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Review Article

An updated meta-analysis on the efficacy and safety of medications administered after non-surgical root canal treatment in managing postoperative pain

Dorsa Samani[1*], Armin Arian[2*], Kimia Kelidari[3*], Mahsa Moosapoor Farkhani[3], Aida Keshavarzi[2], Kimia Sadat Kazemi[4], Sepehr Haghshoar[2], Sharare Jahangiri[5], Fereshteh Molaei[6], Sahar Rajaei[7], Haleh Fakhimi Rezaei[8], Sina Ahmadi[9], Mohaddeseh Belbasi[10], Alireza Mokhtari Sakhvidi[11], Mahdyieh Naziri[12]

[1]Faculty of Dentistry, Tabriz University of Medical Sciences, Tabriz, Iran; [2]Faculty of Pharmacy, Cyprus International University, Nicosia, Cyprus; [3]Faculty of Dentistry, Mashhad University of Medical Sciences, Mashhad, Iran; [4]Faculty of Dentistry, Shahid Beheshti University of Medical Sciences, Tehran, Iran; [5]Faculty of Dentistry, Isfahan University of Medical Sciences, Isfahan, Iran; [6]Faculty of Dentistry, Islamic Azad University, Borujerd, Iran; [7]Faculty of Dentistry, Yazd University of Medical Sciences, Yazd, Iran; [8]Faculty of Dentistry, Nakhchivan State University, Nakhchivan, AZ; [9]Xian Jiaotong University, Xi'an, Shaanxi, China; [10]Students Research Committee, School of Pharmacy, Zanjan University of Medical Sciences, Zanjan, Iran; [11]Dental Faculty, Tehran Medical Sciences, Islamic Azad University, Tehran, Iran; [12]Students Research Committee, School of Medicine, Iran University of Medical Sciences, Tehran, Iran. [*]Equal contributors and co-first authors.

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Abstract: Effective management is one of the most important factors in mitigating postoperative endodontic pain (PEP). The purpose of this network meta-analysis was to compare the therapeutic effects and safety of different drugs commonly used for pain relief after non-surgical endodontic treatment. We searched the Scopus, PubMed, and Google Scholar databases until February 2024. Titles, abstracts, and full texts were identified according to predetermined criteria. Data were extracted from the selected publications, and a quality assessment was performed for the included studies. Sixteen RCTs with 2,021 participants were included in the meta-analysis. All included studies investigated the impact of NSAIDs on pain reduction in nonsurgical endodontic treatment. A statistically significant reduction in pain was observed at 8 h (pooled effect = -3.10, I^2 = 100%), 12 h (pooled effect = -1.69, I^2 = 99.2%), 24 h (pooled effect = -1.48, I^2 = 99.9%), 48 h (pooled effect = -1.42, I^2 = 99.4%), and 72 h (pooled effect = -0.64, I^2 = 73.1%) of follow-up. The funnel plot was symmetrical, and sensitivity analysis excluded one article in 72 h follow-up. Overall, this meta-analysis demonstrated that NSAIDs and corticostreoids are statistically effective in relieving pain after non-surgical endodontic treatment. However, owing to the significant differences between studies and heterogenicity, additional randomized controlled trials are needed to validate this correlation further.

Keywords: Postoperative endodontic pain, network meta-analysis, pain management, non-surgical endodontic treatment

Introduction

Postoperative pain management is an essential part of non-surgical endodontic treatment. It significantly impacts patient comfort and satisfaction with the treatment, as well as the overall outcomes [1]. Despite advances in endodontic techniques and materials, many patients still experience moderate-to-severe pain during the post-treatment stage following root canal procedures [2]. This pain, primarily due to periapical inflammation and tissue damage, may persist for days after treatment and therefore requires appropriate pharmacological intervention [3].

Treatment of postoperative endodontic pain (PEP) has been the subject of numerous pharmacological studies [3]. It is well established that non-steroidal anti-inflammatory drugs (NSAIDs) are first-line medications for pain management in endodontic cases [4], and the effectiveness of their performance in modulating the host inflammatory response with anal-

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gesic effects is well documented [5]. However, the ideal time for administration, dosage, and optimal medication remain controversial among endodontists. Numerous clinical trials have demonstrated that NSAIDs such as ibuprofen and indomethacin effectively manage postoperative root canal pain by inhibiting prostaglandin synthesis. Despite their widespread use, variability in individual responses and potential gastrointestinal side effects remain concerns that limit their universal application [6, 7].

It has been evidenced in many clinical investigations that NSAIDs like ibuprofen and indomethacin are effective in controlling the postoperative pain of the root canal by inhibiting prostaglandin synthesis. Reduction in pain is observed with NSAIDs beginning at 6 hours post-treatment; these continue well beyond that period [8]. To date, it remains one of the most widely used NSAIDs, with a host of recent studies evaluating combination therapy with acetaminophen [9]. Additionally, NSAID premedication has demonstrated improved success rates in achieving local anesthesia, particularly in cases of irreversible pulpitis [10].

NSAIDs are used extensively, however their effectiveness varies depending on the medicine and how it is taken. In contrast to oral delivery, transdermal NSAID patches (such as diclofenac and ketoprofen) have demonstrated encouraging outcomes in lowering pain at 48 hours with fewer gastrointestinal side effects, even if oral formulations are still conventional [11]. NSAID side effects, such as nausea, gastrointestinal distress, dizziness, and sleepiness, have been documented, though [12]. In addition, premedication with corticosteroids could lead to improved pain relief, highlighting the ongoing debate regarding optimal pharmacological management of PEP [13].

Previous studies have examined the use of various NSAIDs, opioids, corticosteroids, and their combinations for the treatment of PEP. One of the most prominent randomized controlled trials (RCT), published by Gopikrishna and Parameswaran (2003), compared the effectiveness of rofecoxib and ibuprofen in the treatment of PEP. Rofecoxib was shown to provide better pain relief than ibuprofen at 12 and 24 hours after starting treatment [14]. Similarly, Arslan et al. (2011) examined the prophylactic use of tenoxicam and ibuprofen and reported that both were effective in relieving early postoperative pain [15]. However, owing to the heterogeneity of study designs, sample sizes, and outcome measures, inconsistencies exist in the literature, making it difficult to reach definitive conclusions regarding the most effective pain management strategies.

