidais via oral (AL-HEZAIMI *et al.*, 2011).

Por outro lado, filmes adesivos podem conter agentes naturais como a curcumina, substância ativa da cúrcuma, também conhecida como açafrão-da-terra. Para cirurgia periodontal de acesso para raspagem, o filme com a curcumina proporcionou menores níveis de dor em comparação ao filme placebo. Além disso, maior quantidade de medicamento de resgate foi consumido pelos pacientes vinculados ao placebo (ANIL; GUJJARI; VENKATESH, 2019).

## 1.5 LASER DE BAIXA POTÊNCIA

O laser de baixa potência tem efeitos analgésicos, anti-inflamatórios e também bioestimulador, e, com amplo uso na Odontologia, possui a capacidade de

minimizar a percepção dolorosa (E SILVA NETO *et al*., 2020), logo também pode ser considerado uma alternativa adjunta no manejo de dor após cirurgias periodontais (ZHAO; HU; ZHAO, 2020).

A aplicação do laser diodo após cirurgia periodontal de acesso para raspagem, quando comparada ao placebo, demonstrou redução da intensidade da dor apenas no sétimo dia de pós-operatório. No entanto, para os pacientes que receberam a fotobioestimulação, a ingestão analgésica foi reduzida (MOLINER, 2009). Resultados semelhantes foram encontrados para o laser de baixa potência após cirurgia periodontal com retalho. Novamente, a redução da intensidade da dor foi detectada apenas durante o sétimo dia do pós-operatório em comparação ao placebo (DOSHI; JAIN; HEGDE, 2014).

Em contrapartida, o laser de baixa potência após cirurgia de acesso para raspagem também ofereceu a pacientes, a partir do segundo dia de aplicação, menores níveis de dor e menor ingestão de analgésicos em comparação aos que não receberam o tratamento com o laser (HEIDARI *et al*., 2018).

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# 2 PROTOCOL FOR POSTOPERATIVE PAIN CONTROL IN PERIODONTAL SURGERY: A SYSTEMATIC REVIEW AND META-ANALYSIS
# PROTOCOLO PARA CONTROLE DE DOR PÓS-OPERATÓRIA EM CIRURGIA PERIODONTAL: REVISÃO SISTEMÁTICA E METANÁLISE

ABSTRACT: Postoperative pain in periodontal surgeries usually range from mild to moderate levels. The pain management after periodontal surgery has been discussed by recent evidence regarding drug classification, nonetheless analgesia protocols were not addressed. Thus the objective of this Systematic Review was to determine the most effective analgesia protocol for postoperative pain control in periodontal surgeries. This study was developed according to the PRISMA statement. Electronic databases and gray literature were investigated for trials using preoperative and postoperative analgesia protocols with oral anti-inflammatories and analgesics. We assessed the risk of bias and then submitted data to quantitative analysis. Publication bias and quality of evidence were also evaluated. A total of 2528 distinct trials were screened. Out of those, 29 were selected for the qualitative analysis and 11 were chosen for the meta-analysis, There was no significant difference between the analgesia protocols compared to placebo within two hours after the surgery. Both preoperative and postoperative protocols showed similar effectiveness in controlling postoperative pain. Under the limitations of this study, preoperative and postoperative analgesia protocols including oral anti-inflammatories and analgesics were considered effective for postoperative pain control after periodontal surgery.

KEYWORDS: Periodontal surgery; Systematic Review/ Meta-analysis; Pain management

## 2.1 INTRODUCTION

Postoperative pain after periodontal surgery can be experienced in different intensities and overall reach from mild to moderate levels and, more rarely, severe levels. [1, 2, 3] This intensities depend intimately on the invasiveness of the procedure: incision extension, duration of the procedure, tissue manipulation [1], bone removal [2], and amount of anesthesia. [3]

Although postoperative pain depends largely on perioperative factors, it is possible to employ pharmacological resources to mitigate this discomfort. A proper postoperative pain management offers better outcomes for the patient and prevents chronic postsurgical pain, morbidity and costs increasement and undermined quality of life. [4]

Furthermore, appropriate postoperative pain control ensures the patient's safety, allied to the determination of risks and benefits predicted by safety pharmacology. [5] Then the administration of a pain control protocol is optimized depending on the patient's requirements, even when they present with pre-existing systemic conditions or continuous medication intake.

Systematic reviews (SR) already approached oral postoperative pain control [6, 7] due to its clinical relevance and the wide variety of medicine and analgesia protocols. Yet these studies were specifically designed to third molar extraction surgeries.

Another SR [8] addressed the effect of different drugs on postoperative pain after periodontal surgery and demonstrated that various types of medication can lead to pain control. However no study has discussed whether the variation in timing of oral administration affects the postoperative pain intensity. Thus there is still no consensus on which analgesia protocol is more effective for this task.

The purpose of this SR was to establish the most effective analgesia protocol for postoperative pain control in periodontal surgeries.

## 2.2 MATERIAL AND METHODS

### 2.2.1 Protocol And Registration

This Systematic Review (SR) was registered in the International Prospective Register of Systematic Reviews (http://www.crd.york.ac.uk/PROSPERO - CRD42020215497) and elaborated according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. [9]

### 2.2.2 Eligibility Criteria

We searched for studies published up to May 2020 with no language restriction using the pre-established “PICOS” categories:

P (Population): patients submitted to periodontal surgery.

I (Intervention): preoperative or postoperative pharmacological regimens using anti-inflammatories or analgesics agents.

C (Comparison): placebo/control medicine (analgesic or anti-inflammatory agent).

O (Outcome): postoperative pain control.
S (Study Design): Randomized Clinical Trials (RCTs).

The question of this SR was: “Which pharmacological analgesic protocol is more efficient to control postoperative pain after periodontal surgery?”

Thus we included split-mouth and parallel RCTs which evaluated different drug protocols agents for postoperative pain control in patients of any age group that underwent periodontal surgery with at least one follow-up measurement.

Trials intervention groups should compare either analgesics, anti-inflammatories, and/or placebo in different drug regimens – preoperative or postoperative. Preoperative medication was considered as medication ingestion until 2 hours before the surgery and postoperative medication was considered as medication ingestion until 30 minutes after the surgery (before the anesthesia effect disappeared).

Studies selected should involve periodontal surgeries such as access for debridement (scaling and root planing), regenerative surgery, crown lengthening, and mucogingival surgery. Pain should be measured through any pain assessment tool: Numerical Pain Rating Scale (NPRS) such as NRS-101, the Visual Analogue Scale (VAS), the Verbal Rating Scale (VRS) such as the 4-point Verbal Rating Scale (VRS-4), MPQ (McGill Pain Questionnarie) and other non-validated tools.

We excluded trials: 1) if the participants took antibiotics preceding the experiment; 2) that reported only implants surgeries; 3) which results did not separate periodontal surgeries from other kinds of oral surgery; 4) which drugs were administered other than orally.

### 2.2.3 Information Sources

We searched eletronic databases (MEDLINE via PubMed, Cochrane Library, Embase, *Literatura Latino-Americana e do Caribe em Ciências da Saúde* [LILACS], *Bibliografia Brasileira de Odontologia* [BBO] and SciELO [Scientific Eletronic Library Online]) and citation databases (Scopus and Web of Science) (*Apêndice A*) in May 2020.

To identify relevant studies in gray literature (*Apêndice A*) we researched The System for Information on Grey Literature in Europe (OpenGrey) database, the WorldCat Library Catalog and Google for government webpages. Additionally,

conference proceedings of the International Association for Dental Research (IADR), American Academy of Periodontology (AAP) and European Federation of Periodontology (EFP) were consulted. Dissertations and theses were located through the *Capes Catálogo de Teses e Dissertaçõe*s and to find non-published and ongoing trials the following registries were utilized: ISRCTN Registry, International Clinical Trials Registry Platform, ClinicalTrials.gov, ReBEC and EU Clinical Trials Register.

### 2.2.4 Search

The search strategy was built on the “Population” and “Intervention” statements from the “PICOS” question. Categories “Comparison” and “Outcome” were not employed since they resulted in a very limited number of studies. Search strategies used a combination of controlled terms (Medical Subject Headings [MeSH]) and free keywords developed to each database based on the search strategy established for MEDLINE (Chart 1) with appropriate adjustments.

Chart 1 - Electronic database MEDLINE and search strategy

| **MEDLINE via PubMed** (27/May/2020) | |
|---|---|
| #1 (Periodontics[MeSH] OR "Oral Surgical Procedures"[Mesh] OR "Surgery, Oral"[Mesh] OR "Surgical Flaps"[Mesh] OR “Periodontal surgery”[Title/Abstract] OR “Periodontal surgical therapy”[Title/Abstract] OR “Periodontal surgical procedure”[Title/Abstract] OR “Periodontal plastic surgery”[Title/Abstract] OR “Gingival surgery”[Title/Abstract] OR “Gum surgery”[Title/Abstract] OR “Osseous surgery”[Title/Abstract] OR “Mucogingival surgery”[Title/Abstract] OR “Mucosal graft”[Title/Abstract] OR “Flap surgery”[Title/Abstract] OR “Apically repositioned flap”[Title/Abstract] OR “Repositioned flap”[Title/Abstract] OR “Modified Widman flap”[Title/Abstract] OR “Replaced flap”[Title/Abstract] OR “Open-flap debridement surgery”[Title/Abstract] OR “Laterally repositioned flap”[Title/Abstract] OR “Double papilla flap”[Title/Abstract] OR “Coronally advanced flap”[Title/Abstract] OR “Root coverage”[Title/Abstract] OR “Connective tissue graft”[Title/Abstract] OR “Pedicle grafts”[Title/Abstract] OR “Pocket elimination”[Title/Abstract] OR “Pocket reduction”[Title/Abstract] OR “Tuberosity reduction”[Title/Abstract] OR “Periodontal regeneration”[Title/Abstract] OR “Enamel matrix derivative”[Title/Abstract] OR “Crown lengthening”[Title/Abstract] OR “Distal wedge procedure”[Title/Abstract]) | #2 ("Anti-Inflammatory Agents"[Mesh] OR Analgesics[Mesh] OR Analgesia[Mesh])<br><br>**#1 AND #2** |

Source: The author

### 2.2.5 Study Selection

After the search, we downloaded the titles and abstracts to EndNote X6 software. We excluded duplicates (same article in more than one database) and then

manually selected the studies through the title and abstract according to the eligibility criteria. We consulted the full-text articles on whether the title and abstract were not enough in information. Two authors (SB and DH) independently performed the selection and any discrepancies were clarified through discussion.

### 2.2.6 Data Collection Process

We assessed the full-text version of the selected articles to extract data. Relevant information was collected using a customized form (*Apêndice B*). Data was compiled independently by three researchers (SB, DH, and JJS). Consensual decisions were made in cases of disagreement.

We contacted the authors by email or through the Research Gate platform in two attempts when the study did not provide all the necessary data. Studies with missing data were kept in the SR, however not considered in the quantitative analysis. We used WebPlotDigitizer Version 4.3 (https://automeris.io/WebPlotDigitizer, 2020) for data extraction when only figures or graphs were available.

### 2.2.7 Data Items

The variables extracted from the articles comprised 1) General characteristics (year of the study, country of origin, name of the authors, funding sources and if it was based on a university or a private facility); 2) Specific characteristics (study design, participants profile with gender and age, sample size, type of periodontal surgery, groups of intervention, medication used and dosage, amount and frequency of follow-up and evaluation tool); and 3) Primary (pain assessment) and secondary outcomes.

We classified every follow-up in postoperative hours. The first postoperative day morning was converted into 24 hours. The second postoperative day morning was converted into 48 hours. The third postoperative day morning was converted into 72 hours. If there were two follow-ups during the day, we considered intervals of 12 hours. If there were three follow-ups during the day, we considered intervals of 8 hours. And finally, if there were four follow-ups during the day, we considered intervals of 6 hours.

