Preoperative *versus* postoperative analgesia protocols for postoperative pain control in periodontal surgery: a systematic review and meta-analysis

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Abstract

Aim: Pain management after periodontal surgery has been discussed in relation to drug classification; however, analgesia protocols have not been addressed. Thus, the objective of this systematic review (SR) was to compare preoperative and postoperative analgesia protocols for postoperative pain control in periodontal surgery.

Materials and Methods: This SR was developed according to PRISMA statements. Electronic databases and gray literature were investigated regarding trials using preoperative and postoperative analgesia protocols with oral anti-inflammatories and analgesics. We evaluated each study for risk of bias and quality of evidence. We submitted the quantitative data to meta-analysis. Only studies categorized as having unclear or low risk of bias were included in the meta-analysis.

Results: A total of 2,528 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 surgery. Both the preoperative and postoperative protocols showed similar effectiveness in controlling postoperative pain.

Conclusions: Preoperative and postoperative analgesia protocols, including oral anti-inflammatories and analgesics, were considered effective for postoperative pain control after periodontal surgery. The overall quality of evidence was moderate (preoperative protocols) and low (postoperative protocols).

Keywords: Periodontal surgery. Adjunctive periodontal therapy. Systematic review. Meta-analysis. Pain.

Introduction

Postoperative pain after periodontal surgery can be experienced at different levels of intensity. It can broadly range from mild to moderate, and, more rarely, can reach severe levels of pain (Seymour, 1983; Trombelli *et al*., 1996; Peres *et al*., 2012; Caporossi *et al*., 2020; Wagner *et al*., 2021). This intensity is highly linked to factors such as the invasiveness of the procedure; the extent of the incision; the duration of the procedure; tissue manipulation; bone removal; and the amount of anesthesia administered (Tucker *et al*., 1996; Pearlman *et al*., 1997; Giorgetti *et al*., 2018; Etikala *et al*., 2019).

Although postoperative pain largely depends on perioperative factors, it is possible to employ pharmacological resources to mitigate this discomfort (Minutello *et al*., 1991; Ong *et al*., 2005; Rashwan, 2009). Appropriate postoperative pain management offers better outcomes for patients and prevents chronic postsurgical pain, morbidity, and increased costs, all of which can undermine quality of life (Vogel *et al*., 1992; Hungund *et al*., 2011; Peres *et al*., 2012; Gan, 2017).

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Furthermore, appropriate postoperative pain control ensures patients' safety when associated with the determination of the risks and benefits predicted by safety pharmacology methods (Pugsley *et al*., 2018). In this approach, 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 a continuous intake of medication (Minutello *et al*., 1991; Gallardo *et al*., 1992; Betancourt *et al*., 2004; Pilatti *et al*., 2006; Steffens *et al*., 2011b; Giorgetti *et al*., 2018).

Systematic reviews (SR) have previously been used to study oral postoperative pain control due to its clinical relevance and the wide variety of medicine and analgesia protocols (Costa *et al*., 2015; Fernandes *et al*., 2019). Yet these studies were specifically designed to focus on third molar extraction surgery. Another SR addressed the effect of different drugs on postoperative pain after periodontal surgery and demonstrated that various types of medication can lead to pain control (Caporossi *et al*., 2020). A recent SR evaluating the use of oral corticosteroids for pain and swelling reduction after different types of oral surgeries (third molar, periodontal, and dental implant) showed evidence supporting the use of oral corticosteroids for this indication appears limited. Nonetheless, optimal medications, doses, and routes/timing of administration remain unclear (Wagner *et al*., 2021). However, no study has discussed whether variations in the timing of oral administration affect the intensity of postoperative pain.

Thus, there is still no consensus on which analgesia protocol is effective for this task. The purpose of this SR was to compare preoperative and postoperative analgesia protocol for postoperative pain control in periodontal surgery.

Materials and Methods

Protocol and registration

This SR was registered in the International Prospective Register of Systematic Reviews (PROSPERO - CRD42020215497) and was written according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Moher *et al*., 2010).

Eligibility criteria

We searched for studies published up to December 2019 with no language restriction using the "PICOS" categories: P (Population): patients submitted to periodontal surgery; I (Intervention): preoperative or postoperative pharmacological regimens using anti-inflammatories or analgesic agents; C (Comparison): placebo/control medicine (analgesic or anti-inflammatory agent); O (Outcome): postoperative pain control; and S (Study Design): randomized clinical trials (RCTs).

The purpose of this SR was to identify which pharmacological analgesic protocol was most efficient in controlling postoperative pain after periodontal surgery.

We included split-mouth and parallel RCTs which evaluated different drug protocols for postoperative pain control in patients of any age group who underwent periodontal surgery with at least one follow-up assessment. The intervention groups had to compare either analgesics, anti-inflammatories or placebos in preoperative or postoperative protocols. The selected studies had to involve any periodontal surgery, and pain had to be measured through any pain assessment tool, either validated or non-validated. We excluded the following trials: 1) if the participants took antibiotics (due to drugs interactions on the bioavailability); 2) if they only reported on implant surgery; 3) if the results did not separate periodontal surgery from other kinds of oral surgery; 4) if drugs were administered other than orally.

