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BASIC RESEARCH:

Effectiveness and Safety Profile of Short-Term NSAIDs Protocols in Dental Implantology. A Systematic Review of Clinical Evidence

Efectividad y perfil de seguridad del uso a corto plazo de protocolos con AINEs en implantología. Revisión sistemática de la evidencia clínica

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ABSTRACT: This systematic review aimed to assess the clinical effectiveness and biological safety of short-term non-steroidal anti-inflammatory drugs (NSAIDs) in managing postoperative pain following dental implant surgery. A comprehensive literature search was conducted across eight databases through March 2023, following PRISMA guidelines. Only randomized controlled trials (RCTs) evaluating short-term (≤7 days) NSAID use in patients undergoing dental implant placement were included. Outcomes assessed included postoperative pain, swelling, need for rescue medication, patient satisfaction, adverse events, and effects on osseointegration. Risk of bias was assessed using GRADE and OCEMB tools. Ten RCTs met the inclusion criteria. NSAIDs studied included ibuprofen, naproxen, meloxicam, piroxicam, lornoxicam, dexketoprofen, and diclofenac. Most studies reported reduced postoperative pain and lower need for rescue medication with NSAIDs compared to placebo. Several trials also found higher patient satisfaction and reduced swelling. No significant adverse effects on marginal bone loss or osseointegration were observed in the short term. Risk of bias varied: three studies were low risk, four had some concerns, and three had high risk due to inadequate blinding or unclear randomization. The short-term use of NSAIDs appears to be effective in reducing postoperative pain and swelling after dental implant placement without negatively affecting osseointegration. However, heterogeneity in study design, protocols, and outcomes prevented meta-analysis. Further high-quality RCTs with standardized protocols are needed to establish clear clinical guidelines.

KEYWORDS: Dental implants; NSAIDs; Postoperative pain; Osseointegration; Short-term analgesia.

RESUMEN: Esta revisión sistemática tuvo como objetivo evaluar la efectividad clínica y el perfil de seguridad biológica del uso a corto plazo de medicamentos antiinflamatorios no esteroideos (AINEs) en el manejo del dolor postoperatorio tras la colocación de implantes dentales. Se realizó una búsqueda exhaustiva de literatura en ocho bases de datos hasta marzo de 2023, siguiendo las directrices PRISMA. Se incluyeron únicamente ensayos clínicos aleatorizados (ECA) que evaluaran el uso a corto plazo (≤7 días) de AINEs en pacientes sometidos a cirugía de implantes dentales. Se analizaron variables como el dolor postoperatorio, inflamación, necesidad de medicación de rescate, satisfacción del paciente, eventos adversos y efectos sobre la oseointegración. El riesgo de sesgo se evaluó mediante las herramientas GRADE y OCEMB. Diez ECA cumplieron con los criterios de inclusión. Los AINEs evaluados incluyeron ibuprofeno, naproxeno, meloxicam, piroxicam, lornoxicam, dexketoprofeno y diclofenaco. La mayoría de los estudios reportaron una reducción del dolor postoperatorio y menor necesidad de medicación de rescate con AINEs en comparación con placebo. Varios ensayos también evidenciaron mayor satisfacción del paciente y menor inflamación. No se observaron efectos adversos significativos en la pérdida ósea marginal ni en la oseointegración en el corto plazo. El riesgo de sesgo fue variable: tres estudios presentaron bajo riesgo, cuatro mostraron algunas preocupaciones y tres presentaron alto riesgo debido a un cegamiento inadecuado o aleatorización poco clara. El uso a corto plazo de AINEs parece ser eficaz para reducir el dolor y la inflamación postoperatoria tras la colocación de implantes dentales, sin afectar negativamente la oseointegración. Sin embargo, la heterogeneidad en los diseños, protocolos y resultados de los estudios impidió realizar un metaanálisis. Se necesitan ECA de alta calidad con protocolos estandarizados para establecer recomendaciones clínicas claras.

PALABRAS CLAVE: Implantes dentales; AINES; Dolor postoperatorio; Oseointegración; Analgesia de corto plazo.