The reasons for study exclusions were separately recorded at this stage.

### 2.2.8 Risk Of Bias In Individual Studies

We evaluated the methodological quality of each study using the The Cochrane Collaboration's tool for assessing risk of bias in randomized trials. [10] The articles were rated based on the sequence generation, allocation concealment, blinding of the participants and examiners, blinding of outcome assessment, completeness of outcome data, selective outcome reporting, and other potential sources of bias. Each domain was scored following the directions of the Cochrane Handbook for Systematic Reviews of Interventions [11] as having low, unclear, or a high risk of bias at a study-level (*Apêndice C*).

Most studies did not fully describe the allocation concealment domain so this category was not retained for the study level risk of bias classification. If all the domains had low risk, the study was rated as low risk of bias. If any domain besides the allocation concealment had unclear risk, the study was qualified as unclear risk of bias. And if any domain besides the allocation concealment had high risk of bias, the study was rated as high risk of bias.

The patient blinding to the medication was considered a key domain when they evaluated their pain through a self-administered questionnaire. When the examiner applied the assessment, their blinding was considered a key domain. Adequate sequence generation was also considered as a key domain.

We assembled the graph using RevMan ([Computer program] Review Manager Version 5.4, The Cochrane Collaboration, 2020). We used the risk of bias to analyze the consistency of the results and not to disqualify studies for the SR. All the quality assessment was the responsibility of three independent reviewers (SB, DH, and JJS) and disagreements were solved through discussion.

### 2.2.9 Summary Measures And Synthesis Of Results

We analyzed quantitative data using RevMan ([Computer program] Review Manager Version 5.4, The Cochrane Collaboration, 2020). The intensity of pain was the outcome studied, characterized as a continuous variable, therefore we considered the average pain per hour and the standard deviation.

If the dispersion was presented as standard error, we converted it into standard deviation. If no dispersion data was available, we borrowed the SD from other studies with similar interventions for the SD imputation, according to the Cochrane handbook for systematic reviews of interventions [11] guidelines.

Since split-mouth trials presented periods of at least two weeks between the first and second interventions, it was considered that the medication doses of one intervention would not effect on the other. Therefore cross-over and parallel trials were combined.

Considering the variability of pain assessment scales (VAS, NRS-101, VRS-4, MPQ), it was necessary to standardize the results to a uniform measure. That way we summarized the outcomes using the Standardized Mean Difference (SMD) with a 95% confidence interval to combining the results. Fixed-effects models were tested, however since there was variability in medication, dosage and type of periodontal surgery, we decided for the random-effects models in all meta-analyses.

We conducted a subgroup analysis of the intensity of postoperative pain. We established the preoperative medication group parallel to the postoperative medication group within each follow-up interval and compared them to the placebo. The postoperative protocol was analyzed at 2 hours of follow-up and the subgroups involved NSAIDs and analgesics. The preoperative protocol was analyzed at 1, 2, 3, 4, 5, and 6 hours of follow-up, and the subgroups involved NSAIDs and SAIDs.

Some studies presented more than one intervention group of interest, therefore the control group was divided into equal parts for subgroup analysis purposes. [11]

We assessed heterogeneity through the $I^2$ statistics. Values until 25% were considered as low heterogeneity; from 25% to 50% were taken as moderate heterogeneity; from 50% to 75% were represented as substantial heterogeneity; and from 75% to 100% were assumed as considerable heterogeneity.

### 2.2.10 Publication Bias

We used the funnel plot technique as a qualitative method for analyzing the publication bias.

Statistical tests for funnel plot assymmetry should be used when there are at least ten studies included in the meta-analysis otherwise the power of tests is low. [11]

So these statistics were not applied to our data since we have a reduced number of studies in each meta-analysis group.

### 2.2.11 Quality Of Evidence

To assess the quality of evidence we employed the GRADE approach (Grading of Recommendations Assessment, Development and Evaluation) (https://www.gradeworkinggroup.org/) for every outcome. This tool allowed us to determine the strength of the evidence and the GRADEpro GDT (GRADEpro Guideline Development Tool [Software], Evidence Prime, Inc., 2020) was useful to assemble the GRADE evidence profile.

The tool consists of the following categories: risk of bias, inconsistency, indirectness, imprecision, and publication bias, each of which was judged as having “no limitations,” “serious limitations,” or “very serious limitations”. Thus the quality of the evidence could be downgraded one or two levels and we obtained the overall rating of the evidence as high, moderate, low, or very low certainty.

## 2.3 RESULTS

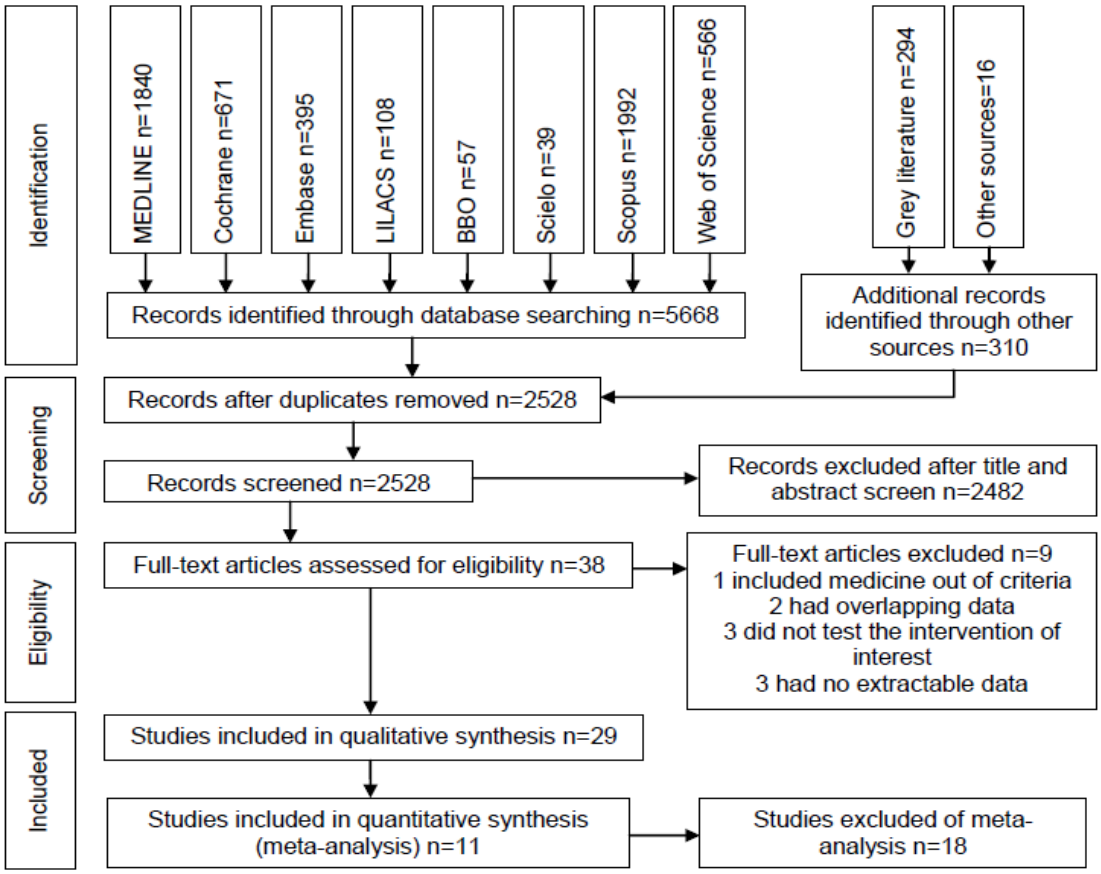
### 2.3.1 Study Selection

We led the initial search on May 18$^{th}$, 2020 with an update on July 25$^{th}$, 2020. We found 5668 studies originated from the scientific bases and 310 studies originated from additional sources. We remained with 2528 studies after duplicates were removed, and 46 studies after title and abstract screening.

Following that selection, we assessed 38 full-text versions and carefully reduced to 29 studies for the SR. [12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40] The reasons for exclusions in this stage are presented in *Apêndice D*.

A flow diagram illustrates the selection in Figure 1.

Figure 1 – Flow diagram of the systematic review according to PRISMA statements




Source: The author

## 2.3.2 Study Characteristics

The characteristics of the 29 studies selected were summarized in Chart 2. This SR yielded studies published from 1964 to 2019. The most prevalent study design was the parallel design [13, 15, 16, 17, 18, 19, 22, 23, 24, 25, 26, 28, 30, 31, 32, 35, 36, 37, 38, 39, 40], although eight used the cross-over split-mouth design. [12, 14, 20, 21, 27, 29, 33, 34]

The patients in these trials were in the range of 10 to 79 years old. Their mean age was 39.4 years old which reveals the preponderance of young adults. Three studies did not indicate the information about the age of their subjects. [20, 30, 32]

Some papers presented a higher prevalence of female participants [12, 16, 17, 18, 19, 22, 26, 27, 29, 35, 37, 38, 39], whereas others displayed a higher prevalence of male participants. [13, 14, 21, 25, 31, 33, 34, 36] One trial reported equal proportions between the female and male genders [32] and the remaining studies did not provide gender data. [15, 20, 23, 24, 28, 30, 40]

To control postoperative pain the investigators used the postoperative protocol [12, 13, 14, 15, 16, 17, 18, 21, 22, 28, 29, 32], the preoperative protocol [19, 20, 23, 24, 26, 27, 33, 34, 35, 36, 37, 40], both protocols [25] and occasionally compared these protocols. [30, 31, 38, 39]

Nonsteroidal anti-inflammatory drugs (NSAIDs) were employed in the majority of studies. [12, 14, 16, 18, 20, 21, 24, 25, 28, 31, 35, 37, 39] Steroidal anti-inflammatories (SAIDs) were used exclusively in only one study [36] just like opioids. [13] In the other trials, there were comparisons between NSAIDs and SAIDs [19, 23, 26, 27, 33, 34, 40], between NSAID and analgesics [15, 17, 29, 30, 38] and between analgesics. [22, 32]

Regarding the type of periodontal surgery approached, most trials reported mucoperiosteal flaps for scaling and root planning [12, 14, 17, 20, 21, 23, 27, 29, 30, 32, 33, 34, 35, 36, 37, 38, 39] and five of these described the possibility of bone involvement if necessary. [14, 30, 37, 38, 39] Three studies involved mucogingival surgery with palate graft. [19, 28, 40], two studies reported the modified Widman Flap technique [15, 18] and another two studies mentioned crown lengthening. [22, 26] A few studies presented diverse types of periodontal surgery [13, 25] and three did not mention the kind of periodontal surgery they performed. [16, 24, 31]

The pain was evaluated through several of validated and non-validated instruments. Fifteen studies [12, 14, 15, 20, 21, 22, 25, 26, 27, 30, 32, 33, 35, 36, 37] employed the 0-10 or the 0-100 visual analogue scale (VAS). The 101-point numeric rating scale (NRS-101) was applied in seven studies [19, 23, 27, 29, 33, 34, 40] and the four-category verbal rating scale (VRS-4) was used in eight studies. [19, 22, 23, 27, 28, 29, 34, 35]

As described previously, seven studies [22, 23, 27, 29, 33, 34, 35] employed a selection of more than one of the previous scales to assess the pain. Only one study implemented the McGill Pain Questionnaire [24] and another seven studies [13, 16, 17, 18, 31, 38, 39] had their own evaluation tool with pain parameters.

The postoperative follow-up had a considerable variation among the studies. The measurements of pain intensity ranged from immediately after the surgery to seven days after the surgery and the periods in between.

