EUROPEAN ENDODONTIC JOURNAL

SYSTEMATIC REVIEW

Medications Used for Prevention and Treatment of Postoperative Endodontic Pain: A Systematic Review

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ABSTRACT

Objective: Prevention and management of postoperative endodontic pain is a common challenge for the endodontists. This systematic review was conducted to evaluate the efficacy and safety of medicament therapeutic protocols in the prevention and management of endodontic pain.

Methods: A literature search was undertaken in MEDLINE, Cochrane Library, LILACs, and SciELO, for articles published until December 2017, without year restriction and written only in English. An additional search was performed in the references of the retrieved studies.

Study eligibility criteria, participants, and interventions: The inclusion criteria were randomised clinical trials that evaluated the use of medications to prevent or control moderate to severe pain in adult patients, using a visual analog scale as a tool for pain measurement. The primary outcome evaluated was the reduction of pain scores. The second outcome evaluated was the need for additional analgesia and the occurrence of adverse events.

Study appraisal and synthesis methods: The quality assessment of the included studies was performed following the Jadad scale to measure the likelihood of bias in pain research reports.

Results: After removing duplicates and excluding the studies that did not meet the selection criteria, ten studies were included tin the systematic review. Among these studies, five studies administered the medications before the endodontic procedures and five studies after. These studies evaluated non-opioid analgesics (acetaminophen), opioid analgesics (tramadol and codeine), nonsteroidal anti-inflammatories (ibuprofen, flurbiprofen, ketorolac tromethamine, etodolac, tenoxicam, and naproxen), steroidal anti-inflammatory (prednisolone) or the association of medications to prevent or control postoperative pain. It was possible to establish a significant relationship between the use of additional analgesics and periapical diagnosis. Adverse events were not observed when the administration occurred before the endodontic procedure. When it was administered after the procedure, adverse reactions were reported in 2 of 3 trials included in the analysis.

Limitations: A restricted number of randomised clinical trials were found, and the difference in the methodology of the studies did not meet the definition of a systemic treatment protocol for prevention or control of postoperative pain.

Conclusion: Nonsteroidal anti-inflammatory drugs are the most common medicament to prevent and control postoperative pain, with ibuprofen being the most investigated. There is a significant association between the use of additional analgesics and periapical diagnoses.

Keywords: Analgesia, endodontics, pain, systematic review, visual analog scale

Please cite this article as: Santini MF, Rosa RA, Ferreira MBC, Barletta FB, Nascimento AL, Weissheimer T, Estrela C, SÓ MVR. Medications Used for Prevention and Treatment of Postoperative Endodontic Pain: A Systematic Review. Eur Endod J 2021;6: 15-24

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Received 20 June 2020,
Accepted 06 August 2020

Published online: February 02 2021
DOI 10.14744/eej.2020.85856

HIGHLIGHTS

- Nonsteroidal anti-inflammatory drugs are the most used for control of postoperative pain.
- There is a significant association between the use of additional analgesics and periapical diagnoses.
- Further studies with consistent methodologies are needed to define systemic treatment protocols for managing of postoperative endodontic pain.

INTRODUCTION

If left untreated, odontogenic pain causes suffering, compromises quality of life, has psychosocial and economic repercussions and is a public health concern (1). Odontogenic pain exacts its toll on sufferers in terms of fewer hours of sleep, reduced accomplishments in activities of daily living, fewer leisure activities, and increased absenteeism at school and work (2).

Pulp and periapical inflammation may have microbiological, physical, and chemical causes. Microbiological causes may involve microorganisms capable of inducing and perpetuating pulp disease or apical periodontitis. Physical causes may include trauma, overinstrumentation and overfilling, or the heat generated during cavity preparation. Chemical causes may include restorative materials, irrigation solutions, intra-canal medications, or filling materials (3). Treatment of endodontic pain may be either local or systemic. Local treatment consists of removing inflamed pulp tissue or neutralizing the toxic contents of pulpal necrosis. Additionally, analgesics (4) and antibiotics may be required to control infection and manage pain (5).

Previous studies have evaluated the association between postoperative pain and patient-related factors (e.g., the existence of preoperative pain), procedures performed (e.g., single-session versus multiple sessions), and medications (e.g., analgesics, antibiotics, and root canal dressings) (6-9).