Insufficient evidence to establish the best NSAID regimen, dosage, and mode of administration for long-term pain management is one of the current gaps in the research. These discrepancies underscore the necessity of additional comparative research assessing the efficacy and safety of various NSAIDs and complementary treatments.

Despite the large volume of research in this area, there is an enormous gap in synthesizing the available evidence to provide clear, evidence-based recommendations for postoperative pain management in the context of non-surgical endodontic treatment.

RCTs conducted in this field, had used different kinds of medications, in different times (before, during, and after dental procedures), and evaluated pain after different intervals. Current inconsistencies in the literature indicate many uncertainties regarding the comparative effectiveness and safety of different medications and interventions, further highlighting the need for such a comprehensive up-to-date meta-analysis.

The aim of the current meta-analysis is to systematically provide evidence for the effectiveness and safety of postoperative medications for pain relief after non-surgical endodontic treatment by synthesizing data from high-quality RCT. Thus, we decided to choose only RCTs which have used medications after procedure to evaluate post-operative medications.

The comparative effectiveness of different pharmacological agents such as NSAIDs, opioids, corticosteroids, and combination therapies are compared, and their safety properties are evaluated. Such recommendations are made to provide evidence-based guidelines for pain management strategies after non-surgical endodontic treatments and to optimize patient care and treatment outcomes.

Table 1. Search strategy for selected databases

Search engine	Search strategy	Additional filters	Total results
Pubmed	((((((((((“analgesic*”[Title/Abstract]) OR (“anti-inflammatory agents”[Title/Abstract])) OR (“anti-bacterial agents”[Title/Abstract])) OR (“antibiotic*”[Title/Abstract])) OR (“acetaminophen”[Title/Abstract])) OR (“paracetamol”[Title/Abstract])) OR (“corticosteroids”[Title/Abstract])) OR (“opioid*”[Title/Abstract])) OR (“medication*”[Title/Abstract])) AND (((((((“root canal therap*”[Title/Abstract]) OR (“root end resection”[Title/Abstract])) OR (“endodontics”[Title/Abstract])) OR (“apicoectomy”[Title/Abstract])) OR (“pulpectomy”[Title/Abstract])) OR (“symptomatic irreversible pulpitis”[Title/Abstract])) OR (“Dental pulp diseases”[Title/Abstract]))) AND (((((“pain”[Title/Abstract]) OR (“pain measurement”[Title/Abstract])) OR (“pain management”[Title/Abstract])) OR (“preoperative pain”[Title/Abstract])) OR (“postoperative pain”[Title/Abstract]))	February 15, 2024	235
Scopus	((TITLE-ABS-KEY(“analgesic*”)) OR (TITLE-ABS-KEY(“anti-inflammatory agents”)) OR (TITLE-ABS-KEY(“anti-bacterial agents”)) OR (TITLE-ABS-KEY(“antibiotic*”)) OR (TITLE-ABS-KEY(“acetaminophen”)) OR (TITLE-ABS-KEY(“paracetamol”)) OR (TITLE-ABS-KEY(“corticosteroids”)) OR (TITLE-ABS-KEY(“opioid*”)) OR (TITLE-ABS-KEY(“medication*”))) AND ((TITLE-ABS-KEY(“root canal therap*”)) OR (TITLE-ABS-KEY(“root end resection”)) OR (TITLE-ABS-KEY(“endodontics”)) OR (TITLE-ABS-KEY(“apicoectomy”)) OR (TITLE-ABS-KEY(“pulpectomy”)) OR (TITLE-ABS-KEY(“symptomatic irreversible pulpitis”)) OR (TITLE-ABS-KEY(“Dental Pulp Diseases”))) AND ((TITLE-ABS-KEY(“pain”)) OR (TITLE-ABS-KEY(“Pain Measurement”)) OR (TITLE-ABS-KEY(“Pain Management”)) OR (TITLE-ABS-KEY(“preoperative pain”)) OR (TITLE-ABS-KEY(“postoperative pain”)))	February 15, 2024	682

Methods

Study design

The present systematic review and meta-analysis was executed in accordance with the guidelines specified in the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) document [16]. To achieve this, we registered the study using PROSPERO with the identifier “CRD42024529596”. The primary aim was to evaluate the efficacy and safety of medication therapy in the management of pain after non-surgical endodontic treatments, based specifically on medication that was prescribed post-treatment.

Data sources and search strategy

A systematic search was performed on PubMed, Scopus, and Google Scholar databases until 15th February 2024. The search strategy used three broad categories of keywords and Medical Subject Headings (MeSH) terms: (1) pain-relieving drugs, (2) non-surgical endodontic procedures, and (3) parameters to measure pain. These categories were joined by Boolean operators with no publication date, type, or language restrictions. Manual searches of lists of relevant systematic reviews and included studies were conducted to minimize the chances of excluding relevant publications. The full search strategy for each database is shown in **Table 1**.

Study selection

Two independent reviewers screened the titles and abstracts of retrieved articles. For potentially eligible studies, full-text articles were obtained and assessed using the following inclusion criteria.

1. Full texts of all articles were available. 2. All articles were in English. 3. Only RCTs were included. 4. All articles included a placebo group, which typically consisted of inert capsules identical in appearance to the active drug. The treatment groups received either NSAIDs, corticosteroids, opioids, or combination medications, administered orally or via injection as specified by the study protocols. 5. The study population underwent non-surgical endodontic treatments. 6. Studies that used medicaments were excluded because our aim was evaluating medications which have taken after procedure and medicaments are used during the dental procedure by dentist. Studies which have used medications before dental treatments were also excluded by the same reason. 7. Articles provided data on the effectiveness and safety of pain medications.

8. Patients' pain was reported using eligible scales.

Disagreements between the reviewers were resolved through discussion or consultation with a third reviewer.

Data extraction and quality assessment

Two reviewers independently extracted data from the included studies using a standardized form. The information extracted included the following.