Only three studies specified a funding source. In the first case [13], both placebo capsules and the pharmacological capsules were supplied by the same company and no statistically significant differences were found between the groups. In the second case [17], the sponsor provided all the drugs used in the study (two active drugs and the placebo). And in the third case [25], the supporter contributed with the study, but they did not specify which drugs were supplied.

Chart 2 - Summary of the studies included in the Systematic Review (it continues)

| Study characteristics | | Population | | | Methods | | | Outcome (pain) |
|---|---|---|---|---|---|---|---|---|
| Author (Y) Country | Study design | n | Age (mean± SD or range) | No. of females | Groups (n) | Protocol | Pain assessment/ Postoperative follow-up | Main finding |
| Aghasizadeh et al. (2011) Iran | Split-mouth | 30 | 32.1±5.8 | 18 | G1: ibuprofen 400mg (1st surgery) and naproxen 250mg (2nd surgery) (n=15)<br>G2: the reverse regimen (n=15) | Postop | VAS/ 1, 2, 6 and 24h | Postoperative naproxen was more effective for open flap debridement |
| Berdon et al. (1964) England | Parallel | 100 | 10 to 59 | 46 | G1: placebo (n=50)<br>G2: placebo plus d-propoxyphene hydrochloride 65mg (n=50) | Postop | Own evaluation tool/ 48h | There was no difference between the groups (soft tissue surgery, vestibular deepening and open flap debridement) |
| Betancourt et al. (2004) USA | Split-mouth | 12 | 25 to 65 | 4 | G1: ibuprofen 400mg with hydrocodone 5mg (n=12)<br>G2: ibuprofen 400mg (n=12) | Postop | VAS/ after surgery and every 2h for 12h | Postoperative ibuprofen with hydrocodone was more effective for open flap debridement |
| Burgos-Quiróz et al. (2019) Peru | Parallel | 39 | 18 to 45 | NS | G1: paracetamol 500mg (n=19)<br>G2: ibuprofen 400mg (n=20) | Postop | VAS/ 2, 8 and 24h | Postoperative paracetamol and ibuprofen were effective for mucogingival surgery |
| Cooper et al. (1983) USA | Parallel | 176 | 45.2±NS | 102 | G1: suprofen 400mg (n=45)<br>G2: suprofen 200ng (n=44)<br>G3: aspirin 650mg (n=43)<br>G2: placebo (n=44) | Postop | Own evaluation tool/ after surgery, hourly for 6h | Postoperative suprofen in both doses were more effective for periodontal surgery involving soft and bone tissues |
| Gallardo; Rossi (1990) Chile | Parallel | 63 | 19 to 52 | 54 | G1: flurbiprofen 100mg (n=20)<br>G2: acetaminophen 500mg (n=21)<br>G3: placebo (n=22) | Postop | Own evaluation tool/ hourly for 3h | Postoperative flurbiprofen was more effective for open flap debridement |
| Gallardo; Rossi (1992) Chile | Parallel | 99 | 23 to 58 | 66 | G1: meclofenamate 100mg (n=34)<br>G2: aspirin 500mg (n=35)<br>G3: placebo (n=30) | Postop | Own evaluation tool/ hourly for 3h | Postoperative meclofenamate was more effective for open flap debridement |

Chart 2 - Summary of the studies included in the Systematic Review (continuation)

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Giorgetti et al. (2018) Brazil | Parallel | 20 | 43.4±15.1 44.3±12.6 | 13 | G1: ibuprofen 400mg (n=10) G2: dexamethasone 4mg (n=10) | Preop | NRS-101, VRS-4/ hourly for 8h, daily for 3 days and VAS/ 1st, 2nd, 3rd and 7th day | Dexamethasone was more effective for root coverage with connective tissue graft |
| Hungund; Thakkar (2011) India | Split-mouth | 40 | NS | NS | G1: ketorolac tromethamine 10mg (n=40) G2: placebo (n=40) | Preop | VAS/ after surgery | Preoperative ketorolac was more effective for open flap debridement |
| Karmkar et al. (2018) India | Split-mouth | 20 | 37.9±7.5 | 6 | G1: diclofenac 25mg with paracetamol 325mg (n=20) G2: diclofenac 50mg with paracetamol 325mg (n=20) | Postop | VAS/ twice a day for 3 days | Both doses of diclofenac were effective so the lowest one is recomended for open flap debridement |
| Kashefimehr et al. (2017) Iran | Parallel | 70 | 25 to 40 | 37 | G1: Novafen (acetaminophen 325mg, ibuprofen 200mg, caffeine 40mg) (n=35) G2: placebo (n=35) | Postop | VAS/ 30 min, 1, 3h and VRS-4/ daily for 3 days | Postoperative Novafen was more effective for crown lenghtening |
| Konuganti; Rangaraj; Elizabeth (2015) India | Parallel | 60 | 18 to 56 | NS | G1: placebo (n=20) G2: dexamethasone 8mg (n=20) G3: etoricoxib 120mg (n=20) | Preop | VRS-4/ hourly for 8h and NRS/ 3 times a day for 3 days | Preoperative etoricoxib and dexamethasone were effective for open flap debridement |
| Minutello et al. (1988) USA | Parallel | 44 | 18 to 60 | NS | G1: diflunisal 500 mg (NS) G2: placebo (NS) | Preop | MPQ/ 6, 6,5h | Preoperative diflunisal was more effective for periodontal surgery |
| Pearlman et al. (1997) Australia | Parallel | 130 | 18 to 79 | 62 | G1: ibuprofen 400mg as directed/ ibuprofen 400mg as required (n=56) G2: placebo as directed/ placebo as required (n=62) | Preop and postop | VAS/ 1$^{st}$ pain, 1, 2, 5, 9h, bedtime | As directed ibuprofen was more effective for open flap debridement, ostectomy, guided tissue regeneration and root resection surgeries |
| Peres et al. (2012) Brazil | Parallel | 28 | 34.4±8.4 33.0±10.9 | 22 | G1: lumiracoxib 400mg (n=14) G2: dexamethasone 4mg (n=14) | Preop | VAS/ 4, 8, 12 and 24h | Lumixacoxib and dexamethasone were effective for crown lengthening |

Chart 2 - Summary of the studies included in the Systematic Review (it continues)

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Pilatti et al. (2006) Brazil | Split-mouth | 20 | 27 to 53 | 11 | G1: placebo (n=20)<br>G2: dexamethasone 4mg (n=20)<br>G3: celecoxib 200mg (n=20) | Preop | VAS, NRS-101, VRS-4/ hourly for 8h; 3 times a day for 3 days | Dexamethasone and celecoxib were effective for open flap debridement |
| Popova; Mlachkova; Emilov (2008) Bulgaria | Parallel | 15 | 18 to 62 | NS | G1: Aulin (nimesulide) 100mg (n=8)<br>G2: ibuprofen 200mg (n=7) | Postop | VRS-4/ hourly for 8h, 3 times a day for 3 days | Aulin and ibuprofen were effective for free gingival graft surgery |
| Rashwan (2009) Egypt | Split-mouth | 15 | 37.9±7.5 | 11 | G1: acetaminophen 500mg with caffeine 30mg (n=15)<br>G2: ibuprofen 400mg (n=15) | Postop | NRS-101, VRS-4/ hourly for 8h, 3 times a day for 3 days | Acetaminophen with caffeine and ibuprofen were effective so the first one is recomended for open flap debridement |
| Reed et al. (1997) USA | Parallel | 5 | NS | NS | G1: preop ketoprofen 100mg and postop ketoprofen 50mg (n=2)<br>G2: preop placebo and postop acetaminophen 500mg with hydrocodone 5mg (n=3) | Preop vs. postop | VAS/ hourly for 8h | Postoperative acetaminophen with hydrocodone was more effective for open flap debridement |
| Salazar et al. (2002) Venezuela | Parallel | 45 | 24 to 45 | 20 | G1: preop nimesulide 100mg (n=15)<br>G2: postop nimesulide 100mg (n=15)<br>G3: placebo (n=15) | Preop vs. postop | Self report/ NS | Nimesulide was effective in both protocols for periodontal surgery |
| Seymour (1983) England | Parallel | 80 | NS | 40 | G1: paracetamol 500mg (n=20)<br>G2: paracetamol 1000mg (n=20)<br>G3: placebo (n=40) | Postop | VAS/ 2h, 8h, 3 times a day for 2 days | Paracetamol 1000mg was more effective for open flap surgery |
| Steffens; Santos; Pilatti (2010a) Brazil | Split-mouth | 6 | 38±7.8 | 2 | G1: placebo (n=6)<br>G2: dexamethasone 8mg (n=6)<br>G3: etoricoxib 90mg (n=6) | Preop | VAS, NRS-101/ hourly for 8h | Etoricoxib was effective for open flap debridement |
| Steffens et al. (2010b) Brazil | Split-mouth | 15 | 40±9.7 | 7 | G1: placebo (n=15)<br>G2: dexamethasone 8mg (n=15)<br>G3: etoricoxib 120mg (n=15) | Preop | NRS-101, VRS-4/ hourly for 8h, 3 times a day for 3 days | Etoricoxib and dexamethasone were effective for open flap debridement |

Chart 2 - Summary of the studies included in the Systematic Review (conclusion)

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Steffens; Santos; Pilatti (2011a) Brazil | Parallel | 56 | 38±8 | 30 | G1: celecoxib 200mg (n=19)<br>G2: etoricoxib 120mg (n=19)<br>G3: placebo (n=20) | Preop | VAS, VRS-4/ hourly for 8h, 3 times a day for 1 day | Celecoxib and etoricoxib were effective for open flap debridement |
| Steffens; Santos; Pilatti (2011b) Brazil | Parallel | 57 | 36.0±6.5<br>39.7±9.3<br>39.0±8.2 | 27 | G1: dexamethasone 4mg (n=19)<br>G2: dexamethasone 8mg (n=18)<br>G3: placebo (n=20) | Preop | VAS/ hourly for 8h | Dexamethasone 8mg was more effective for open flap debridement |
| Trombelli et al. (1996) Italy | Parallel | 43 | 44.0±8.9 | 30 | G1: ketorolac tromethamine 20mg (n=22)<br>G2: placebo (n=21) | Preop | VAS/ after surgery, hourly for 10h, 4 times a day for 2 days | Ketorolac tromethamine was effective for open flap debridement |
| Tucker; Smith; Adams (1996) USA | Parallel | 24 | NS | 13 | G1: preop etodolac 600mg (n=13)<br>G2: postop acetaminophen 500mg with hydrocodone 5mg (n= 11) | Preop vs. postop | Own evaluation tool/ hourly for 8h | Preoperative etodolac and postoperative acetaminophen with hydrocodone were effective for periodontal osseous surgeries |
| Vogel; Desjardins; Major (1992) USA | Parallel | 53 | 49.2±9.7<br>46.8±12.2<br>43.0±12.7 | 28 | G1: preop ibuprofen 600mg (n=19)<br>G2: postop ibuprofen 600mg (n=17)<br>G3: placebo (n=17) | Preop vs. postop | Own evaluation tool/ hourly for 8h | Both protocols were effective, but the postoperative had greater delay of pain for open flap and osseous recontouring surgery |
| Zardo et al. (2013) Brazil | Parallel | 60 | 36.6±9.6 | NS | G1: placebo capsule (n=20)<br>G2: dexamethasone 8mg (n=20)<br>G3: etoricoxib 90mg (n=20) | Preop | NRS-101/ hourly for 8h and 3 times a day for 3 days | Preoperative etoricoxib and dexamethasone were effective for mucogingival surgery |

Abbreviations: RCT= Randomized Controlled Trial; G= group; Postop= postoperative; Preop= preoperative, VAS= Visual Analogue Scale; h= hour/hours; USA= United States of America; NS= No specification; NRS-101= 101-Points Numerical Rating Scale;VRS-4= Four-point Verbal Rating Scale; MPQ= McGill Pain Questionnaire.