Prevention and management of pain is a common practice in the routine of an endodontist. Therefore, the need for scientific evidence to support therapeutic decisions shows the need to review the literature on a topic of extreme importance that affects the quality of treatment and well-being of the patient's health.

Thus, the aim of this study was, through a systematic review of the available literature regarding medications used to prevent and treat postoperative endodontic pain, to evaluate the efficacy and safety of these systemic therapies, in order to verify which therapy is the most indicated for clinical practice, through the following question: "What medications are used to control pain in endodontics?"

MATERIALS AND METHODS

Protocol

This systematic review followed PRISMA recommendations (Preferred Reporting Items for Systematic Review and Meta-Analysis) guidelines (http://www.prisma-statement.org) and was registered on the PROSPERO database under number CRD42020202071.

Search strategy

The search was performed by two independent authors (M.F.S. and R.A.R.) in the following databases: MEDLINE, the clinical trials register of the Cochrane Library, LILACS, and SciELO. The electronic search was conducted for articles published up to December 2017, without year restriction and only included studies written in English. The electronic search strategy was developed using the most cited descriptors in previous studies on this theme, combining Medical Subject Heading (MeSH) terms and text word (tw.).

The following terms were combined for each database: 'Dental Pain', 'Toothache', 'Pain Management', 'Analgesics', 'Analgesia', 'Endodontic', 'Dental Pulp Diseases', 'Pulpitis', 'Dental Pulp Necrosis'. The Boolean operators 'AND' and 'OR' were applied to combine the terms and create a search strategy. Also, a hand search was performed for additional relevant publications in the retrieved studies. A list of selected articles, with their respective abstracts, was created to facilitate the exclusion of duplicate articles.

Eligibility criteria

The eligibility criteria were based on the PICO strategy (PRISMA 2009), as follows:

- Population (P): adult patients subjected to endodontic treatments presenting any type of pulpal or periapical diagnosis.
- Intervention (I): administrate medications used for pain control, before or after the endodontic intervention.
- Comparison (C): placebo or groups using medications to pain reduction.
- Outcome (O):
- Primary: reduction in pain scores, measured with a visual analog scale (VAS), after the administration of medication.
- Secondary: use of additional medication and occurrence of adverse events.

We included only randomised clinical trials (RCTs) that evaluated the reduction of moderate to severe postoperative endodontic pain in adults using VAS.

The exclusion criteria were: studies whose publication was not received in full, clinical trials in which pain was not of endodontic origin, studies whose outcome was an improvement in anesthetic efficacy and not postoperative pain reduction, studies in which the medications were not administered via the oral route, studies performed in animals, systematic reviews with and without meta-analysis, reviews, letters, opinion articles, conference abstracts, case reports, series of cases and in vitro investigations.

Selection of the studies

The first stage consisted of the exclusion of the duplicated studies, considering only once, and examining the retrieved titles and abstracts of the selected studies by two independent authors (M.F.S. and R.A.R.) according to the search strategy. When there was an impossibility to judge the studies by title and abstract, the full text was accessed and read for the final decision. The second stage consisted of reading the full texts of the potentially eligible studies to be included based on the eligibility criteria through the PICO strategy. Disagreements on study inclusion were solved by a consensus with a third author (M.V.R.S.).

Data extraction

Two authors (M.F.S. and R.A.R.) independently collected the data from the included studies. Disagreements were solved by consensus or referral to a third author (M.V.R.S). The authors were not blinded to the journals or authors of the selected studies. The following information was extracted from the included studies: author(s) and year of publication, sample characteristics, pain scores before treatment, information about the analgesic regimen used (drug, dose, dosing interval, route of administration and duration of treatment) and aspects related to the

methodological quality of the studies. In cases of missing data, the authors were contacted three times by e-mail.

Quality assessment

Two authors (M.F.S. and M.V.R.S.) independently assessed the quality of the included studies using a 5-point scale described by Jadad et al. (10). The independent evaluation consists of an instrument to measure the likelihood of bias in pain research reports, which evaluates the quality of randomisation, blinding, and reasons for withdrawal. The Jadad et al. (10) scale gives a maximum of 5 points. Up to 2 points are given for randomisation – 1 point for mentioning randomisation and an additional point if the method of randomisation is appropriate. Up to 2 points are given for blinding – 1 point for mentioning blinding and an additional point if the method of randomisation is appropriate. A final point is given for an account of all patients involved in the trial.