INTRODUCTION

The insertion of dental implants is a widely used and successful therapeutic option for patients with partially and totally edentulous jaws (1). Zarb and Koka (2012) defined dental implant osseointegration as a time-dependent healing process by which clinically asymptomatic rigid fixation of alloplastic materials is achieved and maintained in the bone during functional loading (2). The definition further explains that the stages of osseointegration are divided into three overlapping stages: early immunoinflammatory response, angiogenesis, and osteogenesis. The cells populating the implant surface during the first 24 hours consist primarily of inflammatory cells, and this early phase of implant healing is often referred to as the immunoinflammatory response (3). Over the next 2 to 4 days, more infiltrating macrophages and monocytes appear at the peri-implant area. These cells are responsible for removing waste and secreting large amounts of cytokines and growth factors, responsible for stimulating future mesenchymal cell recruitment and proliferation, angiogenesis, and matrix collagen deposition. Various stimuli can cause tissue injury during these processes, both exogenous and endogenous, which induce a complex reaction in the vascularized connective tissue called inflammation. The vascular response leads to the accumulation of fluid and leukocytes in the extravascular tissues and is closely related to the repair process. The inflammatory response

is necessary to destroy, attenuate, or maintain the injurious agent localized and simultaneously initiates a series of events that will promote the healing of the injured tissue (4). Thus, inflammation is fundamentally a protective response, and in the absence of this process, infections would spread uncontrolled, wounds would never heal, and the injured organs would present suppurative lesions permanently (5, 6).

Inflammation can be systemic when caused by trauma, infection, or surgery or local when caused by external injury. In the latter, inflammatory pain will always be associated with the region where the inflammation is located; thus, implant surgery is accompanied by frequent post-operative pain, primarily during the first four days after the intervention. Prostaglandins, among other inflammatory factors, sensitize peripheral nerve endings and produce electrophysiological changes that result in pain sensation. The surgical damage causes a firing of high-speed myelinated A-delta fibers that, ultimately, transmit the pain signal to the central nervous system, where the inflammatory pain signal is interpreted. Consequently, pain results in the activation of slow, demyelinated C fibers to peak 48 to 72 hours after surgery (7). As a result, inflammatory mediators, such as analgesics, will be more efficient during acute postoperative pain, especially if taken multimodally, including agents capable of inhibiting the perception of pain peripherally.

Research for analgesic protocols to manage postoperative pain after implant surgery includes a variety of approaches using different medications, such as non-steroidal anti-inflammatory drugs (NSAIDs), strict opioids, and dual analgesic modalities. Different pharmacological schemes have also been investigated, such as preventive analgesia and multimodal prescriptions. Reports on the clinical efficacy of these diverse approaches significantly varied because of the different routes, doses, and schedules. The American Society of Anesthesiologists and the American Pain Society declared that the inadequate management of postoperative pain can trigger unpleasant physiological and psychological results. Prevalence of acute pain after implant surgery has been reported to be over 80%, and it has mostly been reported as moderate/severe localized pain which resolves after approximately 4 days (8).

Clinical data indicates that preoperative analgesic medications may effectively inhibit nociceptor hypersensitization and, consequently, reduce postoperative pain (9). However, the use of NSAIDs to treat postoperative pain in dental implantation has been under debate because of possible biological complications arising, especially after chronic use of these analgesics, which may even affect the osseointegration process (10). However, there is still controversy regarding some methodological aspects of the available studies supporting this idea, due to NSAIDs being commonly prescribed to treat this short-term pain. Therefore, considering the biological elements that trigger the placement of dental implants and the body's inflammatory response, we consider the importance to evaluate the available evidence from clinical trials to determine the effect of the administration of NSAIDs in the control of postoperative pain after implant surgery. Considering the above, the present study aimed to evaluate the literature to determine the analgesic effectiveness and biological safety profile on the short-term use of non-steroidal anti-inflammatory medication for the management of postoperative pain in oral implantology.

METHODS

STUDY DESIGN

To address the research's purpose, a systematic review of randomized controlled trials (RCTs) was designed and implemented in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) used by

Moher & Liberati *et al*. 2009 (11), the Cochrane Group fundamentals, and Higgins and Green's recommendations (2011).

CRITERIA FOR STUDY SELECTION

To identify and select the relevant articles reporting the clinical analgesic efficacy and/or safety profile on the short-term use of NSAIDs after dental implant therapy we only considered eligible randomized clinical trials [RCTs] study designs. Observational studies, case reports, and narrative reviews were excluded, as well as in vitro or animal studies, abstracts, and unpublished data. The following Population, Interventions, Control, and Result (PICO) question was proposed:

- Population: Patients undergoing single or multiple dental implant surgery.
- Intervention: Short-term administration of NSAIDs (maximum of 7 days).
- Comparison: Placebo/other analgesics.
- Outcome: Postoperative pain scores (visual analogue scale (VAS), marginal bone loss, safety profile, swelling, use of rescue medication and report of adverse events.