Search strategy

We searched electronic databases (MEDLINE via PubMed, Cochrane Library, Embase, *Literatura Latino-Americana e do Caribe em Ciências da Saúde, Bibliografia Brasileira de Odontologia* and Scientific Electronic Library Online) and citation databases (Scopus and Web of Science) in May 2020. To identify relevant studies in gray literature, we researched The System for Information on Grey Literature in Europe (OpenGrey) database, the WorldCat Library Catalog, and Google for government web pages. 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 Dissertações*. The following registries were utilized in order to locate ongoing trials: ISRCTN Registry; International Clinical Trials Registry Platform; ClinicalTrials.gov; ReBEC; and EU Clinical Trials Register.

The search strategy was constructed based on the "Population" and "Intervention" categories from the "PICOS" system. The search strategies used a combination of controlled terms (medical subject headings [MeSH]) and free keywords based on the search strategy established for MEDLINE (Chart 1), with appropriate adjustments.

We downloaded the titles and abstracts into bibliographic citation management software (Endnote™ X6; Clarivate Analytics™, Philadelphia, PA, USA), excluded duplicates, and manually selected the studies according to the eligibility criteria. Two authors (SB and DH) independently performed the selection and any discrepancies were clarified through discussion.

MEDLINE via PubMed (27/05/2020)	
#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])
#1 AND #2	

Chart 1. Electronic database MEDLINE and search strategy.

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

When a study did not provide all the necessary data we made two attempts to contact the authors by email or through the ResearchGate platform. When only figures or graphs were available we used WebPlotDigitizer Version 4.3 (https://automeris.io/WebPlotDigitizer, 2020) for data extraction.

Risk of bias in individual studies

We evaluated the methodological quality of each study using the Cochrane Collaboration's Tool for Assessing Risk of Bias in Randomized Trials (Higgins *et al*., 2011). The articles were rated based on 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 as having low, unclear, or high risk of bias at study-level (Cumpston *et al*., 2019).

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 having low risk of bias. If any domain had unclear risk, the study was qualified as having unclear risk of bias. If any domain had high risk, the study was rated as having high risk of bias. The patient blinding to the medication was considered a key domain when pain was evaluated by patients 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. The quality assessment was the responsibility of three independent reviewers (SB, DH, and JJS) and disagreements were solved through discussion.

Meta-analysis

We analyzed the data using RevMan ([Computer program] Review Manager, Version 5.4, Cochrane Collaboration, 2020). Only studies categorized as having unclear or low risk of bias in the key domains were included in the meta-analysis (MA).

The intensity of pain was the studied outcome, which was characterized as a continuous variable. Therefore, we considered the average pain per hour and the standard deviation.

Considering the variability of pain assessment scales, it was necessary to standardize the results to the standardized mean difference (SMD) with a 95% confidence interval in order to combine the data. Fixed-effects models were tested; however, since there was variability in the medication, dosage and type of periodontal surgery, we decided to use random-effects models in all the meta-analyses.

The preoperative medication group and the postoperative medication were compared to the placebo. The postoperative protocol was analyzed at two hours of follow-up, and the subgroups involved NSAIDs and analgesics. The preoperative protocol was also analyzed at two hours of follow-up, and the subgroups involved NSAIDs and SAIDs.

Publication bias and quality of evidence

We used the funnel plot technique as a qualitative method to analyze the publication bias. To assess the quality of evidence we employed the GRADE approach (grading of recommendations assessment, development and evaluation) for each meta-analysis.

Results

Study selection and characteristics

We conducted the initial search on May 18th, 2020 with an update on July 25th, 2020. We found that 5,668 studies originated from the scientific bases and 310 studies originated from additional sources. We retained 2,528 studies after the duplicates were removed, and 46 studies were retained after title and abstract screening (Figure 1).

Following that selection, we assessed 38 full-text versions and carefully reduced them to 29 studies for the SR (Berdon *et al*., 1964; Cooper *et al*., 1983; Seymour, 1983; Gallardo and Rossi, 1990; Minutello *et al*., 1991; Gallardo and Rossi, 1992; Vogel *et al*., 1992; Trombelli *et al*., 1996; Tucker *et al*., 1996; Pearlman *et al*., 1997; Reed *et al*., 1997; Salazar *et al*., 2002; Betancourt *et al*., 2004; Pilatti *et al*., 2006; Popova *et al*., 2008; Rashwan, 2009; Steffens *et al*., 2010a; Steffens *et al*., 2010b; Aghasizadeh *et al*., 2011; Hungund and Thakkar, 2011; Steffens *et al*., 2011a; Steffens *et al*., 2011b; Peres *et al*., 2012; Zardo *et al*., 2013; Konuganti *et al*., 2015; Kashefimehr *et al*., 2017; Giorgetti *et al*., 2018; Karmkar *et al*., 2018; Burgos-Quiróz *et al*., 2019). The characteristics of the 29 studies selected were summarized in Table 1.