RESULTS

Selection of studies

Figure 1 presents the flow diagram of the search strategy. Initially, a total of 432 studies were identified after the searches, but 12 were excluded as they were duplicates. Then, from 405 eligible studies, the titles and abstracts analysis resulted in the inclusion of 16 studies. After extensive reading, five studies were excluded for having pain scores measured in scales other than the VAS, and 1 study was excluded due to low quality (score zero).

Finally, a total of 10 studies were selected for the systematic review.

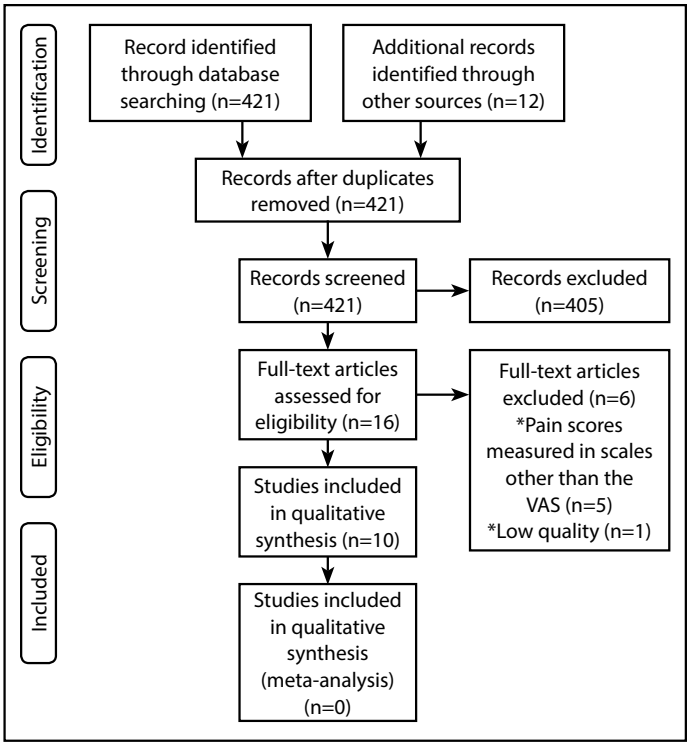

Figure 1. Preferred reporting items for systematic reviews and meta-analyses flow diagram

Data collection and risk of bias

Table 1 summarizes the data collected from the ten clinical trials that met the inclusion criteria (11-20) and their quality scores.

Patient ages ranged from 16 to 68 years. The sample sizes of the included studies varied from 20 to 95 patients, and they were from the United States of America (11, 13-15), Iran (12, 16, 18, 19), Turkey (17), and Brazil (20).

Minimum VAS pain scores ranged between 30 mm and 70 mm. Menke et al. (13), Jalalzadeh et al. (16), and Baradaran et al. (19) did not describe this parameter.

In five studies, the drug was administered before the endodontic procedure, either to prevent postoperative pain (prophylactic use) (13) or to control preoperative pain (12, 15, 16-18). In five studies, the drug was administered after endodontic therapy (11, 14, 18-20).

In eight studies, the control group received a placebo (11, 13-19), except in Sadeghein et al. (12) and Santini et al. (20) studies.

Eight studies used single-dose oral administration for pain control (12-19) except Doroschak et al. (11) and Santini et al. (20).

The participants' characteristics, interventions (dose, intervals, duration), and outcome measures used in the studies were not heterogeneous, making it impossible to carry out a meta-analysis.

Primary outcome

In all clinical trials, reductions in pain scores after administering of different drugs were considered the primary outcome (11-18, 20). Tables 2 and 3 presents the primary outcomes of the included studies.

Five studies that evaluated the analgesic efficacy of medications used before endodontic procedures were included. One study (12) found more significant pain reduction with NSAID (Ketorolac) use when compared to opioid analgesic (acetaminophen/codeine). Menke et al. (13) related a more significant reduction in pain with NSAID (ibuprofen) administration when compared to the use of placebo and a different NSAID (etodolac). Attar et al. (15) found no differences in postoperative pain scores when comparing different formulations of ibuprofen with each other and to placebo. Jalalzadeh et al. (16) found that lower pain scored when a corticosteroid (prednisolone) was administered and compared to a placebo. Finally, Arslan et al. (17) found no differences in pain reduction between a single dose of two separate NSAIDs (tenoxicam and ibuprofen), although both presented more significant pain relief when compared to placebo.