Source: The author

### 2.3.3 Risk Of Bias Assessment

The risk of bias summary, i.e. review authors' judgements about each risk of bias item for each included study is illustrated in Figure 2. The risk of bias graph, i.e. review authors' judgements about each risk of bias item presented as percentages across all included studies is represented in Figure 3.

The random sequence generation was somehow part of every research evaluated so that no study was classified as high risk of bias in this category.

Very few trials [13, 14, 26] presented sufficient information about the allocation concealment domain so most of them had been classified as unclear or high risk of bias. For this reason, this assessment criteria was not retained for the risk of bias classification at a study level.

Not many studies were categorized as having a high risk of bias in blinding of participants and personnel [15, 21, 23, 28, 31, 38] and blinding of outcome assessment domains. [15, 23, 31, 38]

Regarding the incomplete outcome data item, two researches were considered to have a high risk of bias [18, 23] and the selective reporting criteria had a single study with that same rating. [30]

Six trials were classified as high risk due to other biases, including the use of free self-reporting in pain assessment, the lack of homogeneity of the sample, very small sample size and uncertainty of outcomes.

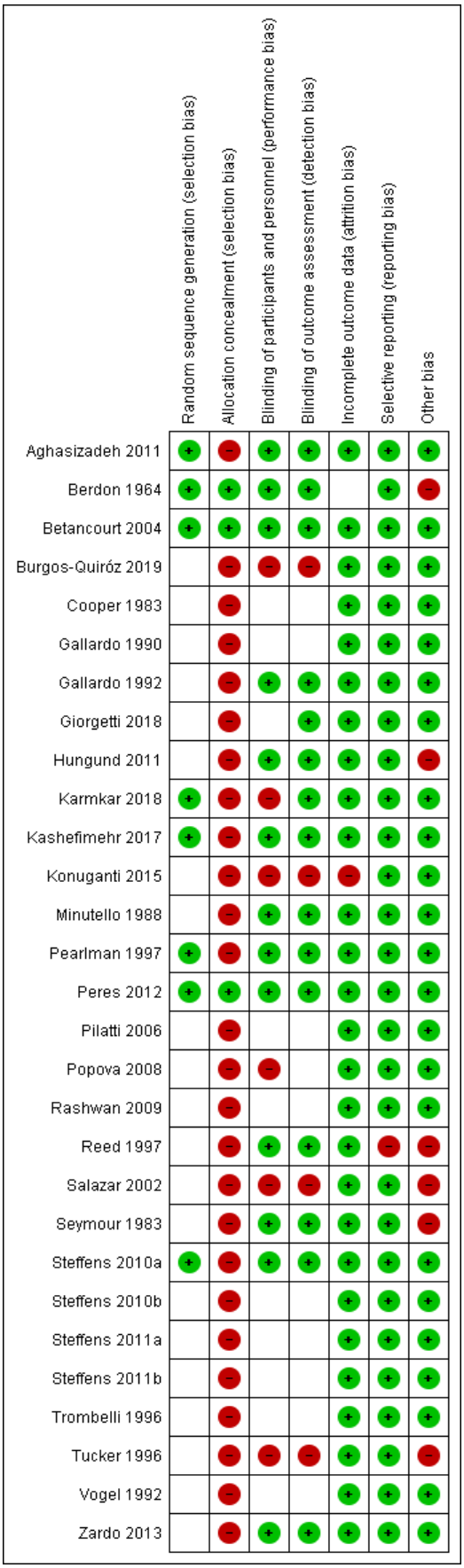
In conclusion, out of 29 surveys, eleven were considered to have a high risk of bias [13, 15, 18, 20, 21, 23, 28, 30, 31, 32, 38], while twelve were rated as having unclear risk of bias [16, 17, 19, 24, 27, 29, 34, 35, 36, 37, 39, 40] and six were deemed as having low risk of bias in terms of a study level. [12, 14, 22, 25, 26, 33]

### 2.3.4 Meta-Analysis

For the meta-analysis, we included the researches considering numerical data availability and grouping of similar pharmacological classes.

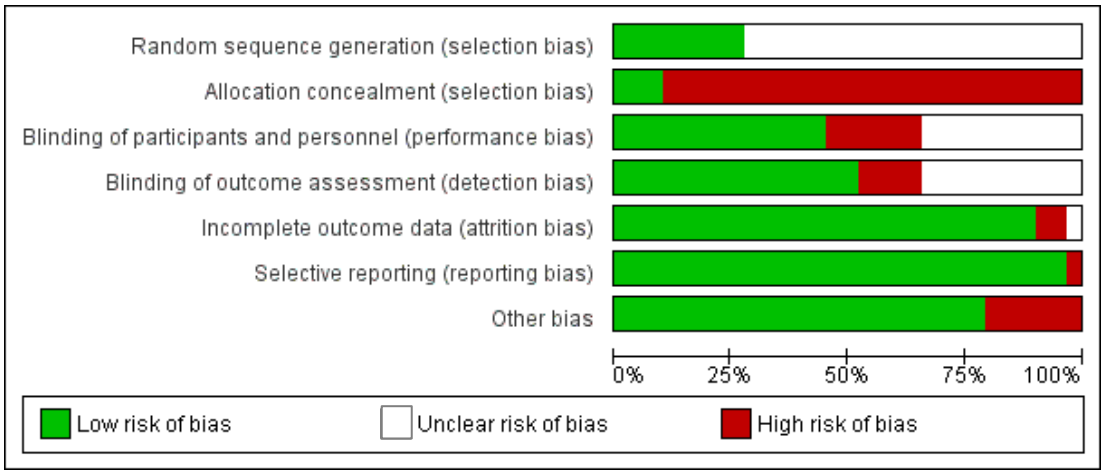
Three studies did not present extractable data [13, 16, 30], two were rated as high risk of bias in the blinding of outcome criteria [14, 38] and another two did not meet any

Figure 2 - Risk of bias summary




Source: The author

Figure 3 – Risk of bias graph




Source: The author

of these requirements. [23, 31] No study was left out of the analysis due to the random sequence generation item.

Only one trial combined the protocols and applied them to all intervention groups. [25] Further studies did not involve placebo comparison. [12, 15, 19, 21, 26, 28, 29] And another three studies presented diverging periods of follow-up. [20, 22, 24] Consequently, these studies were discarded from the meta-analysis as well.

That way we remained with eleven studies in the meta-analysis. [17, 18, 27, 32, 33, 34, 35, 36, 37, 39, 40]

### 2.3.5 Pain Intensity In Postoperative Protocol

Out of 270 patients, 161 were from the intervention group and 109 were from the placebo group. Both intervention subgroups (with analgesics and NSAIDs) presented lower pain intensity compared to the placebo with statistically significant differences ($p<.00001$). The overall SMD was -0.77 [95% CI -1.03, -0.51] and we did not detect heterogeneity in the data ($p=.42$; $I^2=0\%$) (Figure 4).

### 2.3.6 Pain Intensity In Preoperative Protocol

Out of 375 patients, 238 were from the intervention group (with SAIDs and NSAIDs) and 137 were from the placebo group for all preemptive protocol analyses.

2.3.6.1 One Hour Of Follow-Up

The intervention group was more efficient to control pain intensity with statistically significant differences compared to the placebo group (p=.003). The SMD was -0.33 [95% CI -0.54, -0.11]. There was no heterogeneity between the studies (p=.85; $I^2$=0%) (Figure 5).

2.3.6.2 Two Hours Of Follow-Up

Both intervention subgroups provided more pain control than the placebo and there were statistically significant differences between the groups (p<.00001). The general SMD was -0.52 [95% CI -0.74, -0.30] and we did not identify any heterogeneity in the trials (p=.88; $I^2$=0%) (Figure 6).

2.3.6.3 Three Hours Of Follow-Up

Similarly, the intervention subgroups presented less pain intensity than the placebo with statistically significant differences between the intervention and placebo groups (p<.00001). The SMD was -0.89 [95% CI -1.11, -0.66]. We did not find any heterogeneity between the studies (p=.79; $I^2$=0%) (Figure 7).

2.3.6.4 Four Hours Of Follow-Up

Both intervention subgroups provided more pain control than the placebo and there were statistically significant differences between the groups (p<.00001). The overall SMD was -0.81 [95% CI -1.03, -0.58]. Heterogeneity was not detected in the data (p=.57; $I^2$=0%) (Figure 8).

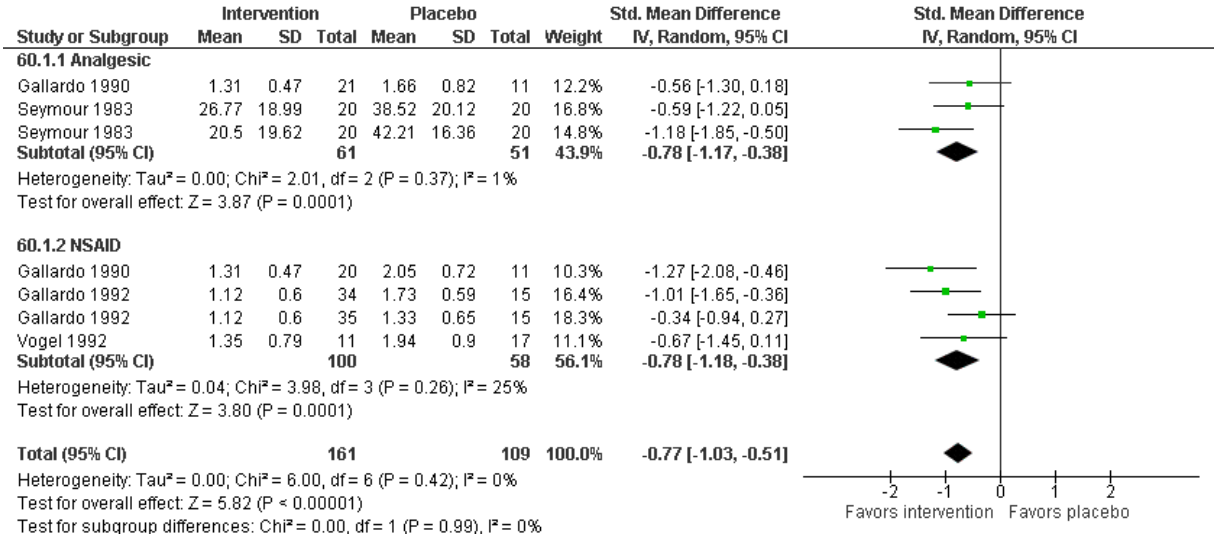
2.3.6.5 Five Hours Of Follow-Up

The pain intensity was lower in the intervention subgroups compared to the placebo. There were statistically significant differences between these groups (p<.00001). The general SMD was -0.74 [95% CI -0.96, -0.52] and we did not identify any heterogeneity between the studies (p=.72; $I^2$=0%) (Figure 9).