1. Study characteristics (authors, location, year, study type). 2. Patient-specific factors (sex, mean/median age). 3. Study design (sample size, sampling method, type of medications, follow-up duration). 4. Results (pain reduction rates). The primary outcome of interest was the pain relief rate, evaluated using standardized pain assessment tools reported in the included studies, most commonly the Visual Analog Scale (VAS). VAS scores, typically ranging from 0 (no pain) to 10 (worst imaginable pain), were recorded at multiple post-treatment time points (8 h, 12 h, 24 h, 48 h, and 72 h). The mean changes in pain scores from baseline were extracted and used to compute pooled effect sizes for comparison across treatment groups. 5. Quality assessment score. This was determined using the Cochrane Collaboration's Risk of Bias tool, which evaluates domains including selection bias, performance bias, detection bias, attrition bias, and reporting bias. Each study was rated as having a "low", "high", or "unclear" risk of bias in each category. The cumulative quality score was derived by counting the number of domains rated as 'low risk', with a higher count indicating better methodological quality. This approach enabled a semi-quantitative comparison of study rigor across the included RCTs.

We used the Cochrane Collaborations risk of bias assessment tool to assess the risk of bias in each included study, following the guidelines in the Cochrane Handbook. This assessment covered areas such as selection bias, performance bias, discovery bias, attrition bias, reporting bias, and other potential biases [17]. Two reviewers independently rated each item as "low risk", "high risk", or "unclear risk of bias". Any disagreements were resolved through consultation with a third reviewer.

Statistical analysis

We performed statistical analyses using STATA 13.1 software (StataCorp LP, College Station, TX, USA). The primary outcome was pain reduction at various time points (8, 12, 24, 48, and 72 h) post-treatment. The results were reported as pooled effect sizes with 95% confidence intervals (CIs) and visualized using forest plots.

We assessed heterogeneity between eligible studies using the I^2 statistic [18] and used the random-effects model when significant heterogeneity was found ($I^2 > 50\%$) [19]. In addition, we performed sensitivity analysis by excluding one study at a time and repeating the meta-analysis. This enabled us to ensure the stability of our results. Finally, to examine the potential for publication bias, we visually inspected funnel plot symmetry and performed Egger's regression analysis [20]. The significance level was set at $P < 0.05$.

Results

Study selection and characteristics

The first search returned 1,003 articles (943 from database searches and 60 from manual searches). Following the removal of duplicates, 653 articles were left for title and abstract screening. Then 92 full-text articles were screened for eligibility, with 16 studies being included for meta-analysis.

The 16 studies included had 2,021 participants, and the sample sizes varied from 37 to 534 individuals. The studies involved more than one country, with the largest numbers being from the United States (n = 9), followed by Iran (n = 5), Sudan, and Pakistan. The detailed characteristics of the included studies are presented in **Table 2**.

Quality assessment

Most of the included studies showed low risk of bias in key areas for methodological considerations. Most of them had at low risk for random sequence generation and allocation concealment, therefore showing methodologically sound approaches. A number indicated some unclear risks regarding participant and personnel blinding and selective reporting. The overall evidence quality was good, though minor varia-

Table 2. Baseline characteristics of the included studies

	Author	Country	Year	Study design	Participants	Sex	Mean/median age	Intervention
The efficacy of pain control following nonsurgical root canal treatment using ibuprofen or a combination of ibuprofen and acetaminophen in a randomized, double-blind, placebo-controlled study	Menhinick et al. [26]	USA	2004	Randomized clinical trial	57 patients with experience of moderate to severe pain	Female: 71.92%	In order of groups: I: 42 II: 40 III: 35	A single dose of followings immediately after endodontic treatment. I: Placebo II: 600 mg ibuprofen III: 600 mg ibuprofen and 1000 mg of acetaminophen
Double-blind randomized placebo-controlled clinical trial of efficiency of nonsteroidal anti-inflammatory drugs in the control of post-endodontic pain	Elzaki et al. [21]	Sudan	2016	Randomized clinical trial	170 participants with criteria of moderate to severe irreversible pulpitis pain on anterior or premolar teeth	Female: 61.17%	33±10.50	A single dose of followings immediately after endodontic treatment. P: 4 gelatinous capsules of Single dose of paracetamol alone. IP: similar cap of Single dose of combined paracetamol/Ibuprofen. MP: combined mefenamic acid/paracetamol. DP: combined diclofenac K/paracetamol. Plb (placebo): doubled gelatinous capsules with no medications as a single dose
Effectiveness of various medications on postoperative pain following root canal obturation	Torabinejad et al. [27]	USA	1994	Perspective study	411	Female: 53%	< 21 (4%) 21-39 (44%) 40-59 (38%) 60-79 (16%) 79 < (1%)	I: Salicylic acid (2 × 250 rag) II: Acetaminophen (2 × 250 mg) III: Ibuprofen (2 × 250 rag) IIII: Ketoprofen (2 × 250 rag) V: Acetaminophen (2 × 250 rag) plus codeine (2 × 250 rag) VI: Penicillin (2 × 250 mg) VII: Erythromycin base (2 × 250 mg) VIII: Penicillin plus ibuprofen (2 × 250 rag) VIIII: Methylprednisolone (2 × 250 rag) plus penicillin (2 × 250 rag) X: Placebo, every 6 h for 72 h
Gender differences in analgesia for endodontic pain. Journal of Endodontics	Ryan et al. [28]	USA	2008	Randomized clinical trial	43 patients	Female: 53.48%	-	1 capsule immediately after treatment and then 4 capsules every 6 h for 24 hours. I: Ibuprofen 600 mg II: Placebo III: Pentazocine 50 mg/0.5 mg naloxane
Effectiveness of various medications on post-operative pain of vital teeth after root canal therapy	Salarpoor et al. [25]	Iran	2014	Randomized clinical trial	82 patients with symptomatic, vital, and one canal tooth	Female: 71%	28.09	1 capsule immediately after treatment and then three times a day for 48 hours. 1. Ibuprofen (400 mg) 2. Betamethsone (2 mg) 3. Indomethacin (75 mg) 4. Placebo
The effect of submucosal injection of corticosteroids on pain perception and quality of life after root canal treatment of teeth with irreversible pulpitis	Yavari et al. [6]	Iran	2019	Randomized clinical trial	197	Not significantly different	32	0.7 mg Submucosal injection of followings. I: Placebo II: Long acting betametazone III: Dexamethasone (4 mg/ml)
Effects of three oral analgesics on postoperative pain following root canal preparation: a controlled clinical trial	Islam et al. [29]	Pakistan	2018	Randomized clinical trial	120 subjects with irreversible pulpitis in any tooth	Female: 50.83%	In order of groups: I: 33.20±9.4 II: 32.0±9.1 III: 32.07±8.9 IIII: 34.47±10.8	A single dose of followings Immediately after appointment. I: Naproxen sodium (550 mg) II: Ibuprofen (400 mg) III: Tramadol (100 mg) IIII: Placebo medication (multivitamin tablet)
Evaluation of meloxicam (A cox-2 inhibitor) for management of postoperative endodontic pain	Nekoofar et al. [7]	Iran	2003	Randomized clinical trial	51 patients	Groups were similar for distribution of sex	Groups were similar for distribution of age	A single dose of I: Meloxicam (15 mg) II: Piroxicam (20 mg) III: Placebo