LITERATURE SEARCH STRATEGY AND DATA EXTRACTION

A systematic search on Google Scholar, MEDLINE/PubMed, SCOPUS, Web of Science, Wiley Online Library, OVID, SCIELO, and Clinicaltrials.gov was made to identify all relevant studies. The search was performed in the above electronic databases until March 2023 without language or publication date restrictions. The search algorithm was: (("NSAIDs"/“Short-term Analgesia”/"postoperative pain"/"Analgesia"/“Ibuprofen”/“Naproxen”/“Acetaminophen”/“Sulindac”/“Etodolac”/“Ketoprofen”/“Celecoxib”/“Diclofenac”/“Meloxicam”/“Ketorolac”/“Flurbiprofen”/“Etoricoxib”/“Piroxicam”/ “Tenoxicam”/ AND "Dental implants") OR ("NSAIDs" /“Short-term Analgesia”/"postoperative pain"/"Analgesia"/“Ibuprofen”/“Naproxen”/“Acetaminophen”/“Sulindac”/“Etodolac”/“Ketoprofen”/“Celecoxib”/“Diclofenac”/“Meloxicam”/“Ketorolac”/“Flurbiprofen”/“Etoricoxib”/“Piroxicam”/ “Tenoxicam”/ AND “Osseointegration”/“Implant Failure")). After completing the search and excluding the duplicated articles, two blinded and previously standardized reviewers independently screened the authors' names, titles, abstracts, keywords, and study design with objective inclusion criteria. Discussion and consensus among the reviewers resolved differences in the screening results. Selected studies were retrieved as full-text papers, and two authors independently extracted the data on a data extraction sheet (11).

RISK OF BIAS ASSESSMENT

The two reviewers who extracted the data appraised the methodological quality and validity of the selected studies independently using the Grading of Recommendations Assessment Development and Evaluation (GRADE) (12) and Oxford Centre for Evidence-Based Medicine (OCEMB) criteria (13). The table reported by Pozos-Guillen *et al*. (2016) was used to reduce potential biases in terms of the quality of RCTs (14). A score was assigned to each segment of the scale, relying on the reviewers' expertise and discernment, with the aim of ascertaining the significance of that segment in influencing the results of each study. The highest score was 16 and correlated to the study's quality, but the individual point was assessed for each study.

RESULTS

RESEARCH RESULTS

The literature search was performed between August 2024 and March 2025. The database search yielded 10,574 non-duplicated titles (Figure 1). After excluding 9,961 papers based on their title and abstract, 603 studies with full-text exami-

nation were excluded for not complying with the inclusion criteria. Studies due to different interventions, case reports, animal studies, and use of NSAIDs for more than 7 days were not included. No additional studies were identified via handsearch. A total of 10 RCT's were included in the qualitive synthesis.

CHARACTERISTIC OF THE INCLUDED STUDIES

The systematic review included 9 parallel RCTs: Bahamam *et al*. 2017, Sanchez-Perez 2018, Bölükbasi *et al*. 2012, Pereira *et al*. 2020, Karabuda *et al*. 2007, Bhutani *et al*. 2019, Meta *et al*. 2017, Alissa, *et al*. 2009, Kumchai, 2025 (16-24) and one crossover RCTs: Rajeswari *et al*. 2017 (25) (Table 1). The studies included the use of NSAIDs: ibuprofen, dexketoprofen, diclofenac sodium, lornoxicam, meloxicam, naproxen AND tenoxicam. The timing of administration was based on a short-term scheme that went from 24hrs to one week posterior to the intervention. The RCTs outcome measure in the included studies was post operative pain, swelling, patient satisfaction, need for rescue medication, adverse events and effects on osseointegration.

RISK OF BIAS

Three studies were evaluated as low risk of bias for all domains (17, 19, 24). Four studies raised some concern due to blinding, randomization and randomization method not being clear or suitable for the design of the study (16, 20,21, 25). Three studies were considered at a high risk of bias (18, 22, 23) due to blinding, randomization method not being suitable for the design and unclear results (Table 2).