### 2.3.6.6 Six Hours Of Follow-Up

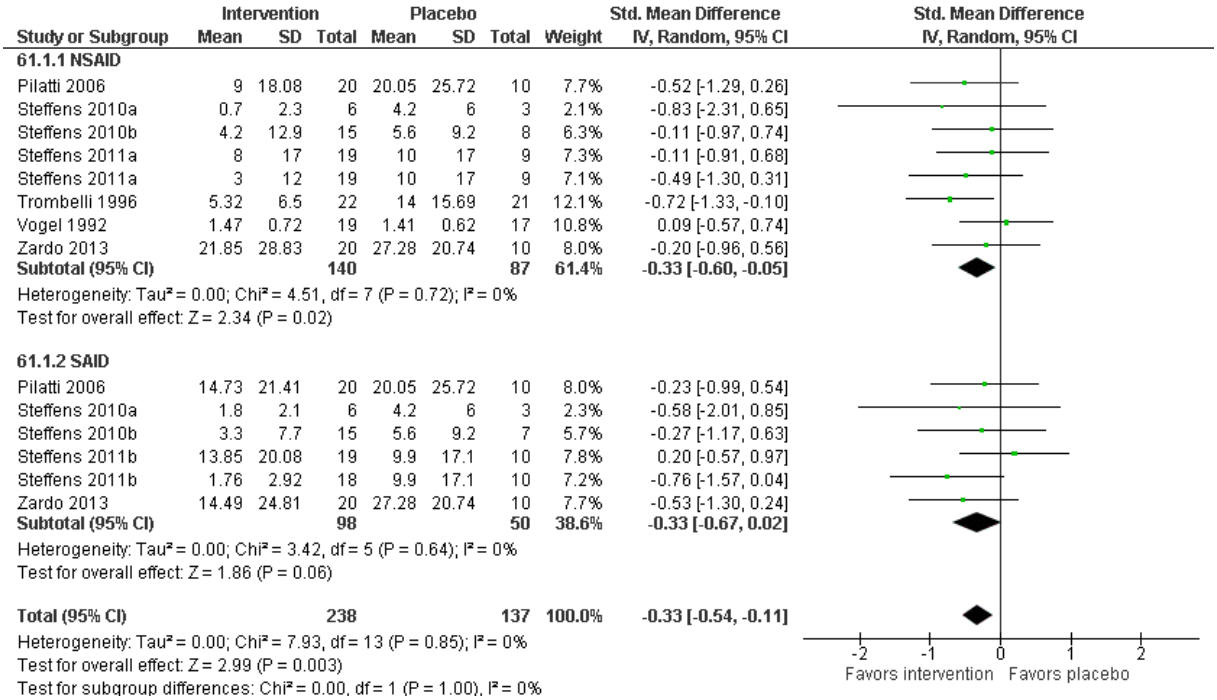
The intervention group was more efficient to control pain intensity with statistically significant differences compared to the placebo group (p=.00001). The overall SMD was -0.59 [95% CI -0.79, -0.40] and heterogeneity was not found in the data (p=.93; $I^2$=0%) (Figure 10).

Figure 4 – Forest plot of the intensity of pain in postoperative protocol at two hours of follow-up



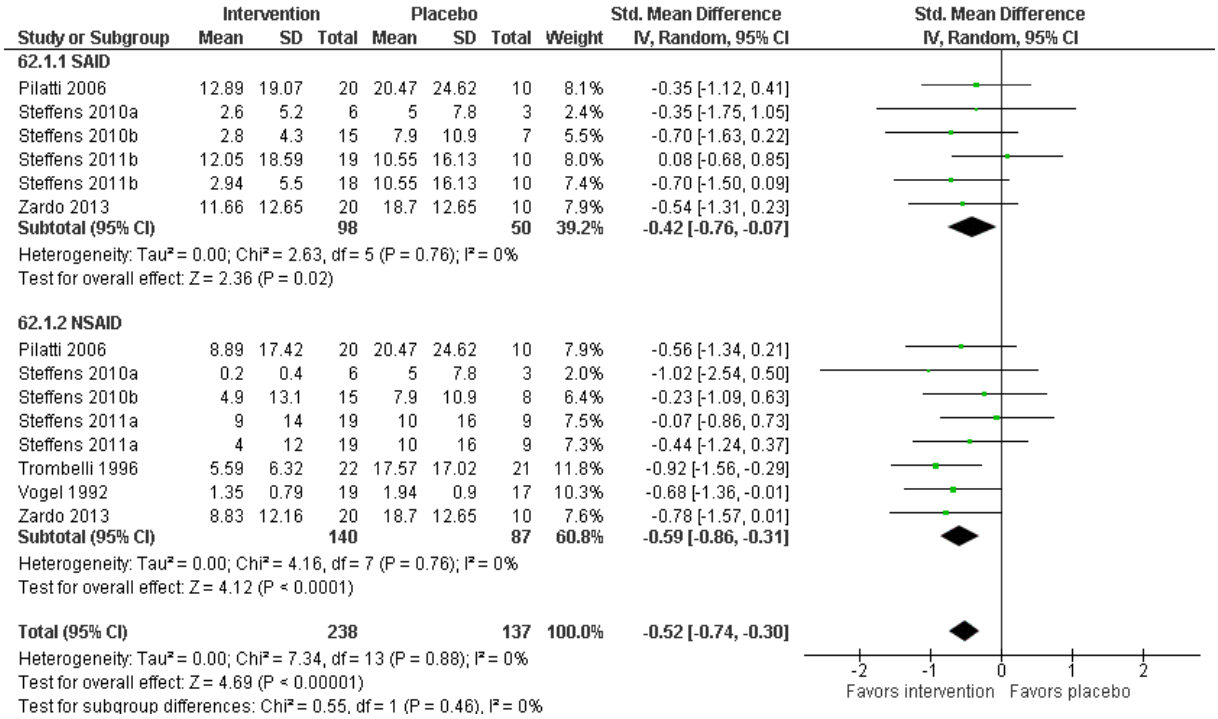

Source: The author

Figure 5 – Forest plot of the intensity of pain in preoperative protocol at one hour of follow-up



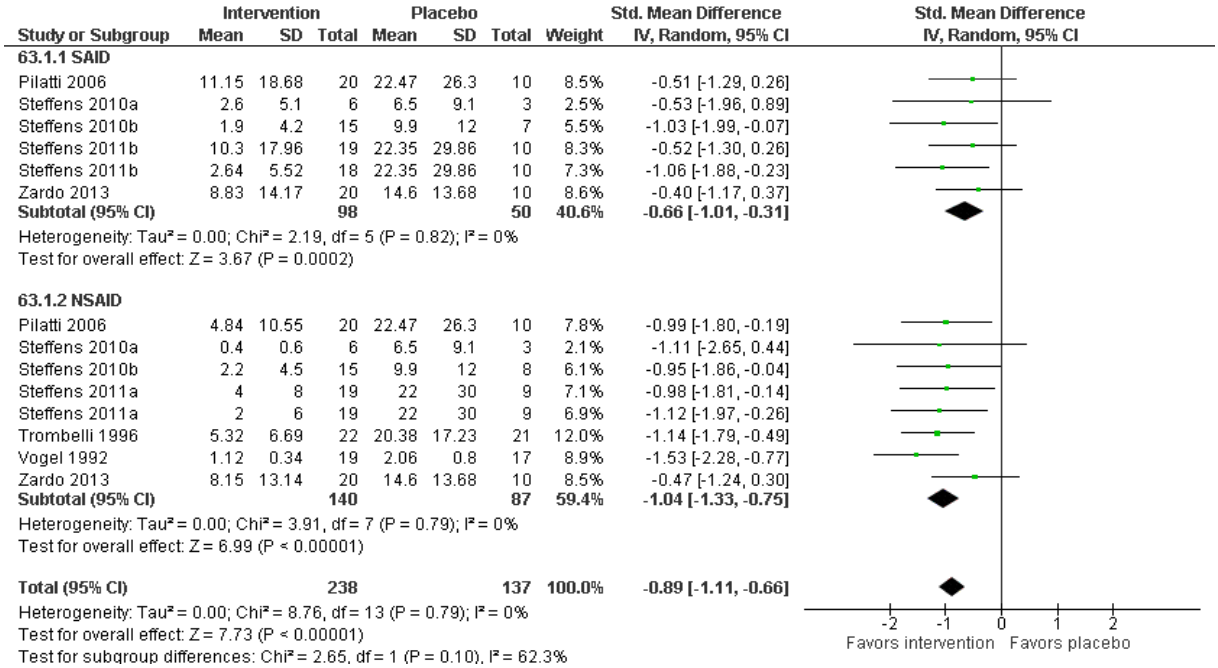

Source: The author

Figure 6 – Forest plot of the intensity of pain in preoperative protocol at two hours of follow-up



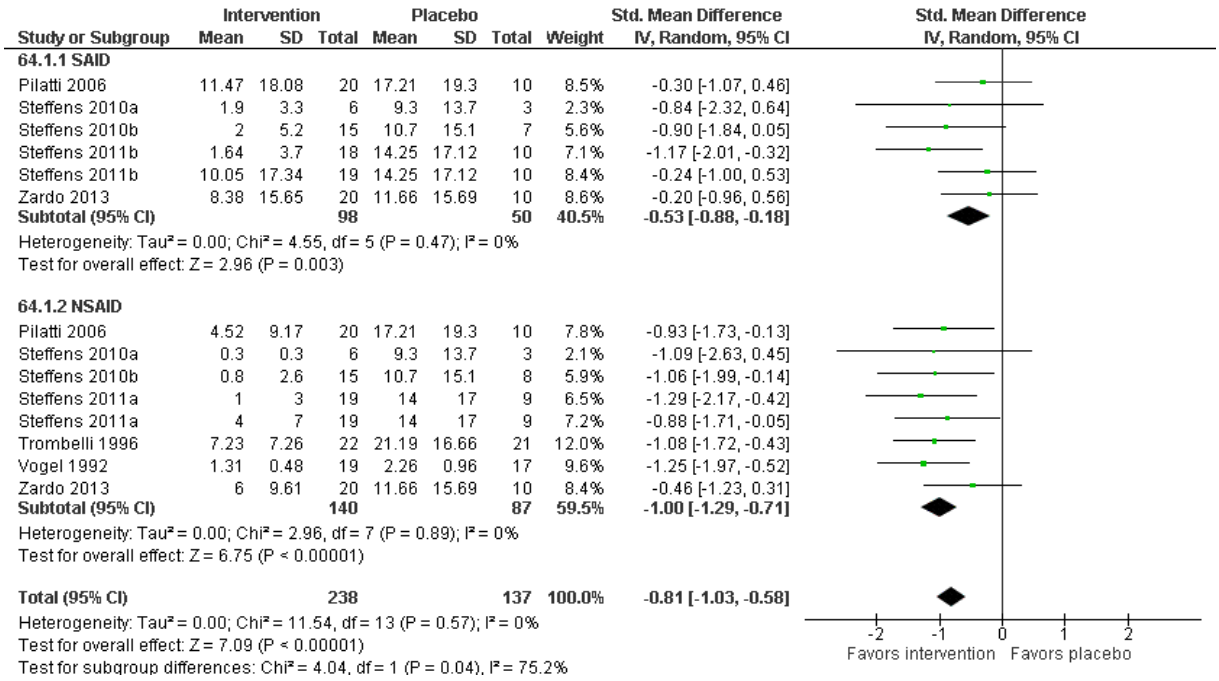

Source: The author

Figure 7 – Forest plot of the intensity of pain in preoperative protocol at three hours of follow-up