Regarding the studies in which the medications were used after the endodontic procedure, again, five studies were included. One study (11) found a more significant reduction of pain when a combination of NSAID and opioid (flurbiprofen/tramadol) was used and compared to placebo. Menhinick et al. (14) found a significant reduction of pain scores in the first hour when an NSAID (ibuprofen) or an NSAID and a non-opioid analgesic (acetaminophen) was administered and compared to placebo. The authors also found that, at four

TABLE 1. Characteristics of the studies included and its quality scores according to Jadad et al. (1996)

Author/year	Sample	Endodontic problem	Baseline pain (mm)*	Endodontic intervention	Systemic intervention	Comparative group	Data collection	Jadad score
Sadeghein et al., 1999	Adults (16-65 years) Iran n=63	Acute Apical Periodontitis.	≥70	Not specified	Single dose of Ketorolac (10 mg) before the endodontic procedures.	Single dose of acetaminophen/ codeine (325 mg/ 15 mg) before the endodontic procedure.	After the administration of the medicament, 10-min intervals for at 90 min.	3
Doroschak et al., 1999	Adults (18-65 years) USA n=49	Not specified (vital and non-vital teeth).	≥30	Pulp chamber access, and instrumentation of canals.	Tramadol (100 mg) or flurbiprofen (50 mg) or flurbiprofen (50 mg)+ tramadol (100 mg), every 6 hours, for 2 days, after the endodontic procedures.	Placebo	6 h after the administration of the medicament, and then on awakening and before bed.	2
Menke et al., 2000	Adults (>18 years) USA n=36	Not specified (teeth requiring root canal treatment).	0 (patients without preoperative pain)	Pulp chamber access, instrumentation, and filling of canals (single session).	Single dose of etodolac (400 mg) or ibuprofen (600 mg) before the endodontic procedures.	Placebo	Immediately, at 4, 8, 12, 24, 48, and 72 h after root canal therapy was initiated.	3
Menhinick et al., 2004	Adults (>18 years) USA n=57	Not specified (teeth with spontaneous pain).	≥50	Pulp chamber access and instrumentation of canals (no intracanal medicament was placed).	Single dose ibuprofen (600 mg) or ibuprofen (600 mg)+ acetaminophen (1000 mg) after the endodontic procedures.	Placebo	1, 2, 3, 4, 6, 8 h after the administration of the medicament.	5
Attar et al., 2008	Does not report age. USA n=39	Not specified (teeth with spontaneous pain).	≥30	Pulp chamber access, instrumentation of canals (use of calcium hydroxide as intracanal medicament).	Single dose of ibuprofen tablet (600 mg) or liquigel (600 mg), before the endodontic procedures.	Placebo	Immediately, at 6, 12, 18 and 24 h after the endodontic procedures.	3
Jalalzadeh et al., 2010	Adults (18-59 years) Iran n=40	Not specified (single or multirooted teeth, premolar and molar, vital and nonvital pulp and asymptomatic and symptomatic teeth).	Not informed.	Pulp chamber access, instrumentation and filling (single session).	Single dose of prednisolone 30 mg before the endodontic procedures.	Placebo	6, 12 and 24 h after the endodontic procedures.	3

TABLE 1. Cont.

Author/year	Sample	Endodontic problem	Baseline pain (mm)*	Endodontic intervention	Systemic intervention	Comparative group	Data collection	Jadad score
Arslan et al., 2011	Adults (18-52 years) Turkey n=48	Not specified.	≥50	Pulp chamber access, instrumentation and filling.	Single dose of ibuprofen (200 mg) or tenoxicam (20 mg) before the endodontic procedures.	Placebo	Immediately, at 6, 12, 24, 48 and 72 h after the endodontic procedures.	4
Mehrvarzfar et al., 2012	Adults (20-60 years) Iran n=95	Irreversible pulpitis in single-rooted premolars or anterior teeth with no clinical or radiographic signs or symptoms of acute or chronic apical periodontitis.	≥40	Pulp chamber access and instrumentation of canals.	Single dose of tramadol (100 mg) or acetaminophen (325 mg)+ ibuprofen (200 mg)+ caffein (40 mg) or naproxen (500 mg) after the endodontic procedures.	Placebo	6, 12 and 24 h after the administration of the medicament.	5
Baradaran et al., 2014	Adults (20–45 years) Iran n=45	Irreversible pulpitis in molars.	Not informed.	Pulp chamber access and instrumentation of canals.	Single dose of ibuprofen (400 mg) or alprazolam (0.5 mg)+ ibuprofen (400 mg) after the endodontic procedures.	Placebo	4, 6, 12, 24, 48 and 72 hours after the administration of the medicament.	3
Santini et al., 2017	Adults (18–68 years) Brazil N=20	Acute perirradicular abscess	≥40	Pulp chamber access and neutralization	Tramadol (37.5 mg)+ acetaminophen (325 mg) every 4 hours for 3 days.	Codeine (30 mg)+ acetaminophen (500 mg) every 4 hours for 3 days,	Immediately, at 6, 12, 24, 48 and 72 h after the administration of the medicament.	5