POSTOPERATIVE PAIN

All the studies investigated the short-term use of NSAIDs. Table 3 shows that 8 studies reported postoperative pain using VAS (16-22, 25). Lower postoperative pain was reported by subjects who were administered ibuprofen *vs*. placebo (16, 19), piroxicam *vs*. placebo (21), dexketoprofen trometamol *vs*. placebo (17), ibuprofen *vs*. placebo (16), and lornoxicam *vs*. placebo (18). The patients treated with ibuprofen and those treated with dexamethasone showed significantly less pain in the morning than the placebo group on days 1, 2, 3, and 4 via the NRS-101 scale ($p<0.01$), but on the afternoon of day 3 there were no significant differences. Notably however, there were no statistically significant differences between ibuprofen and dexamethasone at any time-points (16), neither on ketorolac *vs*. ketorolac + betamethasone (22), nor meloxicam *vs*. teloxicam (20). Inconclusive results were reported in one split-mouth study (25) because unpaired data analysis was applied to paired data (published information was not sufficient to do the statistical analysis).

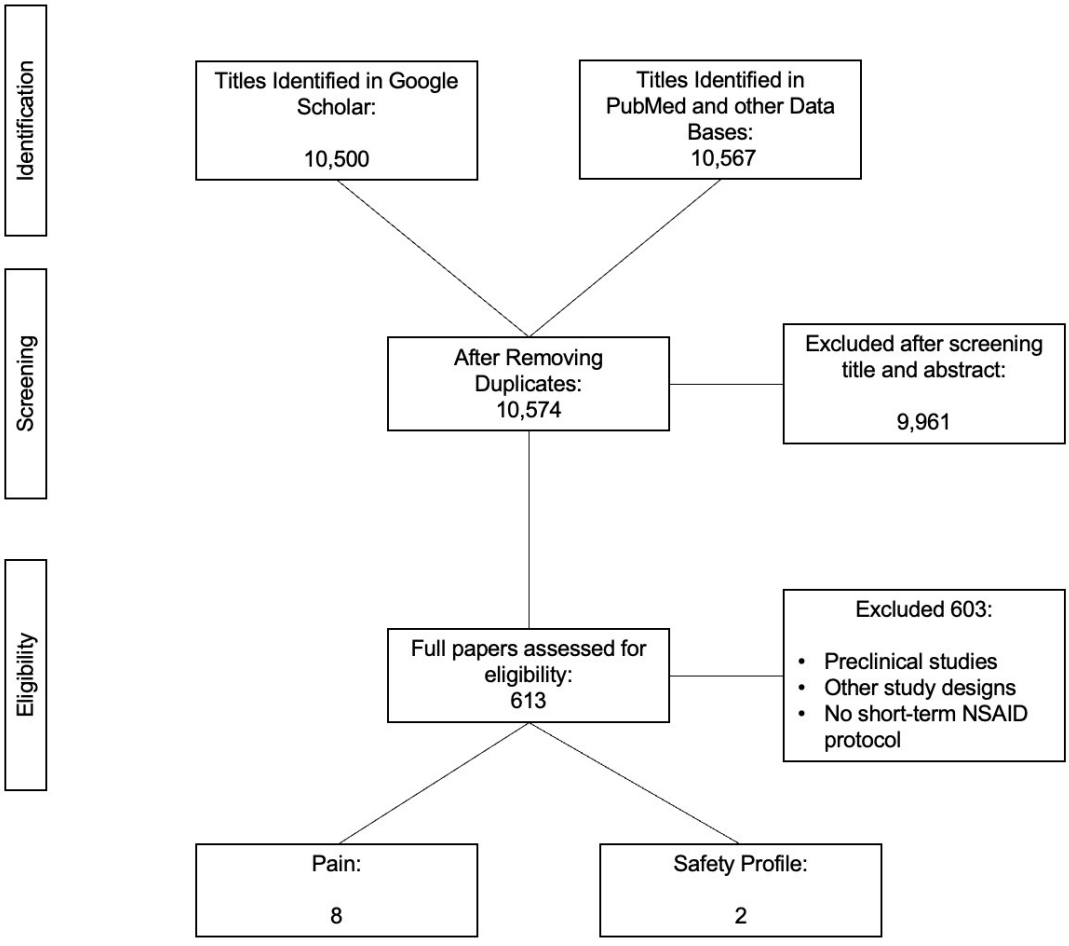

Figure 1. PRISMA study selection flowchart.