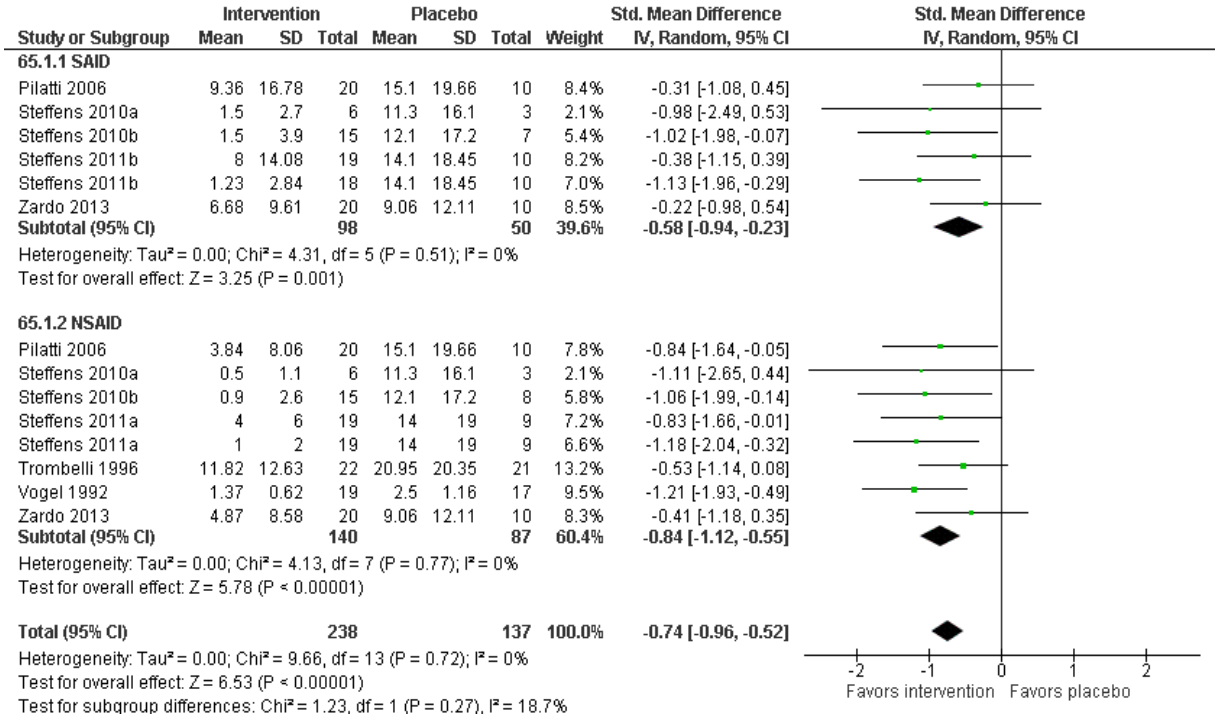

Source: The author

Figure 8 – Forest plot of the intensity of pain in preoperative protocol at four hours of follow-up



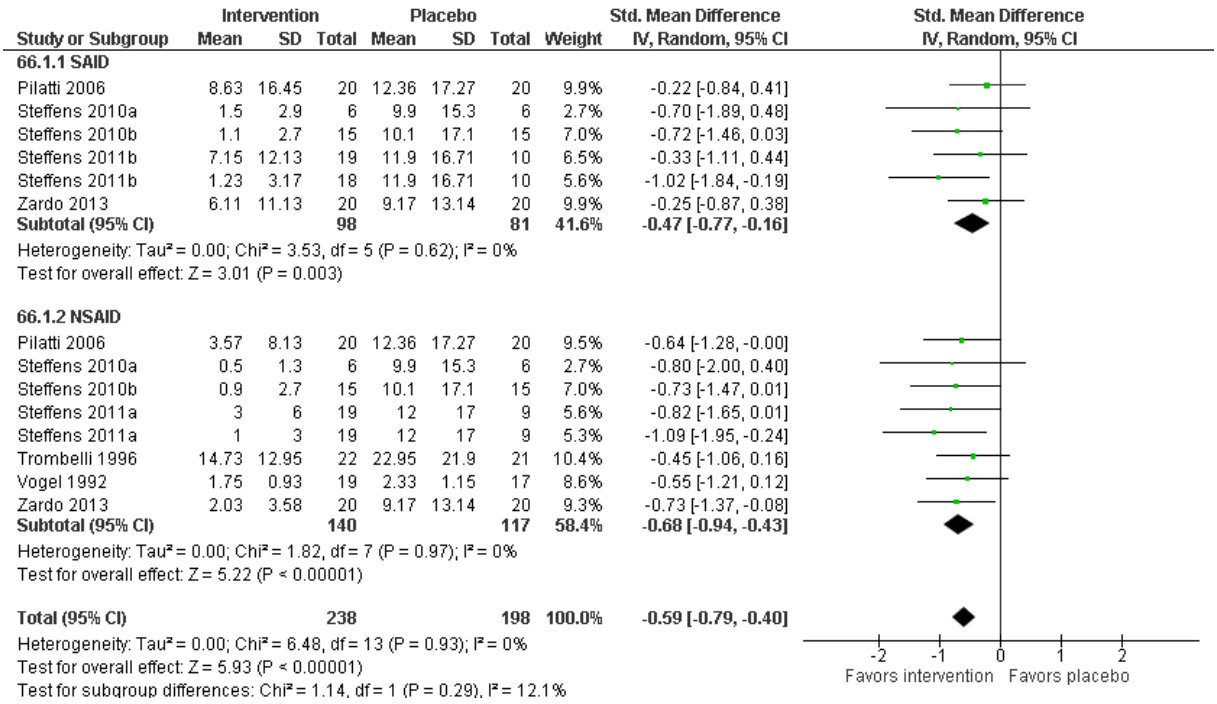

Source: The author

Figure 9 – Forest plot of the intensity of pain in preoperative protocol at five hours of follow-up




Source: The author

Figure 10 – Forest plot of the intensity of pain in preoperative protocol at six hours of follow-up

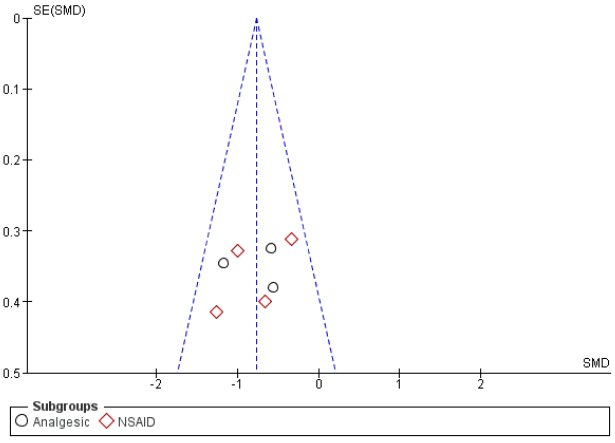



Source: The author

## 2.3.7 Publication Bias

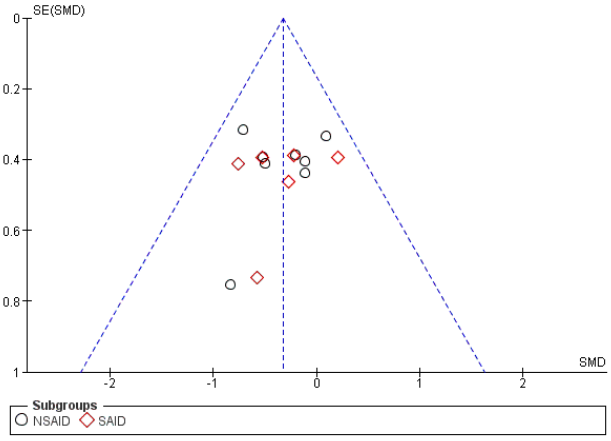
Throughout our visual examination for all the outcomes, we perceived asymmetry in all funnel plots (Figures 11 to 17). Even though we conducted extensive research on grey literature and later tested some modifications for the analyses (such as the fixed-effect models instead of random-effect models and mean difference instead of SMD), the graphs remained asymmetrical.

Figure 11 – Funnel plot of the intensity of pain in postoperative protocol at two hours of follow-up



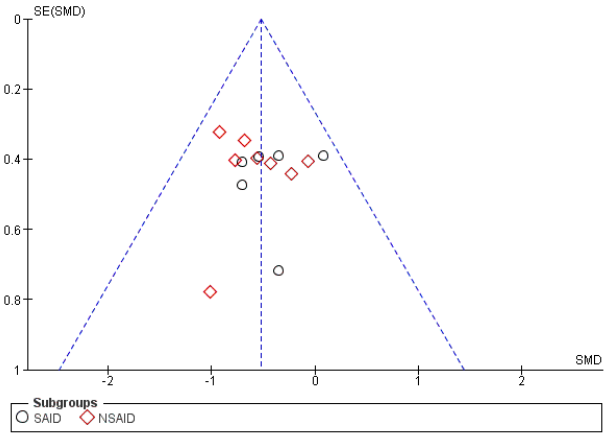

Source: The author

Figure 12 – Funnel plot of the intensity of pain in preoperative protocol at one hour of follow-up



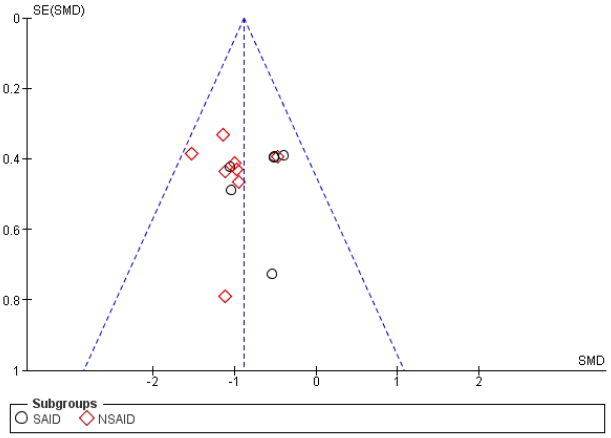

Source: The author

Figure 13 – Funnel plot of the intensity of pain in preoperative protocol at two hours of follow-up



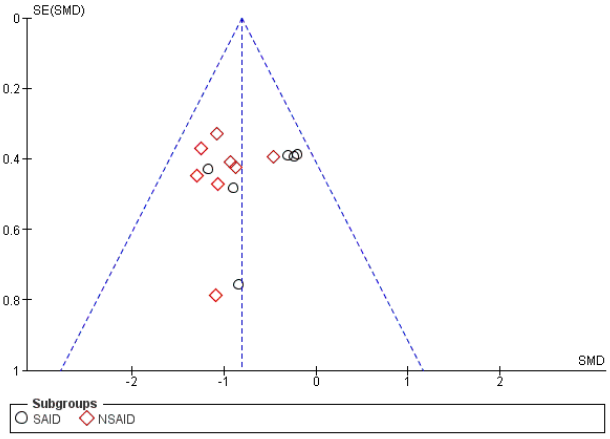

Source: The author

Figure 14 – Funnel plot of the intensity of pain in preoperative protocol at three hours of follow-up



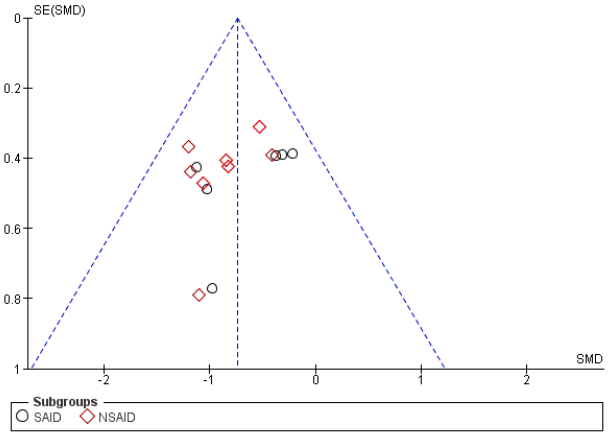

Source: The author

Figure 15 – Funnel plot of the intensity of pain in preoperative protocol at four hours of follow-up



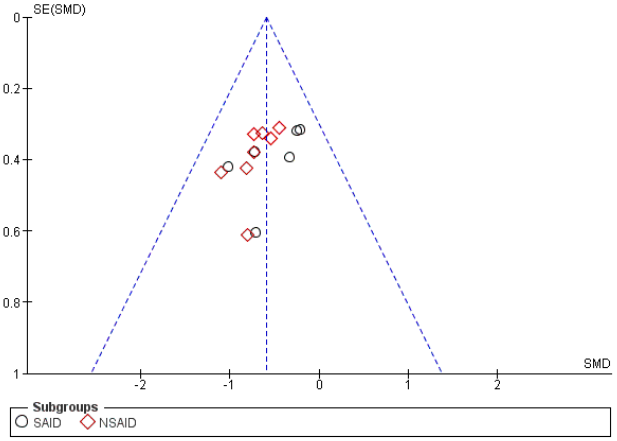

Source: The author

Figure 16 – Funnel plot of the intensity of pain in preoperative protocol at five hours of follow-up




Source: The author

Figure 17 – Funnel plot of the intensity of pain in preoperative protocol at six hours of follow-up




Source: The author

### 2.3.8 Quality Of Evidence Assessment

The quality of evidence for each outcome is presented in the GRADE evidence profile (Chart 3).