Evaluation of the combination of flurbiprofen and tramadol for management of endodontic pain	Doroschak et al. [23]	USA	1999	Randomized clinical trial	49 endodontic emergency patients who underwent pulpectomy	-	-	10 tablets every 6 h, the leading dose to be taken when the patient reaches home after treatment. I: Placebo 1 capsule to start, then every 6 h II: Flurbiprofen 100 mg loading dose, then 50 mg every 6 h III: Tramadol 100 mg loading dose, then 100 mg every 6 h IIII: Combination of flurbiprofen and tramadol leading dose of both 100 mg, then Flurbiprofen 50 mg and tramadol 100 mg every 6 h
Effects of three oral analgesics on postoperative pain following root canal preparation: a controlled clinical trial	Mehrvarzfar et al. [30]	Iran	2012	Randomized clinical trial	95 patients who had anterior or premolar teeth with irreversible pulpitis, without apical periodontitis, and moderate to severe pain	44.21%	I: 31.4±10.7 II: 29.5±6.9 III: 29.6±8.1 IIII: 28.4±7.6	A Single dose immediately after endodontic treatment. I: Placebo II: Tramadol (100 mg) III: Acetaminophen + ibuprofen caffeine anhydrous (325/200/40 mg) > novafen IIII: Naproxen (500 mg)
Alprazolam role in the analgesic effect of ibuprofen on postendodontic pain	Baradaran et al. [31]	Iran	2014	Randomized clinical trial	45 patients	Female: 42.2%	30.4±6.9	A Single dose immediately after endodontic treatment. I: Placebo II: Ibuprofen (400 mg) III: Alprazolam (0.5 mg) + ibuprofen (400 mg)
Comparison of effect of intracanal use of ketorolac tromethamine and dexamethasone with oral ibuprofen on post treatment endodontic pain	Rogers et al. [32]	USA	1999	Randomized clinical trial	48 patients	-	-	A Single dose of followings. I: Oral ibuprofen (600 mg) II: Placebo [third and fourth groups have received dexamethasone and ketorolac tromethamine as intracanal medicaments which are out of our topic]
Effectiveness of various medications on postoperative pain following complete instrumentation	Torabinejad et al. [33]	USA	1994	Randomized clinical trial	544 patients	Female: 52%	< 21 (4%) 21-39 (40%) 40-59 (39%) 60-79 (16%) 79 < (1%)	I: Salicylic acid (650 mg), aspirin II: Acetaminophen (650 mg) III: Ibuprofen (400 mg) IIII: Ketoprofen (50 mg) V: Acetaminophen (325 mg) plus codeine (60 mg) VI: Penicillin (500 mg) VII: Erythromycin base (500 mg) VIII: Penicillin (500 mg) plus ibuprofen (400 mg) VIIII: Methylprednisolone (2 mg) plus penicillin (500 mg) X: placebo
A prospective randomized double-blind trial on efficacy of dexamethasone for endodontic interappointment pain in teeth with asymptomatic inflamed pulps	Glassman et al. [34]	USA	1989	Randomized clinical trial	37 patients with asymptomatic teeth	-	-	Leading dose immediately after treatment and 2 every 4 h. I: Dexamethasone (3 tablets of 4 mg each) II: Dextrose placebo
Management of post treatment endodontic pain with oral dexamethasone: a double-blind study	Krasner and Jackson [35]	USA	1986	Randomized clinical trial	48	-	-	3 tablets immediately after endodontic treatment, then 4 tablets each every 3 h. I: Placebo II: Dexamethasone (0.75 mg)
Postoperative pain management with oral methylprednisolone in symptomatic patients with a pulpal diagnosis of necrosis: a prospective randomized, double-blind study	Fuller et al. [36]	USA	2018	Randomized controlled trial	125	Female: I: 57.145 II: 64.51%	I: 35±12 II: 35±14	4 capsules immediately after the endodontic procedure, 2 capsules for 5 days. I: Oral methylprednisolone (96 mg Immediately after treatment followed by 48 mg each day for 5 consecutive days) II: lactose placebo

Table 3. Quality assessment of included studies using the Cochrane Risk of Bias Tool

	Random Sequence Generation	Allocation Concealment	Selective Reporting	Other Bias	Blinding of Participants and Personnel	Blinding of Outcome Assessment	Incomplete Outcome Data
Menhinick et al. (2004) [26]	+	+	+	+	+	+	+
Elzaki et al. (2016) [21]	+	+	+	+	+	+	+
Torabinejad et al. (1994) [27]	?	?	+	+	+	+	+
Ryan et al. (2008) [28]	+	+	+	+	+	+	+
Salarpoor et al. (2014) [25]	+	+	+	+	+	+	+
Yavari et al. (2019) [6]	+	?	+	+	+	+	+
Islam et al. (2021) [29]	?	?	+	+	+	+	+
Nekoofar et al. (2003) [7]	+	+	+	+	+	+	+
Doroschak et al. (1999) [23]	+	+	+	+	+	+	+
Mehrvarzfar et al. (2012) [30]	+	+	+	+	+	+	+
Baradaran et al. (2014) [31]	+	?	+	+	+	+	+
Rogers et al. (1999) [32]	?	?	+	+	+	+	+
Torabinejad et al. (1994) [33]	?	?	+	+	+	+	+
Glassman et al. (1989) [34]	+	+	+	+	+	+	+
Krasner and Jackson (1986) [35]	+	+	+	+	+	+	+
Fuller et al. (2018) [36]	+	+	+	+	+	+	+

The table summarizes the risk of bias for each study in different areas. Green plus signs (+) indicate a low risk of bias, yellow question marks (?) indicate an unclear risk of bias, and red minus signs (-) indicate a high risk of bias.

tions existed across domains in such a way that one may require interpretation with those limitations. **Table 3** shows the detailed assessment of the quality of each study.