Table 1. Clinical studies included in the systematic review.

Study	RCT Design	Implants	Age	NSAIDs	Protocol	Outcome
Karabuda, 2007	Parallel	Multiple	53 (mean)	Meloxicam *vs* Tenoxicam	1 day before surgery, 1h before surgery and for 2 days after surgery	Postoperative Pain, need for rescue medication
Alissa, 2009	Parallel	Single/multiple	61	Ibuprofen *vs* placebo	600mg 4 times x day for 1 week	Effects on osseointegration (marginal bone loss around dental implants)
Bölükbasi, 2012	Parallel	Single/multiple	18-65	Lornoxicam *vs* Placebo	After surgery	POP, patient satisfaction, adverse events, need for rescue medication
Bahamam, 2017	Parallel	Single	≥ 18	Ibuprofen *vs* dexametha-sone *vs* placebo	1h before + 6h after first dose	POP, patient satisfaction, adverse events, need for rescue medication
Meta, 2017	Parallel	Multiple	40-85	Ketorolac *vs* Ketorolac + bethameta-sone	2h before surgery	POP
Rajeswari, 2017	Cross-over	Single	30-65	Diclofenac diethylamine patches *vs* Oral diclo-fenac sodium	After surgery for 72h	POP, Adverse events, patient satisfaction
Sánchez-Pérez, 2019	Parallel	Single	≥ 18	Dexketo-profen trometamol *vs* placebo	15 min before surgery	POP and adverse events
Bhutani, 2019	Parallel	Single	16-40	Piroxicam *vs* placebo	1h before surgery	POP and swelling
Pereira, 2020	Parallel	Single	37-74	Ibuprofen *vs* placebo	1h before surgery	POP, need for rescue medication
Kumachi, 2025	Parallel	Single	25-76	Naproxen *vs* placebo	After surgery 200mg 3 times a day for 7 days	Effect on osseointegration (marginal bone loss around dental implants and ISQ values)

Table 2. Analysis of Risk of Bias of RCTs included in the systematic review.

Study	RTC design	Sample calculation	Randomization	Randomization Method	Blinding	Follow-up	Response variable	Concordance of measuring method	Assumption of the statistical test	Results	Total
		1: unspecified 2: present	0: Not present 1: unclear 2: present	0: Unsuitable / not described 1: adequate	0: not described 1: not clear 2: present and described	0: incomplete 1: intention to treat / other method 2: complete	0: cualitive subjective 1: cualitive objective 2: quantitive	0: not present 1: unclear	0: not present 1: unclear/ categorical data 2: present and described	0: incomplete 1: complete	
Bahamam 2017	Parallel	2	2	0	0	2	1	1	1	0	9
Sánchez-Pérez 2018	Parallel	2	2	1	2	2	1	1	2	1	14
Bölükbasi 2012	Parallel	1	1	0	0	2	1	1	1	0	7
Pereira 2020	Parallel	1	2	1	1	1	2	1	2	1	12
Rajeswari 2017	Cross-over	1	1	0	0	2	1	1	1	1	8
Karabuda 2007	Parallel	1	1	0	0	2	1	1	1	1	8
Bhutani 2019	Parallel	1	1	0	0	2	1	1	1	1	8
Meta 2017	Parallel	1	1	0	0	2	1	1	1	0	7
Alissa 2009	Parallel	1	1	0	1	2	0	1	1	0	7
Kumchai 2025	Parallel	2	2	0	1	2	2	2	1	1	13

Table 3. Narrative review synthesis of the evaluated outcomes in RCTs.