The quality of evidence was rated as low for the analysis regarding the postoperative protocol. We judged that the pain assessment protocol was not completely elucidated for this case and there were some limitations in study execution, so the risk of bias was taken as serious.

We also considered the findings of publication bias for all the outcomes due to the asymmetry of funnel plots, which was responsible for downgrading the quality of evidence by one level. For this reason, the preoperative analyses were rated as moderate quality of the evidence.

## 2.4 DISCUSSION

Concerning the main purpose of this present SR, we observed that the preoperative analgesia protocol had similar results to the postoperative analgesia protocol when their effects were compared to placebo at two hours of follow-up in pain control after periodontal surgery. There were analyses favoring the intervention in both cases. In this case, the size effect was mildly more significant for the postoperative strategy; nevertheless, both protocols presented moderate effect [41] on pain control.

These results pointed in the same direction as those presented by two SRs published in the early 2000s. [42,43] They evaluated preoperative analgesia for acute postoperative pain in several medical and dental interventions, including NSAIDs and opioids administration. These analgesia protocols did not reduce the pain scores outcome compared to postoperative treatment, so the timing of analgesia had no impact on the quality of pain control. [42,43]

In our additional data, meta-analyses showed significant statistical differences favoring preoperative protocol over placebo at one, three, four, five, and six hours of postoperative pain. They all represented a moderate to large effect [41], representing satisfactory clinical pain control outcomes. Likewise another SR [44] of the medical area published in 2017 confirmed that preoperative analgesia is adequate for

Chart 3 – GRADE profile (it continues)

| Certainty assessment | | | | | | | № of patients | | Effect | | Certainty | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **№ of studies** | **Study design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **intervention protocols** | **placebo** | **Relative (95% CI)** | **Absolute (95% CI)** | | |
| **Postoperative protocol/ 2h follow-up** | | | | | | | | | | | | |
| 4 | randomised trials | serious [a] | not serious | not serious | not serious | publication bias strongly suspected [b] | 161 | 109 | - | SMD **0.77 SD lower** (1.03 lower to 0.51 lower) | ⊕⊕◯◯ LOW | CRITICAL |
| **Preoperative protocol/ 1h follow-up** | | | | | | | | | | | | |
| 8 | randomised trials | not serious | not serious | not serious | not serious | publication bias strongly suspected [b] | 238 | 137 | - | SMD **0.33 SD lower** (0.54 lower to 0.11 lower) | ⊕⊕⊕◯ MODERATE | IMPORTANT |
| **Preoperative protocol/ 2h follow-up** | | | | | | | | | | | | |
| 8 | randomised trials | not serious | not serious | not serious | not serious | publication bias strongly suspected [b] | 238 | 137 | - | SMD **0.52 SD lower** (0.74 lower to 0.3 lower) | ⊕⊕⊕◯ MODERATE | CRITICAL |
| **Preoperative protocol/ 3h follow-up** | | | | | | | | | | | | |
| 8 | randomised trials | not serious | not serious | not serious | not serious | publication bias strongly suspected [b] | 238 | 137 | - | SMD **0.89 SD lower** (1.11 lower to 0.66 lower) | ⊕⊕⊕◯ MODERATE | IMPORTANT |

Chart 3 – GRADE profile (continuation)

**Preoperative protocol/ 4h follow-up**

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 8 | randomised trials | not serious | not serious | not serious | not serious | publication bias strongly suspected [b] | 238 | 137 | - | SMD **0.81 SD lower** (1.03 lower to 0.58 lower) | ⊕⊕⊕◯ MODERATE | IMPORTANT |

**Preoperative protocol/ 5h follow-up**

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 8 | randomised trials | not serious | not serious | not serious | not serious | publication bias strongly suspected [b] | 238 | 137 | - | SMD **0.74 SD lower** (0.96 lower to 0.52 lower) | ⊕⊕⊕◯ MODERATE | IMPORTANT |

**Preoperative protocol/ 6h follow-up**

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 8 | randomised trials | not serious | not serious | not serious | not serious | publication bias strongly suspected [b] | 238 | 137 | - | SMD **0.59 SD lower** (0.79 lower to 0.4 lower) | ⊕⊕⊕◯ MODERATE | IMPORTANT |

CI: Confidence interval; SMD: Standardised mean difference

**Explanations**

a. The pain assessment process was not clear.

b. Asymmetrical funnel plot.

Source: The author

abdominal hysterectomy compared to placebo, still they presented a set of not only preoperative but also postoperative medications to reduce postoperative pain.

Theoretically, preoperative analgesia corresponds to preemptive analgesia, in which the purpose is to prevent the settlement of central sensitization from the incision moment until the initial postoperative period. [45] Given literature, preemptive analgesia outcomes are very controversial compared to postoperative analgesia, given the heterogeneity of medications and methodologies applied in trials. Nonetheless, the combination of preoperative, perioperative, and postoperative interventions that interrupts or decreases nerve transmission pathways and the inflammatory process analgesia is proving to achieve reliable outcomes for minimizing pain intensity and reducing postoperative analgesic consumption. [46, 47, 48] Furthermore, analgesia protocols do not need to be implemented before or after the surgical intervention, considering that the analgesic effectiveness, prolonged analgesic effect, and central sensitization are more relevant elements than the moment of pharmaceutical administration. [46, 49]

Several types of pharmaceutical substances such as anticonvulsants, *antiarrhythmic* agents, sedatives, opioids and non-opioids analgesics, selective and non-selective anti-inflammatories can be implemented through an individual approach for an adequate pharmacological analgesia protocol. [44, 50] Our study included a small range of drugs in each meta-analysis. Both kinds of analyses incorporated NSAIDs, while preoperative had selective COX-2 inhibitors, non-selective NSAIDs, and SAIDs and postoperative had non-opioid analgesics and non-selective NSAIDs. Some of these drugs correspond to the most prescribed medications by dental professionals for postoperative pain, such as NSAIDs. [51] Next to the NSAIDs, non-opioid and opioid analgesics are the most encountered medicines for dentistry pain management. [51] Anyhow, none of our analyses involved opioids. An alternative option for postoperative discomfort is steroidal anti-inflammatory drugs. They are widely employed in dental surgery with good outcomes in reducing inflammation and controlling pain. [52, 53] Their adverse effects are usually addressed in supra-physiologic doses or long-term treatments, and they can provide long-acting effects with a biological half-life of up to 54 hours [54], such as dexamethasone, which was the representative of the SAIDs in this SR.

It is also necessary to consider that even with placebo treatment, all the studies' pain scores were qualified as mild to moderate postoperative pain, and the

only indirect comparison between the protocols was conducted in one moment of the follow-up. Our preoperative protocol analyses considered six hours of postoperative evaluation, while the preoperative protocol had only one analysis, performed with data from the second hour after the periodontal procedure. Thereby we did not cover the full period of the peak of postoperative pain in our analyses. The optimal analysis would be extended from 6 to 8 hours for both protocols, considering the peak for oral procedures on the first day of surgery. [55]

In this SR, we also noticed that the allocation concealment was a vulnerable matter for the studies incorporated. The allocation concealment protects the random sequence generation, so it is part of a crucial set of recommendations to ensure the best health care along with the most accurate research results. [56] Despite its contribution to validate trials, it is relatively common that studies publish inadequate concealment or even fail to outline this process [57], as evidenced in 90% of the papers assessed in this SR. Out of these 29 studies, 26 were rated as high risk of bias for the allocation concealment due to the lack of reference of this category in those researches. Concurrently with these limitations, we did not evaluate the amount of anesthesia or surgery complexity and extension presented in each study, factors that might influence the perception of postoperative pain in periodontal surgery. [3] Neither we considered the presence or absence of periodontal disease since the patients' profile was pretty assorted in age and surgery needs.

Regardless of the use of resources, it was not possible to diminish the publication bias of our analyses. Yet, it is not uncommon for evidence to be biased, favoring positive results in experimental interventions due to difficulty in publishing and citing statistically non-significant results. [58] Thus these outcomes are less likely to be detected in SRs. Our findings must also be considered with prudence as, regarding quality of evidence, the postoperative analysis was rated as low, and the preoperative analyses were graded as moderate. Additional studies with at least an eight-hour follow-up period and combining preoperative and postoperative measures to prevent postoperative pain in periodontal surgical procedures are necessary to evaluate the analgesic effectiveness and medication consumption.

## 2.5 CONCLUSION

Preoperative and postoperative analgesia protocols may be considered useful for postoperative pain management in periodontal surgery. Both presented at least a moderate effect on pain control over placebo.

In practice, since pain is a subjective matter, every dental practitioner should customize an analgesia protocol considering each patient's requirements and the most convenient protocol to be implemented.

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## CONSIDERAÇÕES FINAIS

A analgesia com várias frentes de ação é bastante explorada dentro da área médica, especialmente em cirurgia. E, dentro de proporções diferentes, as intervenções odontológicas também exigem controle da dor pós-operatória.

Através de distintas técnicas, o controle da dor é viável após cirurgias periodontais. Fármacos com administração via tópica, via oral, laserterapia de baixa potência e barreiras mecânicas aplicadas diretamente à ferida cirúrgica são algumas opções exploradas, no entanto o universo da analgesia e da dor são bastante abrangentes e interdependentes.

Os protocolos dispostos com medicamentos via oral são comprovadamente eficazes, e, se combinados a outras medidas não farmacológicas de analgesia, podem reduzir a quantidade de analgésico e/ou anti-inflamatório consumido. Deste modo, os efeitos indesejáveis dos medicamentos podem ser minimizados com o uso da menor dose eficaz dentro do menor tempo necessário para controlar os sintomas.

Além disso, o paciente pode usufruir do benefício de um protocolo individualizado com a predição dos níveis de dor através do perfil deste paciente, considerando escolha de anestésicos, tipo de técnica cirúrgica pretendida, momento de início para analgesia, efetividade e duração analgésica.

Para pacientes com predição de dor moderada, que serão submetidos a cirurgias periodontais mais extensas e com ressecção óssea, é possível a utilização do protocolo analgésico farmacológico com medicamentos de média a longa duração e seguimento com técnicas analgésicas adjuntas (não farmacológicas) no período pós-operatório. Para pacientes com predição de dor leve, que serão submetidos a cirurgias mucogengivais e de menor extensão, é possível utilizar protocolos analgésicos mais simples.

É importante salientar que, considerando a similaridade da eficácia entre protocolos analgésicos pré e pós-operatório farmacológicos, o método mais prático pode ser adotado. Ou seja, aquele que o paciente esteja mais habituado a receber e o profissional mais habituado a prescrever, ou, ainda, levar em consideração os custos, acesso e também preferências do paciente. Não obstante a isso, todos os protocolos são passíveis de adequações durante o andamento do pós-operatório conforme necessidades analgésicas.