VAS: Visual Analogue Scale

and eight hours, the association of medicaments promoted the more significant reduction of pain scores. Finally, during the follow-up, the use of NSAID isolated did not differ from placebo. Mehrvarzfar et al. (18) found a reduction in pain when a single dose of NSAID (naproxen), an association of medications (acetaminophen/ibuprofen/caffeine) or an opioid analgesic (tramadol) was used and compared to placebo. Also, it found that a single dose of tramadol was significantly less effective. Baradaran et al. (19) showed that the combination of an NSAID (ibuprofen) with a benzodiazepine (alprazolam) presents a significant reduction of pain scores at four and six hours after treatment when compared to isolated ibuprofen and placebo, and a significant reduction at twelve hours when compared to placebo. Finally, Santini et al. (20) found that the administration of two combinations of opioid (codeine or tramadol) and non-opioid (acetaminophen) analgesics resulted in a decrease in the pain scores, without differences regarding analgesic efficacy.

Secondary outcomes

The use of additional medication and the occurrence of adverse events were considered secondary outcomes.

Eight trials provided additional medication in cases where the tested drugs did not control pain (11, 13-17, 19, 20).

In the studies that evaluated the safety of these medications, no adverse events occurred when the drug was administered before the endodontic procedure (12, 16, 17). When drug

TABLE 2. Main results in the articles in which the medications were used previously the endodontic procedure

Author/year	Analgesic efficacy	Additional analgesic consumption	Adverse reactions occurrence
Sadeghein et al., 1999	Ketorolac was more effective than acetaminophen/codeine (P=0.005).	Not informed.	No adverse reactions were reported by patients.
Menke et al., 2000	Ibuprofen determined greater reduction in pain scores at 4h (P=0.0111) and 8 h(P=0.0397), being statistically different from etodolac and placebo. In other times, the groups were not statistically different.	Additional analgesic: the same tested medication in each experimental group. Twenty-two patients (61%) required additional medication. It was not specified which group these patients belonged. There was a relationship between periapical diagnosis (P=0.007) and need for additional medication. For patients with acute apical periodontitis and Phoenix abscess, there was a significant increase in the need for additional medication. There was no relationship between pulp diagnosis and the need for additional medication.	Not informed.
Attar et al., 2008	There was no significant difference in scores of postoperative pain of ibuprofen formulations, when compared to each other or placebo.	Additional analgesics: acetaminophen (dose not reported). No patient used additional analgesic.	Not informed.
Jalalzadeh et al., 2010	At 6, 12 and 24 h, prednisolone determined lower pain scores (P<0.05). Both patients in the placebo group, and the prednisolone group had higher intensity of postoperative pain in non-vital teeth. After 6 h, 30% of patients in the placebo group and 75% in the prednisolone group had mild to moderate pain. After 12 h, 25% of patients in the placebo group and 80% in the prednisolone group had mild pain or no pain. After 24 h, 15% of patients in the placebo group and 85% of the prednisolone group had no pain.	Additional analgesic: Ibuprofen or acetaminophen (dose not reported). Fourteen patients in the placebo group and nine in the prednisolone group consumed additional medication and were excluded from the study.	No adverse reactions were reported by patients.
Arslan et al., 2011	In the period of 6 h, there was no difference between tenoxicam and ibuprofen (P=0.723). Both promoted greater pain relief than placebo (P=0.000). At 12, 24, 48 and 72 h, there was no difference between tenoxicam, ibuprofen and placebo (P>0.05).	Additional analgesic: the same tested medication in each experimental group. No patient used additional analgesic.	No adverse reactions were reported by patients.

administration occurred after the endodontic procedure, adverse reactions were reported in three of four trials included in the analysis (11, 14, 20).