Post-operative pain synthesis	
Karabuda, 2007	No difference between meloxicam *vs* tenoxicam
Bölükbasi, 2012	Lower with lornoxicam *vs* placebo
Bahamam, 2017	Lower with ibuprofen or dexamethasone *vs* placebo, No difference between ibuprofen *vs* dexamethasone
Meta, 2017	No difference between ketorolac *vs* ketorolac + betamethasone
Rajeswari, 2017	Inconclusive results
Sánchez-Pérez, 2019	Lower with Dexketoprofen trometamol *vs* placebo
Bhutani, 2019	Lower with Piroxicam *vs* placebo
Pereira, 2020	Lower with Ibuprofen *vs* placebo
Safety profile synthesis	
Alissa, 2009	No significant difference in mean marginal bone level changes from baseline between ibuprofen *vs* placebo
Kumchai, 2025	No significant difference in mean marginal bone level and ISQ values changes from baseline between naproxen *vs* placebo
Patient's satisfaction synthesis	
Bölükbasi, 2012	Higher with lornoxicam *vs* placebo
Bahammam, 2017	Higher with ibuprofen or dexamethasone vs placebo, No difference between ibuprofen *vs* dexamethasone
Rajeswaeri, 2017	Higher with trasdermal diclofenac diethylamine patch *vs* oral diclofenac sodium
Swelling synthesis	
Bhutani, 2019	Lower with piroxicam *vs* placebo
Need for rescue medication synthesis	
Karabouda, 2007	No difference between meloxicam *vs* lornoxicam
Bölükbasi, 2012	Lower with lornoxicam *vs* placebo
Bahammam, 2017	Lower with ibuprofen or dexamethasone *vs* placebo, No difference between ibuprofen *vs* dexamethasone
Rajeswari, 2017	Lower with transdermal diclofenac diethylamine patch *vs* oral diclofenac sodium
Pereira, 2020	Lower with ibuprofen vs placebo
Adverse events synthesis	
Bölükbasi, 2012	None
Bahammam, 2017	None
Rajeswari, 2017	Lower with trasdermal diclofenac diethylamine patch *vs* oral diclofenac sodium
Sánchez-Pérez, 2018	More bleeding with dexketoprofen trometamol *vs* placebo

EFFECTS OF NSAIDS ON OSSEOINTEGRATION

One study reported the safety profile on the short-term use of NSADs (23). Preoperative radiographic examination including panoramic and/or periapical radiographs was taken for all patients. After implant placement, the marginal bone level was assessed by measuring the distance in millimeters between the reference point to the lowest observed point of marginal bone contact with the implant. The radiographs were readable for marginal bone level assessment for 89 implants (73%) of the 122 implants, 41 implants in the ibuprofen group and 48 implants in the placebo group. The overall mean marginal bone levels relative to the reference point in the ibuprofen group was -1.11 mm at the 3-month and -1.09 mm at the 6-month radiographic evaluation, while the corresponding values for the placebo group were -0.92mm and -1.19 mm respectively. The short-term use (1 week) of NSADs had no significant difference in marginal bone loss in comparison to the placebo group from the baseline to 3- and 6-month follow-up.

Kumchai *et al*. 2025 (24), on a placebo-controlled pilot study, did not observe any statistically significant differences marginal bone loss after up to 16 weeks of follow-up between subjects from naproxen and placebo groups. Marginal bone level was defined as the maximum distance from the implant-abutment interface on the implant side to the marginal bone The marginal bone level was measured from the mesial and distal sides of an implant in millimeters using CLINIVIEW 11 (Dexis, Pennsylvania, USA). Only the vertical marginal bone level was measured. Two clinicians recorded the mesial and distal aspects of each implant and intraclass correlation coefficient was calculated.

Regarding ISQ values, no significant increases were observed at 4 weeks compared to baseline in subjects receiving naproxen, whereas subjects receiving placebo had an increased ISQ (+41%), although this difference was considered not statistically significant. Similarly, they observed a smaller increase in ISQ values in the naproxen group (+34%) compared to the placebo group (+67%) at 16 weeks, although this difference was not statistically significant between groups. Similarly, we observed no statistically significant difference in marginal bone loss between groups at any time point. The estimated required sample sizes were done using a power analysis at 80% and 90% power at the 0.05 level of significance for both ISQ and marginal bone levels.

PATIENT SATISFACTION

Three studies looked into the patient's satisfaction during the postoperative period (16, 18, 25). Higher patient's satisfaction was reported with ibuprofen *vs*. placebo (16), ibuprofen or dexamethasone *vs*. placebo (16), and lornoxicam vs. placebo (18) in the early postoperative period (12-48 h).

In a split-mouth study (25), the majority of patients preferred transdermal diclofenac diethylamine over oral diclofenac sodium.

SWELLING

Only one study investigated swelling after dental implants placement. The swelling in each patient was measured using following measurements: (1) the distance between the lateral corner of the eye and the angle of the mandible; (2) the distance between the tragus of the ear and the outer corner of the mouth. The preoperative sum of these two measurements was considered as the base value. The measurements were also recorded on the first third and fifth postoperative days. The difference between the measurement values and base values indicated the facial swelling for that day and graded as 0 ("no swelling", <10 mm), grade I ("mild swelling," 10-20 mm), grade

II ("moderate swelling," 20-30 mm), and grade III ("severe swelling," >30 mm). Lower swelling was reported with piroxicam vs. placebo (21).