Por fim, a literatura é vasta em controle da dor pós-operatória na Odontologia, principalmente dentro de medidas farmacológicas. Porém, raramente integra as técnicas para controle da dor em suas análises, como combinações entre intervenções farmacológicas e não farmacológicas. De qualquer forma, o manejo da dor pós-operatória em cirurgia periodontal comporta técnicas eficazes, que, se combinadas individualmente, podem gerar maior conforto e segurança para o paciente na rotina ambulatorial do cirurgião-dentista.

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# APÊNDICE A – ESTRATÉGIAS DE BUSCA

| Electronic database and search strategy | |
|---|---|
| Cochrane Library (27/May/2020) | |
| #1 "MeSH descriptor: [Periodontics] explode all trees"<br>#2 "MeSH descriptor: [Oral Surgical Procedures] explode all trees"<br>#3 "MeSH descriptor: [Surgery, Oral] explode all trees"<br>#4 "MeSH descriptor: [Surgical Flaps] explode all trees"<br><br>(#1 or #2 or #3 or #4) and (#5 or #6 or #7) | #5 "MeSH descriptor: [Anti-Inflammatory Agents] explode all trees"<br>#6 "MeSH descriptor: [Analgesics] explode all trees"<br>#7 "MeSH descriptor: [Analgesia] explode all trees" |

| Electronic database and search strategy | |
|---|---|
| Embase (27/May/2020) | |
| 1 ('periodontics'/exp OR periodontics OR 'oral surgery'/exp OR 'oral surgery' OR 'surgical flaps'/exp OR 'surgical flaps' OR 'periodontal surgery' OR 'periodontal surgical therapy' OR 'periodontal surgical procedure' OR 'periodontal plastic surgery' OR 'gingival surgery' OR 'gum surgery' OR 'osseous surgery' OR 'mucogingival surgery' OR 'mucosal graft' OR 'flap surgery' OR 'apically repositioned flap' OR 'repositioned flap' OR 'modified widman flap' OR 'replaced flap' OR 'open-flap debridement surgery' OR 'laterally repositioned flap' OR 'double papilla flap' OR 'coronally advanced flap' OR 'root coverage' OR 'connective tissue graft' OR 'pedicle grafts' OR 'pocket elimination' OR 'pocket reduction' OR 'tuberosity reduction' OR 'periodontal regeneration' OR 'enamel matrix derivative' OR 'crown lengthening' OR 'distal wedge procedure':ab,kw,ti)<br><br>1 AND 2 AND [embase]/lim AND ([controlled clinical trial]/lim OR [randomized controlled trial]/lim) AND ([young adult]/lim OR [adult]/lim OR [middle aged]/lim OR [aged]/lim OR [very elderly]/lim) AND ([embase]/lim OR [pubmed-not-medline]/lim) AND [<1966-2019]/py | 2 ('antiinflammatory agent'/exp OR 'antiinflammatory agent' OR 'analgesic agent'/exp OR 'analgesic agent' OR 'analgesia'/exp OR analgesia:ab,kw,ti) |

| Electronic database and search strategy | |
|---|---|
| LILACS (27/May/2020) | |
| 1 (tw:((Periodontics OR Periodoncia OR Periodontia OR Periodontal OR 'Periodontal surgery' OR 'Cirugia periodontal' OR 'Cirurgia periodontal')))<br><br>1 AND 2 | 2 (tw:(('Anti-Inflammatory Agents' OR Antiinflamatorios OR 'Anti-inflamatorios' OR Analgesics OR Analgesicos OR Analgesia))) |

| Electronic database and search strategy | |
|---|---|
| BBO (27/May/2020) | |
| 1 (tw:((Periodontics OR Periodoncia OR Periodontia OR Periodontal OR 'Periodontal surgery' OR 'Cirugia periodontal' OR 'Cirurgia periodontal')))<br><br>1 AND 2 | 2 (tw:(('Anti-Inflammatory Agents' OR Antiinflamatorios OR 'Anti-inflamatorios' OR Analgesics OR Analgesicos OR Analgesia))) |

| Electronic database and search strategy | |
|---|---|
| SciELO (18/May/2020) | |
| 1 (Periodontics OR Periodoncia OR Periodontia OR Periodontal OR 'Periodontal surgery' OR 'Cirugia periodontal' OR 'Cirurgia periodontal')<br><br>1 AND 2 | 2 ('Anti-Inflammatory Agents' OR Antiinflamatorios OR 'Anti-inflamatorios' OR Analgesics OR Analgesicos OR Analgesia) |

| Electronic database and search strategy | |
|---|---|
| Scopus (27/May/2020) | |
| 1 TITLE-ABS-KEY(Periodontics OR "Oral surgery" OR "Surgical flaps" OR "Periodontal surgery" OR "Periodontal surgical therapy" OR "Periodontal surgical procedure" OR "Periodontal plastic surgery" OR "Gingival surgery" OR "Osseous surgery" OR "Mucogingival surgery" OR "Mucosal graft" OR "Flap surgery" OR "Apically repositioned flap" OR "Repositioned flap" OR "Modified Widman flap" OR "Replaced flap" OR "Open-flap debridement surgery" OR "Laterally repositioned flap" OR "Double papilla flap" OR "Coronally advanced flap" OR "Root coverage" OR "Connective tissue graft" OR "Bone grafting" OR "Gum surgery" OR "Pedicle grafts" OR "Subepithelial connective tissue graft" OR "Pocket elimination" OR "Pocket reduction" OR "Tuberosity reduction" OR "Periodontal regeneration" OR "Guided tissue regeneration" OR "Enamel matrix derivative" OR "Guided tissue regeneration" OR "Crown lengthening" OR "Distal wedge procedure")<br><br>1 AND 2 | 2 TITLE-ABS-KEY("Anti-Inflammatory Agents" OR Analgesics OR Analgesia) |

| Electronic database and search strategy | |
|---|---|
| Web of Science (27/May/2020) | |
| 1 TS=(Periodontics OR "Oral surgery" OR "Surgical flaps" OR "Periodontal surgery" OR "Periodontal surgical therapy" OR "Periodontal surgical procedure" OR "Periodontal plastic surgery" OR "Gingival surgery" OR "Osseous surgery" OR "Mucogingival surgery" OR "Mucosal graft" OR "Flap surgery" OR "Apically repositioned flap" OR "Repositioned flap" OR "Modified Widman flap" OR "Replaced flap" OR "Open-flap debridement surgery" OR "Laterally repositioned flap" OR "Double papilla flap" OR "Coronally advanced flap" OR "Root coverage" OR "Connective tissue graft" OR "Bone grafting" OR "Gum surgery" OR "Pedicle grafts" OR "Subepithelial connective tissue graft" OR "Pocket elimination" OR "Pocket reduction" OR "Tuberosity reduction" OR "Periodontal regeneration" OR "Guided tissue regeneration" OR "Enamel matrix derivative" OR "Guided tissue regeneration" OR "Crown lengthening" OR "Distal wedge procedure")<br><br>1 AND 2 | 2 TS=("Anti-Inflammatory Agents" OR Analgesics OR Analgesia) |

| Grey literature source and search strategy |
| --- |
| Open Grey (http://www.opengrey.eu/) (10/Jun/2020)<br>“Periodontal surgery” |
| World Cat (https://www.worldcat.org/) 10/Jun/2020<br>“Periodontal surgery” and (“Anti-inflammatory” or analgesics or analgesia) |
| Google (https://www.google.com/advanced_search) (10/Jun/2020)<br>allintitle: “periodontal surgery” and pain |
| IADR (and all division) abstracts (2005 to 2019) |
| AAP (2015 to 2019) |
| EFP EuroPerio 2009, 2012, 2015, 2018 |
| Capes Catálogo de Teses e Dissertações ( https://catalogodeteses.capes.gov.br/catalogo-teses/#!/)<br>“Cirurgia periodontal” |
| ISRCTN Registry (http://www.isrctn.com/)<br>“Periodontal surgery” |
| International Clinical Trials Registry Platform (http://apps.who.int/trialsearch/)<br>“Periodontal surgery” |
| ClinicalTrials.gov (www.clinicaltrials.gov)<br>“Periodontal surgery” |
| ReBEC (www.rebec.gov.br)<br>“Cirurgia periodontal” |
| EU Clinical Trials Register (https://www.clinicaltrialsregister.eu)<br>“Periodontal surgery” |

# APÊNDICE B – FORMULÁRIO PARA EXTRAÇÃO DE DADOS

| | | |
|---|---|---|
| Data Collection Form | | |
| Article ID: | | |
| Title: | | |
| General characteristics | Year of the study | |
| | Country of origin | |
| | Authors | |
| | Funding Source | |
| | University/private practice based | |
| Specific characteristics | Study design | |
| | Participants profile (gender, age) | |
| | Sample size | |
| | Type of periodontal surgery | |
| | Groups of intervention | |
| | Control group | |
| | Inclusion criteria | |
| | Exclusion criteria | |
| | Follow-up (amount, frequency) | |
| Outcomes | Evaluation tool | |
| | Primary | |
| | Secondary | |
| | Sample Loss | |
| | Mean | |
| | Standard Deviation | |
| Risk of Bias | Random sequence generation | |
| | Allocation concealment | |
| | Blinding of participants and researchers | |
| | Blinding of outcome assessment | |
| | Incomplete outcome data | |
| | Selective reporting | |
| | Other bias | |

# APÊNDICE C – PARÂMETROS DO RISCO DE VIÉS

| Parameters used for risk of bias judgement | |
|---|---|
| Sequence generation | Low risk of bias when a random number generation was used such as computer softwares |
| | Unclear risk of bias when the randomization was poorly explained |
| | High risk of bias when randomization was not addressed |
| Allocation concealment | Low risk of bias when operators were unaware of the randomization sequence such as with sequentially numbered opaque envelopes |
| | Unclear risk of bias when the allocation concealment was poorly explained |
| | High risk of bias when the allocation concealment was not addressed |
| Blinding of participants and examiners | Low risk of bias when participants and examiners were clearly blinded to the intervention |
| | Unclear risk of bias when there was not enough information to determine if the participants and examiners were blinded or not |
| | High risk of bias when the study was single blinded |
| Blinding of outcome assessment | Low risk of bias when the outcome assessor was blinded to the intervention |
| | Unclear risk of bias when there was not enough information to determine if the outcome assessor was blinded or not |
| | High risk of bias when the outcome assessor knew about the interventions |
| Completeness of outcome data | Low risk of bias if there was no missing data, or missing data was balanced across the groups |
| | Unclear risk of bias when the missing data was poorly explained |
| | High risk of bias if if there was no reporting of exclusions and a large amount of missing data |
| Selective outcome reporting | Low risk of bias if all prespecified outcomes were reported |
| | Unclear risk of bias when the funding might had influenced the results |
| | High risk of bias if the prespecified outcomes were not reported |
| Other potential bias | Low risk of bias if there was no evidence of any other biases |
| | If there was not enough information to make decisions |
| | High risk of bias if it was not proposed a questionnaire for pain evaluation, or there was no homogeneity of the sample, or the sample was too small, or the arrangement of the study was not compatible with a RCT, or the outcomes were confusing |

# APÊNDICE D – ESTUDOS "*FULL TEXT*" EXCLUÍDOS

| Characteristics of excluded articles | |
|---|---|
| Article ID | Reason for exclusion |
| Cooper1986 | 1 |
| Getter1973 | 2 |
| Mehlisch1980 | 2 |
| Moore1987 | 3 |
| Or1988 | 3 |
| Pilatti2011 | 4 |
| Seymour1983b | 2 |
| Steffens2009 | 4 |
| Vansteenberghe1986 | 3 |
| 1- included medicine out of criteria; 2- had no extractable data; 3- did not test the intervention of interest; 4- had overlapping data from other included study | |