DISCUSSION

This systematic review identified ten studies that evaluated the effectiveness of oral analgesics and anti-inflammatory drugs to treat odontogenic pain measured by VAS. It was difficult to obtain more robust evidence because of the small sample sizes for each of the drugs and the dosing regimens studied.

The majority of RCTs investigating pharmacological control of postoperative pain in dentistry use extractions of impacted third molars as dental pain models (21, 22). This model includes

TABLE 3. Main results in the articles in which the medications were used after the endodontic procedure

Author/year	Analgesic efficacy	Additional analgesic consumption	Adverse reactions occurrence
Doroschak et al., 1999	Pain decreased in all groups over time. In the first two times of measurement, the flurbiprofen/ tramadol association showed greater pain reduction compared to placebo. Patients who used flurbiprofen showed lower pain scores in the morning after treatment as compared to those who received placebo and tramadol.	Additional analgesic: Acetaminophen 650 mg. Not informed if any patient used.	Flurbiprofen group: dyspepsia (25%) and one case of headache. Tramadol group: sedation, nausea, emesis, and euphoria. Flurbiprofen/tramadol group: combined gastrointestinal/central nervous system symptoms (sedation, nausea, emesis, and euphoria)
Menhinick et al., 2004	In all groups, there was a reduction in pain scores in the first hour after thetreatment (P<0.001). The reductions were 71% for placebo, 76% for ibuprofen and 96% foribuprofen/ acetaminophen. At 4 and 8 h, there was a significant difference between ibuprofen/ acetaminophen and placebo (P<0.001) and between ibuprofen and ibuprofen/acetaminophen (P=0.025). During the 8 h of following up, ibuprofen and placebodid not differ (P=0.481).	Additional analgesic: acetaminophen 300 mg+ codeine 30 mg. Three patients from the placebo group, one from the ibuprofen group and one from acetaminophen/ ibuprofen group required additional analgesic (diagnosis: irreversible pulpitis and acute apical periodontitis).	Of the 57 participants, a total of 23 reported adverse side effects. Placebo group: highest degree of headache, dizziness or drowsiness (53%) and nausea or emesis (21%). Ibuprofen group: headache, dizziness or drowsiness (30%) and nausea or emesis (5%) and others (5%). Ibuprofen/ acetaminophen group: headache, dizziness or drowsiness (28%) and nausea or emesis (6%).
Mehrvarzfar et al., 2012	At 6, 12 and 24 h, the intensity of pain was lower in the experimental groups than in the placebogroup (P<0.01). There were no differences between naproxen and acetaminophen/ibuprofen/ caffeine (P>0.05). Tramadol was the lesseffective (P<0.05).	Does not provide additional analgesic. Two patients in group acetaminophen/ibuprofen/ caffeine and one patient in each group-tramadol, naproxen and placebo-made use of additional analgesics and were excluded from the study.	Not informed.
Baradaran et al., 2014	The VAS scores in alprazolam+ ibuprofen group were significantly lower at 4 hours (P<0.0001) after treatment when compared to the other groups. Six hours after treatment, the VAS score in ibuprofen+alprazolam group was significantly lower than ibuprofen group (P=0.018) and placebo group (P=0.018). Twelve hours after the treatment, the VAS score in ibuprofen+alprazolam group was significantly lower than the placebo group (P<0.001). The comparison of VAS score at 24, 48 and 72 hours between the three groups showed no significant differences (P>0.05).	Additional analgesic: acetaminophen 325 mg No patient used.	Not informed.
Santini et al., 2017	In both groups, pain decreased over time. Administration of codeine/ acetaminophen presented a significant reduction in pain scores	Additional analgesic: acetaminophen 500 mg, every 4 hours. Forty percent of patients in each group used the additional drug, a number that is not different between the groups	There was no difference between the groups regarding the frequency of adverse reactions (P ≅ 0.999). Eight patients

TABLE 3. Cont.

Author/year	Analgesic efficacy	Additional analgesic consumption	Adverse reactions occurrence
	after 12, 24, 48 and 72 hours of treatment (P<0.05). The scores at 48 and 72 hours were also lower than the 6 hours scores Administration of tramadol/ acetaminophen decreased pain scores in all experimental periods of time compared to baseline (P<0.05)	(P≅0.999). An average of 1.5 and 1.6 additional tablets per patient was used in the codeine/ acetaminophen and tramadol/ acetaminophen groups, respectively.	(80%) form each group experienced at least one adverse reaction, including dizziness, drowsiness, nausea, headache, vomiting and others.

healthy patients undergoing elective procedures, in which the inflammatory process originates from surgical trauma. In contrast, endodontic pain often stems from pulp and periapical pathologies caused by microorganisms. Therefore, the therapeutic approaches suggested in surgical articles cannot be directly extrapolated to situations of odontogenic pain.