This SR yielded studies that were published from 1964 to 2019. The most prevalent study design was parallel design (Berdon *et al*., 1964; Cooper *et al*., 1983; Seymour, 1983; Gallardo and Rossi, 1990; Minutello *et al*., 1991; Gallardo and Rossi, 1992; Vogel *et al*., 1992; Trombelli *et al*., 1996; Tucker *et al*., 1996; Pearlman *et al*., 1997; Reed *et al*., 1997; Salazar *et al*., 2002; Popova *et al*., 2008; Steffens *et al*., 2011a; Steffens *et al*., 2011b; Peres *et al*., 2012; Zardo *et al*., 2013; Konuganti *et al*., 2015; Kashefimehr *et al*., 2017; Giorgetti *et al*., 2018; Burgos-Quiróz *et al*., 2019), although eight studies used the cross-over split-mouth design (Betancourt *et al*., 2004; Pilatti *et al*., 2006; Rashwan, 2009; Steffens *et al*., 2010a; Steffens *et al*., 2010b; Aghasizadeh *et al*., 2011; Hungund and Thakkar, 2011; Karmkar *et al*., 2018).

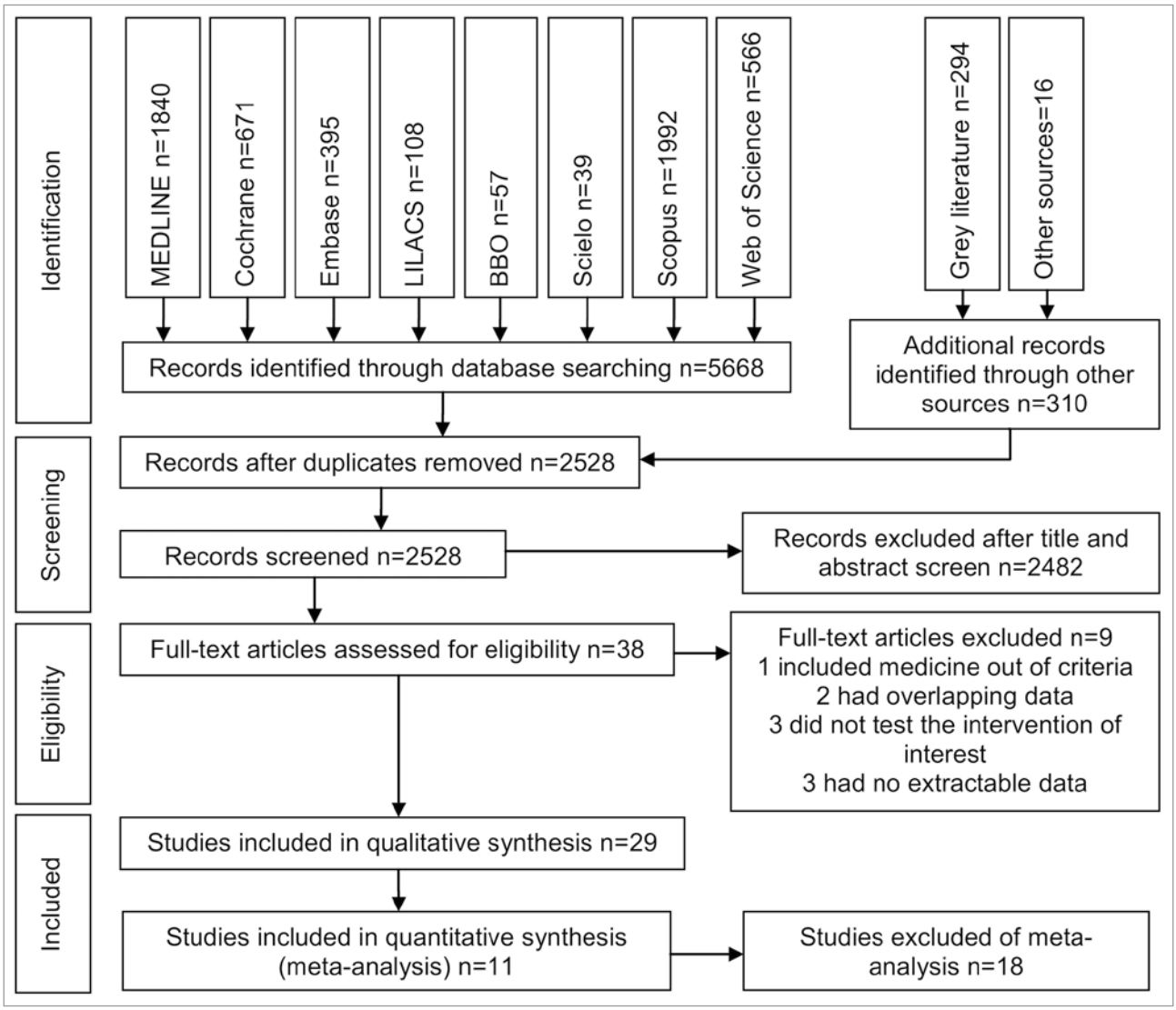

Figure 1. Flow diagram of the systematic review according to PRISMA guidelines.

Table 1. Summary of the studies included in the Systematic Review.

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) 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) 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) 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) 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) G2: suprofen 200ng (n=44) G3: aspirin 650mg (n=43) 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) G2: acetaminophen 500mg (n=21) 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) G2: aspirin 500mg (n=35) G3: placebo (n=30)	Postop	Own evaluation tool/ hourly for 3h	Postoperative meclofenamate was more effective for open flap debridement
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) G1: ketorolac tromethamine 10mg (n=40)	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	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 recommended 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 lengthening

Table 1. Summary of the studies included in the Systematic Review (it continuation).