Participant demographics

Regarding sex, four articles did not provide the necessary information, and two studies simply stated that there was no significant difference between their study groups. In the remaining ten articles, the proportion of female participants ranged from 42.2% to 71.92%.

Five studies did not determine the mean age of the participants, and one study claimed that there was no significant difference between groups without numerical confirmation. In other studies, a mean age of 28-45 years was recorded.

Inclusion criteria and intervention characteristics

Seven studies had the following specific inclusion criteria regarding tooth conditions: (1) Asymptomatic teeth. (2) Anterior/premolar teeth with irreversible pulpitis without apical periodontitis and moderate to severe pain. (3) Endodontic emergency patients who underwent pulpectomy. (4) Irreversible pulpitis in any tooth. (5) Symptomatic, vital and one canal tooth. (6) Moderate to severe irreversible pulpitis pain on anterior/premolar teeth. (7) Moderate to severe pain.

The interventions were administered as either a single dose or multiple doses. In all studies except one, the medications were administered orally; in the remaining trial, they were injected subcutaneously.

Medication classifications

Based on the pharmacologic groups, the prescribed medications were classified into 12 categories: NSAIDs, Opioids, Acetaminophen, Aspirin, Antibiotics, Corticosteroids, Acetaminophen + Opioids, Acetaminophen + NSAIDs, Opioids + NSAIDs, Antibiotic + NSAIDs, Benzodiazepines + NSAIDs, Antibiotics + Corticosteroids (**Table 2**).

Efficacy of postoperative medications

Our meta-analysis revealed a statistically significant pain reduction across all the time points evaluated ($P < 0.05$).

1. 8 h post-treatment: pooled effect = -3.10 (95% CI: -4.48, -1.71), $I^2 = 100\%$. 2. 12 h post-treatment: pooled effect = -1.69 (95% CI: -1.88, -1.50), $I^2 = 99.2\%$. 3. 24 h post-treatment: pooled effect = -1.48 (95% CI: -1.96, -1.00), $I^2 = 99.9\%$. 4. 48 h post-treatment: pooled effect = -1.42 (95% CI: -1.93, -0.92), $I^2 = 99.4\%$. 5. 72 h post-treatment: pooled effect = -0.64 (95% CI: -1.22, -0.05), $I^2 = 73.1\%$.

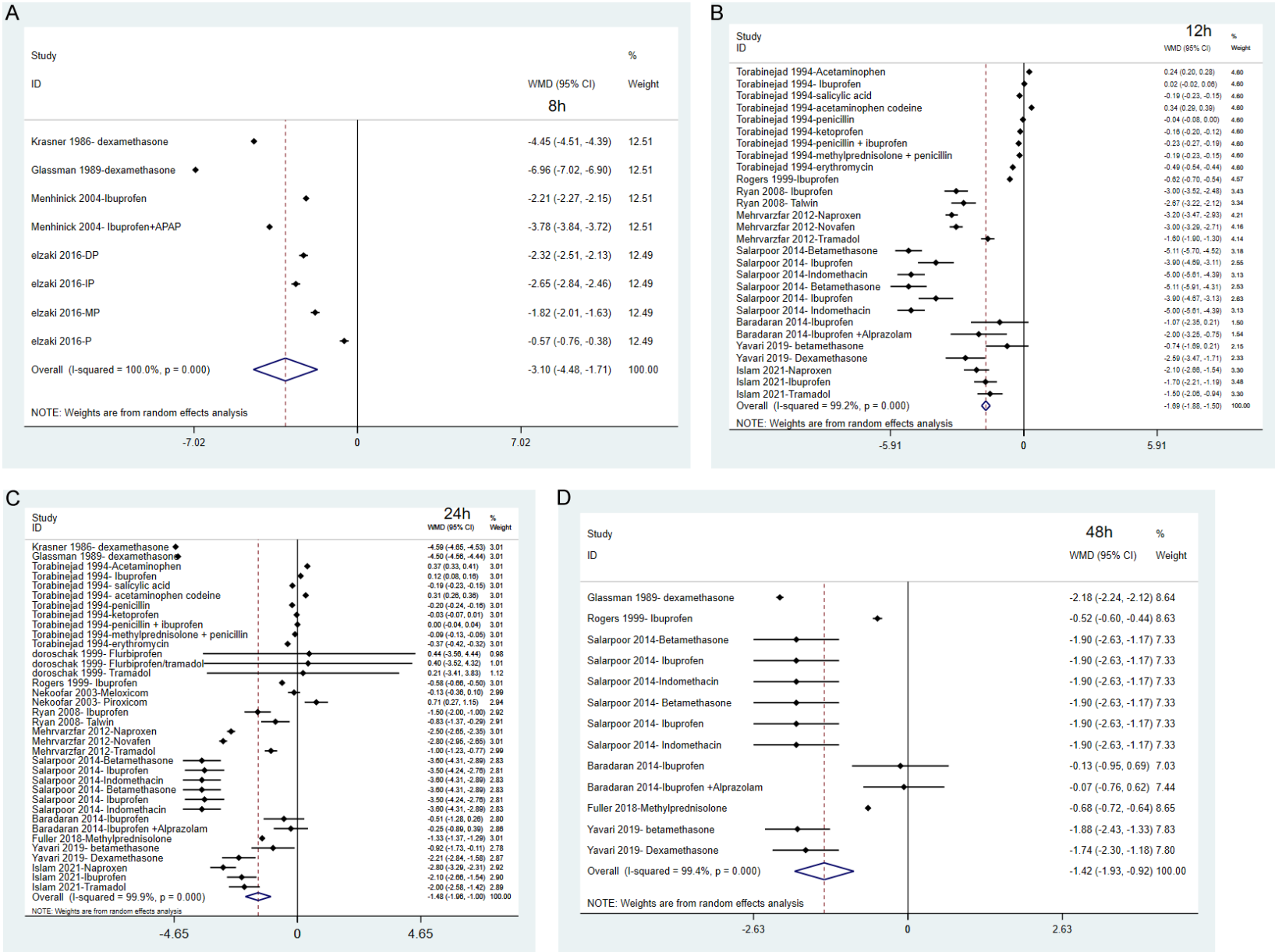
Figure 1 presents forest plots for each time point, illustrating the individual and pooled effect sizes.