NEED FOR RESCUE MEDICATION

Five of the included RCTs reported the need for a rescue medication during the postoperative period (16, 18-20, 25). Lower need for rescue medication was reported with ibuprofen *vs*. placebo (16, 19), dexamethasone *vs*. placebo (16), and lornoxicam *vs*. placebo (18). All patients in the placebo group required rescue medication. There was no significant difference in the numbers of rescue medication pills taken in the ibuprofen and dexamethasone groups, and in both groups the numbers taken were lower than the number taken in the placebo group. Time to first rescue medication was also lower in the placebo group than in the ibuprofen and dexamethasone groups ($p<0.01$) (16).

Karabouda *et al*., 2007 (20) findings showed pain intensity and the consumption of rescue analgesics were recorded based on the VAS scores on day 1 after surgery. Sixty-six percent of the patients in group A and 54% of the patients in group B used rescue analgesics on day 1. There were no statistical differences between the groups with regard to the consumption of rescue analgesics during the postoperative period ($x2=1.05$; $P=0.30$). After day 2, most of the patients did not need to use rescue analgesics.

In a split-mouth study (25), the patients did not need rescue medication after transdermal diclofenac diethylamine, but the information was unclear for the subjects on diclofenac sodium.

ADVERSE EVENTS

Finally, five studies reported the occurrence of adverse events (16-19, 25). Bleeding was more frequent with dexketoprofen trometamol *vs*. placebo (17). On statistical evaluation of the 3 scales, the P value suggested that there was no significant difference between the 2 routes of diclofenac at any of the time intervals reported between transdermal diclofenac diethylamine vs. oral diclofenac sodium (25). No adverse events were reported in 3 of the trials (16, 18, 19).

DISCUSSION

Dental implant surgery is known to be a safe procedure, and reducing its post-operative pain may be considered a key component to the overall success of the treatment. This systematic review is focused on the effectiveness and safety profile of the strict, short-term use of NSAIDs in dental implant surgery.

The present study analyzed the relevant clinical trials comparing the use of NSAIDs for the management of post-surgical pain on dental implant therapy, with the aim to evaluate and determine the analgesic effectiveness and the effect on osseointegration of the short-term use of non-steroidal anti-inflammatory use for the management of postoperative pain on dental implant surgery.

Opioids, such as codeine and fentanyl, have well-known analgesic effects, but secondary effects should be considered when administered for postsurgical pain, such as dependency, which has led to be one of the most misused drugs, reporting high levels of abuse (Wehler 2021) (26). Therefore, these types of analgesics should be prescribed only when an alternative therapy is not possible or effective and only for a short period of time. In post-surgical implant placement, pain is usually mild or moderate, although some patients may experience severe pain (25) therefore, analgesic strategies should focus on controlling pain and swelling with the lesser side effects. NSAIDs are widely used in clinical dentistry to manage post-operative pain and inflammation.

Owing to its efficacy in reducing pain and inflammation, NSAIDs are amongst the most popularly used analgesics, confirmed in the WHO's Model List of Essential Medicine (28).

NSAIDs prevent the synthesis of prostaglandin E2 (PGE2) by inhibiting the cyclooxygenase (COX) enzymes, COX1 and COX2 (29); However, PGE2 is part of an inflammatory signaling pathway that is critically important for bone healing and repair. However, animal studies have illustrated that these effects strongly depend on the timing, dose, and duration of NSAIDs treatment (30). No systematic review has assessed the short term use of NSAIDs on the management of post- operative pain and the influence of the safety profile on dental implant surgery.

Two studies have reviewed the literature concerning the possible influence of NSAIDs on the osseointegration of titanium dental implants. Gomes *et al*., 2015 (10), concluded that osseointegration is impaired in the presence of conventional NSAIDs, whilst the review conducted by Kalyvas *et al*., 2008 (31) concluded that short-term post-operative NSAIDs do not appear to negatively impact osseointegration. Two other more recent literature reviews have looked into the use of overall analgesic drugs in the management of pain in dental implant surgery. The authors included experimental studies, *in vitro* studies and animal models. Both reviews concluded that there's insufficient evidence to recommend an analgesic regimen following dental implant surgery (32, 33).