Study characteristics		Population			Methods			Outcome (pain)
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/ 1st 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
Pilatti et al. (2006) Brazil	Split-mouth	20	27 to 53	11	G1: placebo (n=20) G2: dexamethasone 4mg (n=20) 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) 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) 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 recommended for open flap debridement
Reed et al. (1997) USA	Parallel	5	NS	NS	G1: preop ketoprofen 100mg and postop ketoprofen 50mg (n=2) 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) G2: postop nimesulide 100mg (n=15) 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) G2: paracetamol 1000mg (n=20) 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) G2: dexamethasone 8mg (n=6) 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) G2: dexamethasone 8mg (n=15) 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

Table 1. Summary of the studies included in the Systematic Review (it continuation).

Study characteristics		Population			Methods			Outcome (pain)
Steffens; Santos; Pilatti (2011a) Brazil	Parallel	56	38±8	30	G1: celecoxib 200mg (n=19) G2: etoricoxib 120mg (n=19) 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 39.7±9.3 39.0±8.2	27	G1: dexamethasone 4mg (n=19) G2: dexamethasone 8mg (n=18) 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) 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) 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 46.8±12.2 43.0±12.7	28	G1: preop ibuprofen 600mg (n=19) G2: postop ibuprofen 600mg (n=17) 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) G2: dexamethasone 8mg (n=20) 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.

The patients in these trials were aged from 10 to 79 years. Their mean age was 39.4 years, which reveals the preponderance of young adults. Three studies did not indicate information about the age of their subjects (Seymour, 1983; Reed *et al*., 1997; Hungund and Thakkar, 2011). Some papers presented a higher prevalence of female participants (Cooper *et al*., 1983; Gallardo and Rossi, 1990; Gallardo and Rossi, 1992; Vogel *et al*., 1992; Trombelli *et al*., 1996; Tucker *et al*., 1996; Pilatti *et al*., 2006; Rashwan, 2009; Aghasizadeh *et al*., 2011; Steffens *et al*., 2011b; Peres *et al*., 2012; Kashefimehr *et al*., 2017; Giorgetti *et al*., 2018), whereas others displayed a higher prevalence of male participants (Berdon *et al*., 1964; Pearlman *et al*., 1997; Salazar *et al*., 2002; Betancourt *et al*., 2004; Steffens *et al*., 2010a; Steffens *et al*., 2010b; Steffens *et al*., 2011a; Karmkar *et al*., 2018).

One trial reported equal proportions of female and male participants (Seymour, 1983), and the remaining studies did not provide data regarding gender (Minutello *et al*., 1991; Reed *et al*., 1997; Popova *et al*., 2008; Hungund and Thakkar, 2011; Zardo *et al*., 2013; Konuganti *et al*., 2015; Burgos-Quiróz *et al*., 2019). To control postoperative pain researchers used a postoperative protocol (Berdon *et al*., 1964; Cooper *et al*., 1983; Seymour, 1983; Gallardo and Rossi, 1990; Gallardo and Rossi, 1992; Betancourt *et al*., 2004; Popova *et al*., 2008; Rashwan, 2009; Aghasizadeh *et al*., 2011; Kashefimehr *et al*., 2017; Karmkar *et al*., 2018; Burgos-Quiróz *et al*., 2019), a preoperative protocol (Minutello *et al*., 1991; Trombelli *et al*., 1996; Pilatti *et al*., 2006; Steffens *et al*., 2010a; Steffens *et al*., 2010b; Hungund and Thakkar, 2011; Steffens *et al*., 2011a; Steffens *et al*., 2011b; Peres *et al*., 2012; Zardo *et al*., 2013; Konuganti *et al*., 2015; Giorgetti *et al*., 2018), both protocols (Pearlman *et al*., 1997), and occasionally compared these protocols (Vogel *et al*., 1992; Tucker *et al*., 1996; Reed *et al*., 1997; Salazar *et al*., 2002).

Nonsteroidal anti-inflammatory drugs (NSAIDs) were employed in the majority of studies (Cooper *et al*., 1983; Minutello *et al*., 1991; Gallardo and Rossi, 1992; Vogel *et al*., 1992; Trombelli *et al*., 1996; Pearlman *et al*., 1997; Salazar *et al*., 2002; Betancourt *et al*., 2004; Popova *et al*., 2008; Steffens *et al*., 2010b; Aghasizadeh *et al*., 2011; Hungund and Thakkar, 2011; Karmkar *et al*., 2018).

Steroidal anti-inflammatories (SAIDs) were used exclusively in only one study (Steffens *et al*., 2011a) just like opioids (Berdon *et al*., 1964). In the other trials there were comparisons between NSAIDs and SAIDs (Pilatti *et al*., 2006; Steffens *et al*., 2010a; Steffens *et al*., 2010b; Peres *et al*., 2012; Zardo *et al*., 2013; Konuganti *et al*., 2015; Giorgetti *et al*., 2018), between NSAIDs and analgesics (Gallardo and Rossi, 1990; Tucker *et al*., 1996; Reed *et al*., 1997; Rashwan, 2009; Burgos-Quiróz *et al*., 2019), and between analgesics (Seymour, 1983; Kashefimehr *et al*., 2017).