Subgroup and sensitivity analyses

Subgroup analyses according to medication classes (NSAIDs, opioids, corticosteroids, and combinations) showed that NSAIDs, especially ibuprofen and indomethacin, had consistent efficacy at all time points. Corticosteroids (betamethasone and dexamethasone) provided greater pain relief at all periods of follow-up. Sensitivity analyses excluding each individual study did not appreciably change overall pooled effects, demonstrating result robustness. Effect estimates were consistent at 8, 12, and 24-hour time points with little variability in pooled effect sizes overall at 48 hours (-2.59 to -2.35). At 72 hours, the variability increased to -2.68 to -1.48 because some studies had larger outcome effects, and in sensitivity analyses, one article was excluded from analysis at 72 hours. The Supplementary Materials (Figure S1) contain the results of the sensitivity analysis.

Publication bias

Publication bias was assessed using funnel plots (see **Figure 2**), Begg's test, and Egger's test at different time intervals (8, 12, 24, 48, and 72 h). Funnel plots of all time points are symmetrical and therefore present a very low risk of publication bias. The spread at 8 h is narrow within the 95% confidence limits, indicating consistent evidence. The 12, 24 and 48 h charts show an even spread around the pooled effect, further supporting this pattern. The symmetry remains after 72 h, further increasing the reliability of the results. In general, this means that the results regarding the effectiveness and safety of postoperative medications for pain relief after non-surgical endodontic treatment are reliable, with little concern for publication bias.