Senerby *et al*. (34), reported that administration of different doses of indomethacin, 1 and 4 mg/kg, for 3 weeks did not influence bone healing around implants in rabbits. Endo *et al*. showed that etodolac (20 mg/kg) administered for 3 weeks significantly affected bone healing in tibia fractures in rats. Martins *et al*. found that ketoprofen (12.5 mg/kg) administered for 30 days in rats with tibia fractures led to increased bone density in the first week of the study but significantly affected bone healing after 21 days of administration (35). Goodman *et al*. (36) evaluated the effect of rofecoxib (12.5 mg/day) administered for 6 weeks on bone growth in surgical trauma of the tibia in rabbits during 3 different time periods: the initial 2 weeks, the final 2 weeks, and continuously for 6 weeks. The results showed that a reduction of bone growth occurred when the drug was administered continuously, but this unwanted effect on bone healing was not observed after 2 weeks of administration. Therefore, it has been suggested that the time of administration of NSAIDs should be considered by clinicians after implant surgery.

As for post-operative pain management, two recent studies looked into the use of analgesics in dental implant surgery. Khouly *et al*. 2021 (32) on a recent systemic review and meta-analysis, concluded that post-operative pain and swelling following oral implant procedures typically subsides following the third post-operative day, and that pain management is most critical for 3 days following surgery. Melini *et al*. 2021 (33), on a recent systemic review stated that the use of analgesics, including NSAIDs, may improve post-operative pain and swelling compared to placebo. Both studies concluded that there is still insufficient data to make a strong clinical recommendation of the use of these analgesics after implant surgery.

The primary limitation of this systematic review is the available evidence and the restricted number of RCTs assessing pain management in dental implant surgery in short periods of time. Also, this review concluded that the heterogeneity of the interventions implemented on these RCTs, the outcomes assessed, and follow-up times, made it impossible to conduct a meta-analysis and provide stronger clinical evidence on the use of NSAIDs in short-term protocols.

Some of the studies included in the review revealed a high risk of bias (18, 22, 23) due to

blinding and the randomization method not being suitable for the study design guiding to unclear results. The heterogeneity of the analgesic drugs prescribed, the analgesic protocols used, and the time for evaluation of pain, prohibited the merging of the results, thus limiting the summary of the findings to a narrative synthesis. Nevertheless, this review suggests that the short-term administration of NSAIDs may provide some advantages in the management of postoperative pain after dental implant placement, whilst maintaining a safety profile. The present review determined the short-term period as less than a week of continuous use of the analgesic, although, as demonstrated in other studies, the possible analgesic protocols should focus on the first 3 days after surgery, reducing the possible undemonstrated effect of NSAIDs on bone healing. Literature offers some analgesic protocols for dental pain based on anticipated post-procedural pain levels (37), but specific evidence-based analgesic schemes for dental implant surgery remain undefined. Unfortunately, the wide variability of surgical procedures used in implantology practice, the different responses of patients to molecules, and the large quantity of therapies and protocols available in the literature make it difficult to provide indications about the ideal treatment for postoperative pain control. After reviewing the published studies and weighing the undesirable effects of other analgesics (opioids), the authors consider that the short-term use of NSAIDs is safe in terms of osseointegration and effective for post-operative implant surgery pain, but further methodologically strong standardized clinical research is desirable.

AUTHOR CONTRIBUTION STATEMENT

Conceived the study design and objectives: M.M.A. and D.C.B.
Designed the search strategy and eligibility criteria M.M.A., D.C.B. and V.E.V.
Conducted the literature search and compiled the initial list of studies: M.B.R.
Independently screened studies and resolved disagreements through discussion: M.B.R. and V.E.V.
Performed data extraction and quality control: V.E.V. and A.P.G.
Assessed risk of bias using the GRADE and OCEBM tools: M.B.R. and D.C.B.
Conducted the data synthesis and interpreted the results: M.B.R., M.M.A. and D.C.B.
Wrote the first draft of the manuscript. All authors reviewed and approved the final manuscript: M.B.R.
Supervised the project and ensured methodological consistency: D.C.B.
Literature search and data extraction: M.B.R., M.M.A., V.E.V. and D.C.B.
Risk of bias analysis: M.B.R., V.E.V. and A.P.G.
Draft and editing: M.B.R., M.M.A, A.P.G., and D.C.B

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