Regarding the type of periodontal surgery that was studied, most trials reported on mucoperiosteal flaps for scaling and root planning (Seymour, 1983; Gallardo and Rossi, 1990; Vogel *et al*., 1992; Trombelli *et al*., 1996; Tucker *et al*., 1996; Reed *et al*., 1997; Betancourt *et al*., 2004; Pilatti *et al*., 2006; Rashwan, 2009; Steffens *et al*., 2010a; Steffens *et al*., 2010b; Aghasizadeh *et al*., 2011; Hungund and Thakkar, 2011; Steffens *et al*., 2011a; Steffens *et al*., 2011b; Konuganti *et al*., 2015; Karmkar *et al*., 2018); five of these studies described the possibility of bone involvement where necessary (Vogel *et al*., 1992; Trombelli *et al*., 1996; Tucker *et al*., 1996; Reed *et al*., 1997; Betancourt *et al*., 2004). Three studies involved mucogingival surgery with palate graft (Popova *et al*., 2008; Zardo *et al*., 2013; Giorgetti *et al*., 2018), two studies reported on the modified Widman flap technique (Gallardo and Rossi, 1992; Burgos-Quiróz *et al*., 2019), and a further two studies discussed crown lengthening (Peres *et al*., 2012; Kashefimehr *et al*., 2017). A few studies presented diverse types of periodontal surgery (Berdon *et al*., 1964; Pearlman *et al*., 1997), and three did not mention the type of periodontal surgery that was performed (Cooper *et al*., 1983; Minutello *et al*., 1991; Salazar *et al*., 2002).

Pain was evaluated using several validated and non-validated instruments. Fifteen studies employed the 0-10 or the 0-100 visual analogue scale (VAS) (Seymour, 1983; Trombelli *et al*., 1996; Pearlman *et al*., 1997; Reed *et al*., 1997; Betancourt *et al*., 2004; Steffens *et al*., 2010a; Aghasizadeh *et al*., 2011; Hungund and Thakkar, 2011; Steffens *et al*., 2011a; Steffens *et al*., 2011b; Peres *et al*., 2012; Kashefimehr *et al*., 2017; Karmkar *et al*., 2018; Burgos-Quiróz *et al*., 2019). The 101-point numeric rating scale (NRS-101) was applied in seven studies (Pilatti *et al*., 2006; Rashwan, 2009; Steffens *et al*., 2010a; Steffens *et al*., 2010b; Zardo *et al*., 2013; Konuganti *et al*., 2015; Giorgetti *et al*., 2018), and the four-category verbal rating scale (VRS-4) was used in eight studies (Pilatti *et al*., 2006; Popova *et al*., 2008; Rashwan, 2009; Steffens *et al*., 2010b; Steffens *et al*., 2011b; Konuganti *et al*., 2015; Kashefimehr *et al*., 2017; Giorgetti *et al*., 2018). As described previously, seven studies employed a selection of more than one of the previously mentioned scales to assess pain (Pilatti *et al*., 2006; Rashwan, 2009; Steffens *et al*., 2010a; Steffens *et al*., 2010b; Steffens *et al*., 2011b; Konuganti *et al*., 2015; Kashefimehr *et al*., 2017). Only one study implemented the McGill Pain Questionnaire (Minutello *et al*., 1991), and another seven studies used their own tool to evaluate pain parameters (Berdon *et al*., 1964; Cooper *et al*., 1983; Gallardo and Rossi, 1990;

Gallardo and Rossi, 1992; Vogel *et al.*, 1992; Tucker *et al.*, 1996; Salazar *et al.*, 2002).

There was a considerable variation between the studies regarding postoperative follow-up. The measurement of pain intensity ranged from immediately after surgery to seven days after surgery, as well as periods in between.

Risk of bias assessment

The risk of bias summary is shown in Figure 2. The random sequence generation was part of every evaluated study and consequently no study was classified as having high risk of bias in this category. Very few trials presented sufficient information about the allocation of the concealment domain so most of them were classified as either unclear or high risk of bias (Berdon *et al.*, 1964; Betancourt *et al.*, 2004; Peres *et al.*, 2012). For this reason, this assessment criterion was not retained for the risk of bias classification at study-level.

Few studies were categorized as having a high risk of bias regarding the blinding of participants and personnel (Tucker *et al.*, 1996; Salazar *et al.*, 2002; Popova *et al.*, 2008; Konuganti *et al.*, 2015; Karmkar *et al.*, 2018; Burgos-Quiróz *et al.*, 2019), and the blinding of outcome assessment domains (Tucker *et al.*, 1996; Salazar *et al.*, 2002; Konuganti *et al.*, 2015; Burgos-Quiróz *et al.*, 2019). Regarding the incomplete outcome data item, two studies were considered to have a high risk of bias (Gallardo and Rossi, 1992; Konuganti *et al.*, 2015), and the selective reporting criteria had a single study with that same rating (Reed *et al.*, 1997). Six trials were classified as having high risk due to other biases, including the use of free self-reporting in relation to pain assessment, the lack of homogeneity of the sample, very small sample size, the design not corresponding to an RCT, and uncertainty of outcomes.