A
Study
ID
WMD (95% CI)
%
Weight
8h
Krasner 1986- dexamethasone -4.45 (-4.51, -4.39) 12.51
Glassman 1989-dexamethasone -6.96 (-7.02, -6.90) 12.51
Menhinick 2004-Ibuprofen -2.21 (-2.27, -2.15) 12.51
Menhinick 2004- Ibuprofen+APAP -3.78 (-3.84, -3.72) 12.51
elzaki 2016-DP -2.32 (-2.51, -2.13) 12.49
elzaki 2016-IP -2.65 (-2.84, -2.46) 12.49
elzaki 2016-MP -1.82 (-2.01, -1.63) 12.49
elzaki 2016-P -0.57 (-0.76, -0.38) 12.49
Overall (I-squared = 100.0%, p = 0.000) -3.10 (-4.48, -1.71) 100.00
NOTE: Weights are from random effects analysis
-7.02
0
7.02
B
Study
ID
12h
WMD (95% CI)
%
Weight
Torabinejad 1994-Acetaminophen 0.24 (0.20, 0.28) 4.60
Torabinejad 1994- Ibuprofen 0.02 (-0.02, 0.06) 4.60
Torabinejad 1994-salicylic acid -0.19 (-0.23, -0.15) 4.60
Torabinejad 1994-acetaminophen codeine 0.34 (0.29, 0.39) 4.60
Torabinejad 1994-penicillin -0.04 (-0.08, 0.00) 4.60
Torabinejad 1994-ketoprofen -0.16 (-0.20, -0.12) 4.60
Torabinejad 1994-penicillin + ibuprofen -0.23 (-0.27, -0.19) 4.60
Torabinejad 1994-methylprednisolone + penicillin -0.19 (-0.23, -0.15) 4.60
Torabinejad 1994-erythromycin -0.49 (-0.54, -0.44) 4.60
Rogers 1999-Ibuprofen -0.62 (-0.70, -0.54) 4.57
Ryan 2008- Ibuprofen -3.00 (-3.52, -2.48) 3.43
Ryan 2008- Talwin -2.67 (-3.22, -2.12) 3.34
Mehrvarzfar 2012-Naproxen -3.20 (-3.47, -2.93) 4.21
Mehrvarzfar 2012-Novafen -3.00 (-3.29, -2.71) 4.16
Mehrvarzfar 2012-Tramadol -1.60 (-1.90, -1.30) 4.14
Salarpoor 2014-Betamethasone -5.11 (-5.70, -4.52) 3.18
Salarpoor 2014- Ibuprofen -3.90 (-4.69, -3.11) 2.55
Salarpoor 2014-Indomethacin -5.00 (-5.81, -4.39) 3.13
Salarpoor 2014- Betamethasone -5.11 (-5.91, -4.31) 2.53
Salarpoor 2014- Ibuprofen -3.90 (-4.67, -3.13) 2.63
Salarpoor 2014- Indomethacin -5.00 (-5.81, -4.39) 3.13
Baradaran 2014-Ibuprofen -1.07 (-2.35, 0.21) 1.50
Baradaran 2014-Ibuprofen +Alprazolam -2.00 (-3.25, -0.75) 1.54
Yavari 2019- betamethasone -0.74 (-1.69, 0.21) 2.15
Yavari 2019- Dexamethasone -2.59 (-3.47, -1.71) 2.33
Islam 2021-Naproxen -2.10 (-2.66, -1.54) 3.30
Islam 2021-Ibuprofen -1.70 (-2.21, -1.19) 3.48
Islam 2021-Tramadol -1.50 (-2.06, -0.94) 3.30
Overall (I-squared = 99.2%, p = 0.000) -1.89 (-1.88, -1.50) 100.00
NOTE: Weights are from random effects analysis
-5.91
0
5.91
C
Study
ID
24h
WMD (95% CI)
%
Weight
Krasner 1986- dexamethasone -4.59 (-4.65, -4.53) 3.01
Glassman 1989- dexamethasone -4.50 (-4.56, -4.44) 3.01
Torabinejad 1994-Acetaminophen 0.37 (0.33, 0.41) 3.01
Torabinejad 1994- Ibuprofen 0.12 (0.08, 0.16) 3.01
Torabinejad 1994- salicylic acid -0.19 (-0.23, -0.15) 3.01
Torabinejad 1994- acetaminophen codeine 0.31 (0.26, 0.36) 3.01
Torabinejad 1994-penicillin -0.20 (-0.24, -0.16) 3.01
Torabinejad 1994-ketoprofen -0.03 (-0.07, 0.01) 3.01
Torabinejad 1994-penicillin + ibuprofen 0.00 (-0.04, 0.04) 3.01
Torabinejad 1994-methylprednisolone + penicillin -0.09 (-0.13, -0.05) 3.01
Torabinejad 1994-erythromycin -0.37 (-0.42, -0.32) 3.01
doroschak 1999- Flurbiprofen 0.44 (-3.56, 4.44) 0.98
doroschak 1999- Flurbiprofen/tramadol 0.40 (-3.52, 4.32) 1.01
doroschak 1999- Tramadol 0.21 (-3.41, 3.83) 1.12
Rogers 1999- Ibuprofen -0.58 (-0.66, -0.50) 3.01
Nekoofar 2003-Meloxicom -0.13 (-0.36, 0.10) 2.99
Nekoofar 2003- Piroxicom 0.71 (0.27, 1.15) 2.94
Ryan 2008- Ibuprofen -1.50 (-2.00, -1.00) 2.92
Ryan 2008- Talwin -0.83 (-1.37, -0.29) 2.91
Mehrvarzfar 2012-Naproxen -2.50 (-2.65, -2.35) 3.01
Mehrvarzfar 2012-Novafen -2.80 (-2.95, -2.65) 3.01
Mehrvarzfar 2012-Tramadol -1.00 (-1.23, -0.77) 2.99
Salarpoor 2014-Betamethasone -3.60 (-4.31, -2.89) 2.83
Salarpoor 2014- Ibuprofen -3.50 (-4.24, -2.76) 2.81
Salarpoor 2014-Indomethacin -3.60 (-4.31, -2.89) 2.83
Salarpoor 2014- Betamethasone -3.60 (-4.31, -2.89) 2.83
Salarpoor 2014- Ibuprofen -3.50 (-4.24, -2.76) 2.81
Salarpoor 2014- Indomethacin -3.60 (-4.31, -2.89) 2.83
Baradaran 2014-Ibuprofen -0.51 (-1.28, 0.26) 2.80
Baradaran 2014-Ibuprofen +Alprazolam -0.25 (-0.89, 0.39) 2.86
Fuller 2018-Methylprednisolone -1.33 (-1.37, -1.29) 3.01
Yavari 2019- betamethasone -0.92 (-1.73, -0.11) 2.78
Yavari 2019- Dexamethasone -2.21 (-2.84, -1.58) 2.87
Islam 2021-Naproxen -2.80 (-3.29, -2.31) 2.92
Islam 2021-Ibuprofen -2.10 (-2.66, -1.54) 2.90
Islam 2021-Tramadol -2.00 (-2.58, -1.42) 2.89
Overall (I-squared = 99.9%, p = 0.000) -1.48 (-1.96, -1.00) 100.00
NOTE: Weights are from random effects analysis
-4.65
0
4.65
D
Study
ID
48h
WMD (95% CI)
%
Weight
Glassman 1989- dexamethasone -2.18 (-2.24, -2.12) 8.64
Rogers 1999- Ibuprofen -0.52 (-0.60, -0.44) 8.63
Salarpoor 2014-Betamethasone -1.90 (-2.63, -1.17) 7.33
Salarpoor 2014- Ibuprofen -1.90 (-2.63, -1.17) 7.33
Salarpoor 2014-Indomethacin -1.90 (-2.63, -1.17) 7.33
Salarpoor 2014- Betamethasone -1.90 (-2.63, -1.17) 7.33
Salarpoor 2014- Ibuprofen -1.90 (-2.63, -1.17) 7.33
Salarpoor 2014- Indomethacin -1.90 (-2.63, -1.17) 7.33
Baradaran 2014-Ibuprofen -0.13 (-0.95, 0.69) 7.03
Baradaran 2014-Ibuprofen +Alprazolam -0.07 (-0.76, 0.62) 7.44
Fuller 2018-Methylprednisolone -0.68 (-0.72, -0.64) 8.65
Yavari 2019- betamethasone -1.88 (-2.43, -1.33) 7.83
Yavari 2019- Dexamethasone -1.74 (-2.30, -1.18) 7.80
Overall (I-squared = 99.4%, p = 0.000) -1.42 (-1.93, -0.92) 100.00
NOTE: Weights are from random effects analysis
-2.63
0
2.63