While the role of drug treatment for the prevention and control of odontogenic pain has been investigated, the administration routes, instruments for measuring pain and the doses and drugs have varied (23-25).

It was found that NSAIDs are used every day to treat odontogenic pain (11-18). A recent systematic review noticed that ibuprofen is the most studied NSAID (26). Although clinical trial results indicate analgesic activity, at this time, there are insufficient data to recommend the use of ibuprofen for relieving postoperative endodontic pain in patients with preoperative pain (26). Besides, it may be challenging to justify NSAID use for pain not associated with other signs of inflammation, such as swelling, local heat, and hyperemia, given the gastrointestinal and cardiovascular side effect profiles of NSAIDs. Accordingly, NSAID use should be very well justified before use in this setting.

To mitigate the undesirable effects of non-selective NSAIDs, cyclooxygenase-2 (COX-2) selective inhibitors are now widely used. In this review, tenoxicam exhibited performance similar to that of ibuprofen within 6 hours (17). However, despite the potential advantages of selective COX-2 inhibition, systematic reviews have shown no difference in analgesic efficacy between selective and non-selective NSAIDs (27, 28). Furthermore, in light of these drugs' associations with cardiovascular and hepatotoxicity events, a careful review of their potential benefits and risks is warranted before use.

Several studies investigated the use of analgesic combinations, such as acetaminophen with codeine (12, 20), acetaminophen with tramadol (20), acetaminophen with NSAIDs (14, 18), and tramadol with NSAIDs (11). These combinations, when used after endodontic therapy, were generally more effective in controlling pain than the other drugs evaluated (11, 14, 18) because of the different receptor sites and mechanisms of action employed by the component medications. Non-opioid analgesics, such as acetaminophen and NSAIDs, act by inhibiting the synthesis of prostaglandins, and opioids act by binding to specific opioid receptors.

Only one study evaluated the use of corticosteroids (prednisolone) for postoperative analgesia, with effects superior to those of placebo (16). From a clinical point of view, it is essential to compare a prospective medication with analgesic regimens already used by endodontic professionals. Furthermore, given the goal of obtaining pain relief, it would likely be most appropriate to use drugs with analgesic characteristics. Corticosteroids are used to reduce the inflammatory response when the risks of physiological inflammation outweigh the benefits. However, in situations with defined infection, as in pulp necrosis cases, fighting inflammation may not be appropriate, as a well-coordinated inflammatory response is essential to locate an injury and combat microorganisms.

In the clinical trials in which an analgesic was administered before the endodontic procedure, no adverse events were noted (12, 16, 17). However, in the other three studies involving analgesic administration after the endodontic procedure, adverse effects were reported in association with opioids and NSAIDs, both alone and in combination (11, 14, 20). Four clinical trials included in our review did not evaluate the occurrence of adverse reactions (13, 15, 18, 19).

The use of a single dose to evaluate the primary outcome complicates the analysis of the drugs' analgesic efficacy because, in the case of moderate to severe pain, the majority of patients require additional analgesia. In previous studies, this analgesia was performed, in general, with the different drugs tested (14, 15, 16, 19). The use of different experimental drugs during the follow-up period may confound the analgesia by the tested drug and add adverse reactions. To obtain evidence with greater clinical applicability relevance, studies with larger sample sizes, multiple doses, and longer follow-ups are necessary.

It is known that postoperative pain involving vital pulp results from periapical tissue damage (e.g., overinstrumentation, sodium hypochlorite injection into periapical tissues, overfilling, perforation) (29). For pain control after root canal procedures, some studies have investigated prophylactic analgesics (13, 15-17, 19). However, the inclusion of teeth with normal or inflamed pulp in some cases may lead to misinterpretation of the results. In that event, it cannot be claimed that the absence of postoperative pain is due to either preserved integrity of the periapical tissues or medication efficacy. Some authors have justified the inclusion of these two groups through the similar distribution of pulpal and periapical pathology in all

experimental groups (13, 15, 16). Similarly, it was revealed that prophylactic analgesics could prevent postoperative pain. However, once inflamed pulp tissue was removed, there was no need for systemic analgesic administration.