In conclusion, out of 29 surveys, eleven were considered to have a high risk of bias (Berdon *et al.*, 1964; Seymour, 1983; Gallardo and Rossi, 1992; Tucker *et al.*, 1996; Reed *et al.*, 1997; Salazar *et al.*, 2002; Popova *et al.*, 2008; Hungund and Thakkar, 2011; Konuganti *et al.*, 2015; Karmkar *et al.*, 2018; Burgos-Quiróz *et al.*, 2019), twelve were rated as having unclear risk of bias (Cooper *et al.*, 1983; Gallardo and Rossi, 1990; Minutello *et al.*, 1991; Vogel *et al.*, 1992; Trombelli *et al.*, 1996; Rashwan, 2009; Pilatti *et al.*, 2006; Steffens *et al.*, 2010b; Steffens *et al.*, 2011a; Steffens *et al.*, 2011b; Zardo *et al.*, 2013; Giorgetti *et al.*, 2018), and six were deemed to have low risk of bias at study-level (Pearlman *et al.*, 1997; Betancourt *et al.*, 2004; Steffens *et al.*, 2010a; Aghasizadeh *et al.*, 2011; Peres *et al.*, 2012; Kashefimehr *et al.*, 2017).

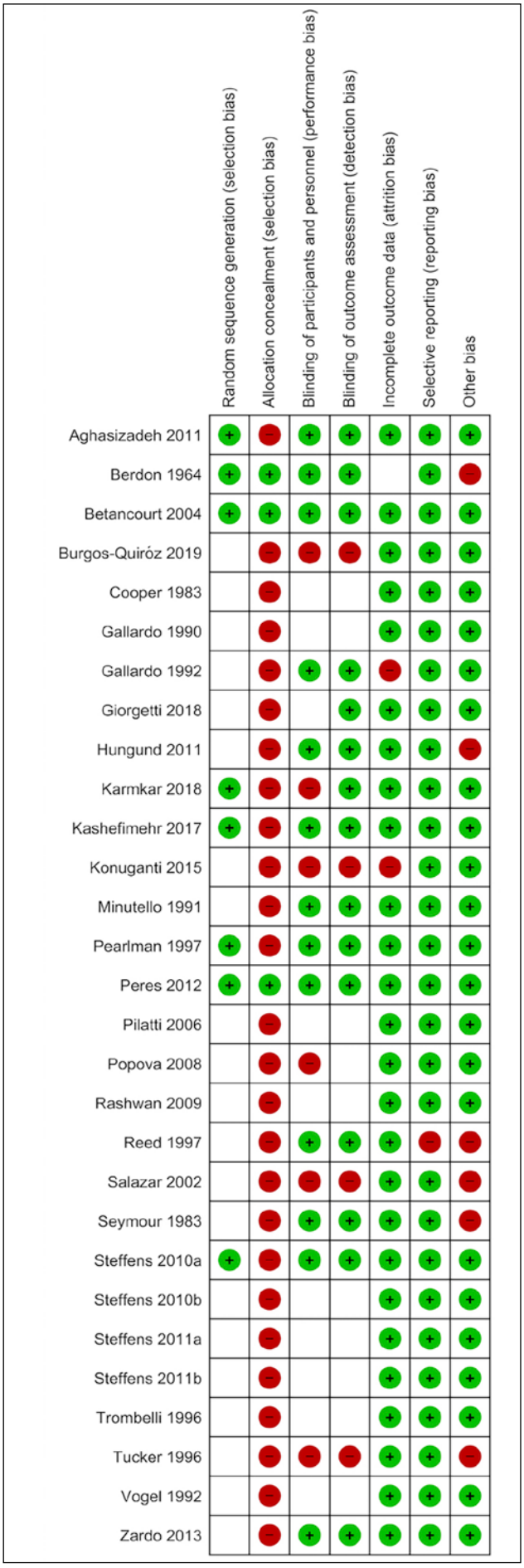

Figure 2. Risk of bias summary.

Meta-analysis

For the meta-analysis, we included the studies regarding numerical data availability, and their classification as low or unclear risk of bias for the random sequence generation and blinding of outcome domains (key domains). Three studies did not present extractable data (Berdon *et al*., 1964; Cooper *et al*., 1983; Reed *et al*., 1997), two were rated as having high risk of bias in the blinding of outcome criterion (Tucker *et al*., 1996; Betancourt *et al*., 2004), and another two did not meet any of these requirements (Salazar *et al*., 2002; Konuganti *et al*., 2015). 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 (Pearlman *et al*., 1997). Some studies did not involve a placebo comparison (Popova *et al*., 2008; Rashwan, 2009; Aghasizadeh *et al*., 2011; Peres *et al*., 2012; Giorgetti *et al*., 2018; Karmkar *et al*., 2018; Burgos-Quiróz *et al*., 2019), and another three studies presented diverging follow-up periods (Minutello *et al*., 1991; Hungund and Thakkar, 2011; Kashefimehr *et al*., 2017). Consequently, the aforementioned studies were also discarded from the meta-analysis. Thus, eleven studies remained for the meta-analysis (Seymour, 1983; Gallardo and Rossi, 1990; Gallardo and Rossi, 1992; Vogel *et al*., 1992; Trombelli *et al*., 1996; Pilatti *et al*., 2006; Steffens *et al*., 2010a; Steffens *et al*., 2010b; Steffens *et al*., 2011a; Steffens *et al*., 2011b; Zardo *et al*., 2013).

Regarding the pain intensity in terms of the preoperative analgesia protocol, out of 375 patients, 238 were from the intervention group (with SAIDs and NSAIDs) and 137 were from the placebo group (Figure 3A). At two hours of follow-up, both the 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=0.88; I^2=0%) (Figure 3A).

Concerning the pain intensity in terms of the postoperative analgesia 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<0.00001). The overall SMD was -0.77 [95% CI -1.03, -0.51] and we did not detect heterogeneity in the data (p=0.42; I^2=0%) (Figure 4A).

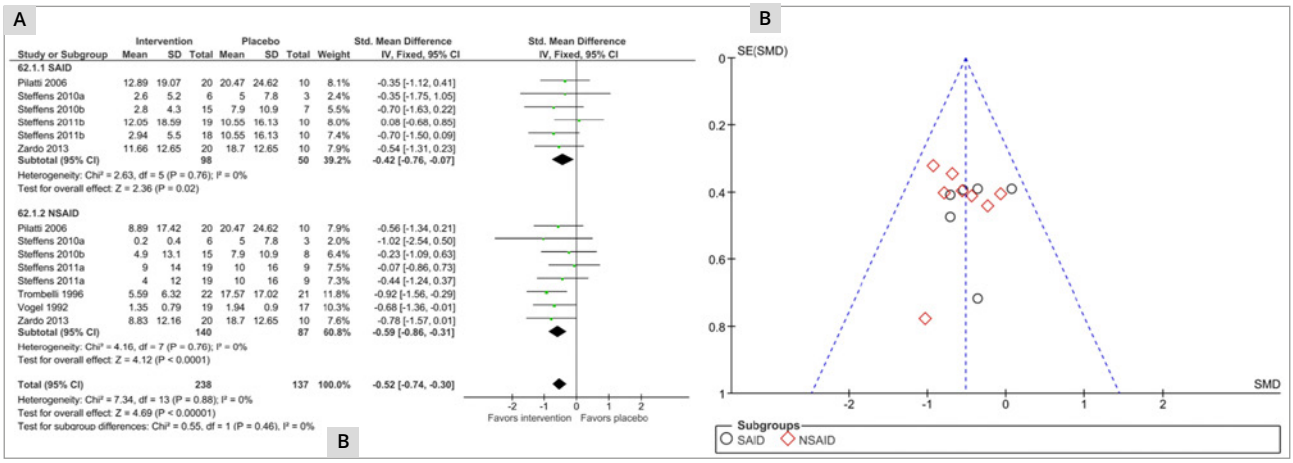

Figure 3. Forest plot (A) and Funnel plot (B) of the intensity of pain in preoperative protocol at two hours of follow-up.

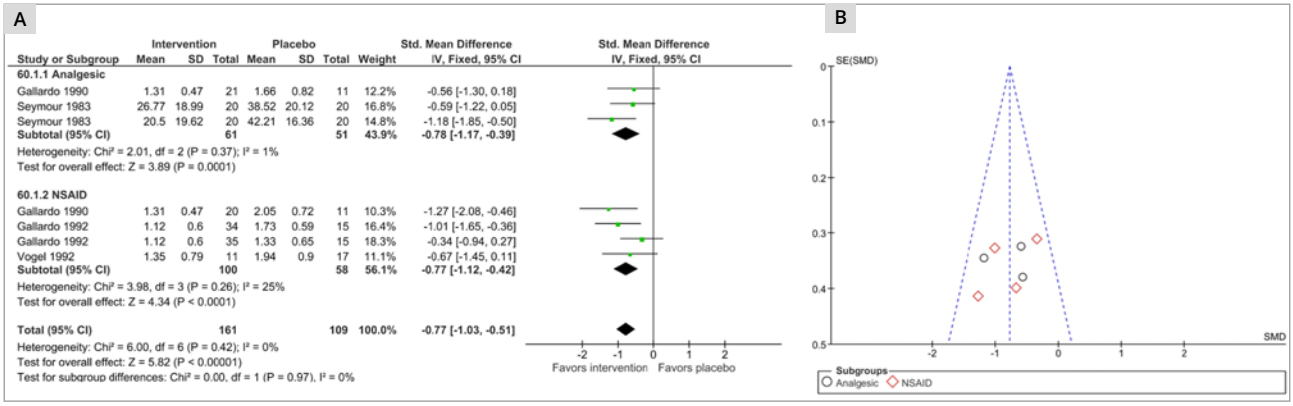

Figure 4. Forest plot (A) and Funnel plot (B) of the intensity of pain in postoperative protocol at two hours of follow-up.

Publication bias and quality of evidence

Throughout our visual examination for all the outcomes we perceived asymmetry in all the funnel plots (Figures 3B and 4B). Even though we conducted extensive research in gray literature and later tested some modifications for the analyses (such as the fixed-effects models instead of random-effects models, and mean difference instead of SMD) the graphs remained asymmetrical.

The quality of evidence for each outcome is presented in the GRADE evidence profile (Table 2). 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. There were some limitations in study execution, so the risk of bias was taken as serious. We also considered 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 the moderate quality of the evidence.

Discussion

We observed that the preoperative analgesia protocol had similar results to the postoperative analgesia protocol when their effects were compared to the placebo at two hours follow-up in pain control after periodontal surgery. The analyses favored the intervention in both cases. In this case, the size effect was mildly more significant for the postoperative strategy; nevertheless, both protocols presented a moderate effect on pain control.