Another way to analyze the effectiveness of analgesia is to evaluate the need for additional analgesics. In a study by Menke et al. (13), there was an association between diagnosis and the need for additional analgesics. The results indicated that the treatment of vital pulp, regardless of analgesic administration, significantly relieved pain. The results showed that patients with severe preoperative pain and pain with percussion had a greater need for additional medication for pain relief (13).

Baseline VAS pain scores differed among trials. Based on the categorization of pain levels as mild (10 to 30 mm), moderate (40 to 60 mm) and severe (70 to 100 mm) (30), it is apparent that in most of the reviewed studies, initial VAS scores were equal to or greater than 30 mm (11, 12, 14, 15, 17-20). In the study of Menke et al. (13), patients had no pain before the procedure, and Jalalzadeh, et al. (16) did not mention this parameter. None of the studies was the potential association between severe preoperative pain and analgesic efficacy evaluated as measured by VAS.

Some studies used, associated with VAS, other scales to measure the relief of pain promoted by the medications (11, 14, 15). Categorical pain scales and Heft-Parker are the most used (11, 14, 15). The authors observed that the scales were highly correlated, confirming that VAS alone is sufficient to measure the pain intensity. Because it is widely used in clinical trials, this literature review sought articles that used VAS as an instrument for measuring pain, which allowed comparisons with available data, including number needed to treat (NNT) values (31, 32).

The evaluation of the quality of the articles included in the review was based on the scoring system proposed by Jadad et al. (10). This scale assesses the quality of clinical trials of analgesic efficacy, assigning scores ranging from 0 to 5. Of the ten articles reviewed, one received a score of 4, and three received 5. However, most of the articles presented methodological flaws, such as a lack of information on randomisation methods (11, 12, 15, 16, 19), outputs, or losses of patients during the observation period (17). Additionally, the number of individuals allocated to each experimental group was small, and only five studies described sample size calculations (11, 14, 17, 18, 20).

This study indicates a lack of homogeneity on the data presented by those included. For these reasons, a meta-analysis could not be performed. The need to establish therapeutic protocols based on scientific evidence is imperious since pain presents a strong influence on the patient's well-being before, during and after the endodontic intervention. However, future studies on the subject must have standardisation concerning their methodologies, in order to be possible to compare and choose one therapy over another.

The pain scores established for inclusion in the study, the drugs used, the employed analgesic schemes, and the follow-up were different among the RCTs. Furthermore, most of the studies grouped patients with vital pulp and those with pulp necrosis (11, 13-17).

Ultimately, we believe that the incidence of postoperative pain is related to the quality of the treatment performed by the dentist, and then it could be a positive influence on postoperative endodontic pain. This statement indicates that effective endodontic treatment will decrease the pulp inflammatory response or the numbers of microbes necessary for a better outcome.

CONCLUSION

Based on the data collected in this systematic review, there is an insufficient number of RCTs using a consistent methodological standard to define systemic treatment protocols for managing postoperative endodontic pain. NSAIDs are the most common medication used to control postoperative pain, with ibuprofen being the most investigated. Secondarily, it was possible to establish a significant association between the use of additional analgesics and periapical diagnoses.

Disclosures

Conflict of interest: The authors declare that there is no conflict of interest.

Ethics Committee Approval: Not applicable.

Peer-review: Externally peer-reviewed.

Financial Disclosure: The authors declare that they have not received any type of funding for this work.

Authorship contributions: Concept – M.V.R.S., M.F.S., R.A.R.; Design – M.V.R.S., M.F.S., R.A.R.; Supervision – M.V.R.S., M.F.S., R.A.R., M.B.C.F.; Funding - M.V.R.S., M.F.S., R.A.R., M.B.C.F., F.B.B., A.L.N., T.W., C.E.; Materials - None; Data collection &/or processing – M.V.R.S., M.F.S., R.A.R.; Analysis and/or interpretation – M.V.R.S., M.F.S., R.A.R.; Literature search – M.V.R.S., M.F.S., R.A.R.; Writing – M.V.R.S., M.F.S., R.A.R., M.B.C.F., F.B.B., A.L.N., T.W., C.E.; Critical Review – M.V.R.S., M.F.S., R.A.R., M.B.C.F., F.B.B., A.L.N., T.W., C.E.

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