These results were similar to those presented by two SRs published in the early 2000s (Møiniche *et al*., 2002; Ong *et al*., 2005). The latter evaluated preoperative analgesia for acute postoperative pain in several medical and dental interventions, including the administration of NSAIDs and opioids. 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 (Møiniche *et al*., 2002; Ong *et al*., 2005). On the order hand, another study showed evidence supporting the use of oral corticosteroids for this indication appears limited (Wagner *et al*., 2021).

Overall, preoperative analgesia corresponds to preemptive analgesia. Its purpose is to prevent the settlement of central sensitization from the incision moment until the initial postoperative period. Preemptive analgesia outcomes are very controversial, given the heterogeneity of methodologies applied in trials. Nonetheless, combinations of preoperative, transoperative, and postoperative interventions that interfere with the inflammatory process have shown promising results in reducing pain intensity and postoperative analgesic consumption (Pogatzki-Zahn *et al*., 2006; Katz *et al*., 2011). Furthermore, analgesia protocols do not need

Table 2. Grading of Recommendations Assessment, Development and Evaluation Approach (GRADE).

	Certainty assessment						Nº of patients		Effect		Certainty	Importance
Nº of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention protocols	Placebo	Relative (95% CI)	Absolute (95% CI)		
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
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

[a]The pain assessment process was not clear. [b]Asymmetrical funnel plot. CI. Confidence interval. SMD. Standardized mean difference.

to be implemented before or after surgical intervention, considering that factors such as analgesic effectiveness, prolonged analgesic effect, and central sensitization are more relevant elements than the moment of pharmaceutical administration (Pogatzki-Zahn and Zahn, 2006; Vadivelu *et al*., 2014).

Our study included a small range of drugs in each meta-analysis. Both kinds of analyses incorporated NSAIDs: the preoperative protocols included selective COX-2 inhibitors, non-selective NSAIDs and SAIDs; the postoperative protocols included non-opioid analgesics and non-selective NSAIDs. Some of these drugs corresponded to the most frequently prescribed medications by dental professionals for postoperative pain, such as NSAIDs (Etikala *et al*., 2019). However, NSAIDs are frequently associated with adverse effects at regular dosages, such as gastric ulcer and discomfort; and gastric hemorrhage and renal toxicity at high dosages (Reed *et al*., 1997; Peres *et al*., 2012). The pharmacological group is a determinant of adverse effects regardless of the protocol used (Rashwan, 2009; Trombelli *et al*., 1996). An alternative pharmacological group option for postoperative discomfort is steroidal anti-inflammatory drugs (Fernandes *et al*., 2019; Wagner *et al*., 2021). These are employed in dental surgery and have good outcomes in reducing inflammation and controlling pain. SAIDs provide long-acting effects and have a biological half-life of up to 54 hours; their adverse effects (peptic ulcers, hypertension, edema, muscle weakness, delayed wound repair, hyperglycemia, suppressed response to infection, cataracts, osteoporosis, depression, and psychosis) are usually addressed by supra-physiologic doses or long-term treatments such as dexamethasone, which was the SAID included in this SR (Alexander and Throndson, 2000).

Our results showed that the main SMD for the preoperative protocol was -0.52, while postoperative protocol was -0.77. It indicates that both protocols presented a moderate effect on pain control (Sawilowsky, 2009). This result also suggests that postoperative strategy had an additional 32% on size effect due to the absence of SAIDs in this analysis. Preoperative protocol gathered NSAID and SAIDs groups and postoperative protocol gathered only NSAIDs and analgesics groups. Our analysis was performed two hours postoperatively. SAIDs present a delayed onset of action and peak plasma concentration (up to 2 hours for the included drug) (Alexander and Throndson, 2000; Zardo *et al*., 2013) compared to NSAIDs and analgesics (15 to 45 minutes for the included drugs) (Trombelli *et al*., 1996; Rashwan, 2009; Costa *et al*., 2015).

It is also necessary to consider that even with placebo treatment, all the studies' pain scores were qualified as mild to moderate postoperative pain. Each protocol considered only one moment of postoperative evaluation according to data availability; therefore, we did not cover the full period of the peak of postoperative pain in our analyses, which corresponded to six and eight hours of follow-up (Reed *et al*., 1997; Pilatti *et al*., 2006; Rashwan, 2009; Zardo *et al*., 2013; Caporossi *et al*., 2020). In this SR, we also noticed that allocation concealment was a vulnerable issue for the included studies; 90% of the papers assessed in this SR were affected. Additional studies, including a minimum eight-hour follow-up period, as well as a combination of preoperative and postoperative measures to prevent postoperative pain in periodontal surgical procedures, are necessary to evaluate analgesic effectiveness and medication consumption. None of the RCTs included in this SR assessed patient-centered outcomes. The assessment of comfort after periodontal surgery with anti-inflammatory drugs for postoperative pain control constitutes patient-centered care. It measures patient satisfaction with the intervention and should be considered in clinical trials.

Conclusions

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 compared to placebos. In practice, since pain is a subjective matter all dental practitioners should customize an analgesia protocol to consider each patient's requirements and the most convenient protocol to be implemented.

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