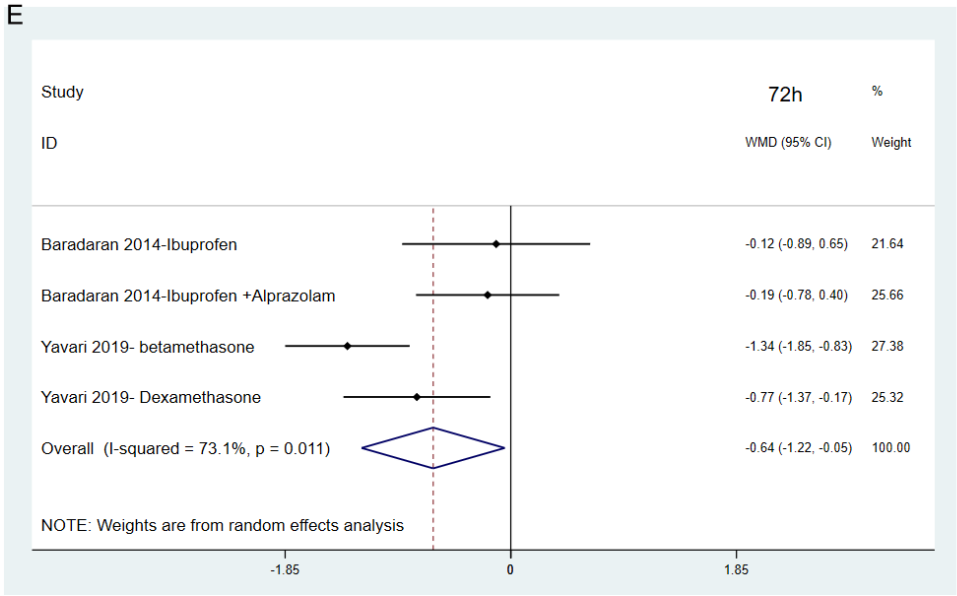


Figure 1. Forest plots for the effectiveness of medications in managing postoperative endodontic pain: (A) for 8 h, (B) for 12 h, (C) for 24 h, (D) for 48 h, and (E) for 72 h.

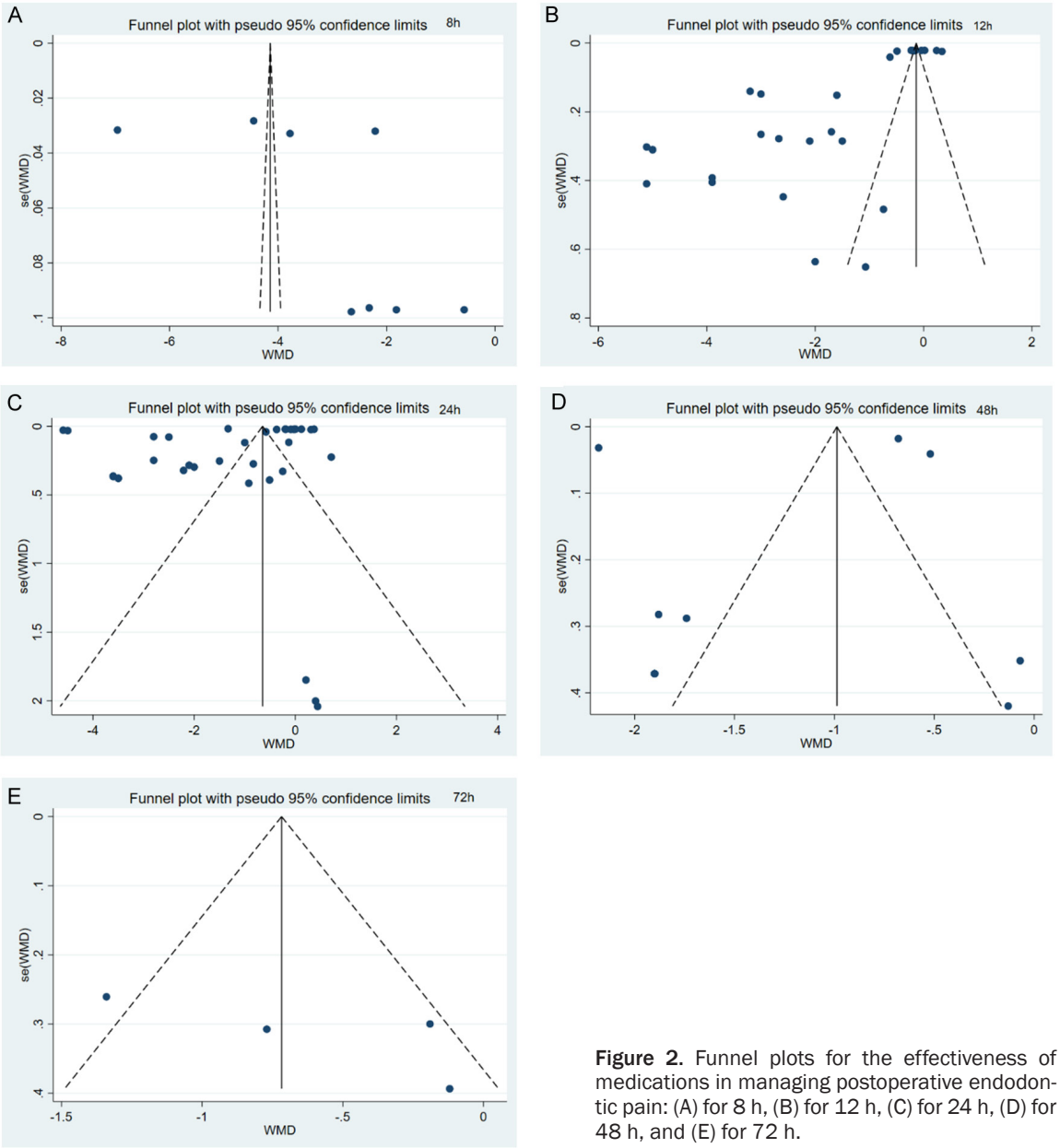


Figure 2. Funnel plots for the effectiveness of medications in managing postoperative endodontic pain: (A) for 8 h, (B) for 12 h, (C) for 24 h, (D) for 48 h, and (E) for 72 h.

After 8 h, the funnel plot was symmetrical, while Begg's test result showed no significance (P = 0.262). In contrast, Egger's test result showed a small-study effect with P = 0.008. For the 12 and 24 h time points, neither the Begg nor the Egger test was significant (12 h: P = 0.323 and P = 0.079, respectively; 24 h: P = 0.097 and P = 0.173, respectively), which is due to a indicates low heterogeneity, probability of publication bias. At 48 h there is no evidence of significant bias by Begg's test (P = 0.760), but an effect was found by Egger's test in a small study with P = 0.002. The sensitivity analysis showed that the overall estimated effect is quite robust. The 72 h analysis provided the strongest evidence of publication bias. In contrast, Begg's test was not significant with P = 0.142, while Egger's test with P < 0.001 showed very strong evidence of effects in small studies.

In conclusion, while small-study effects and publication bias are unlikely at the later time points - particularly at 48 and 72 h - there is evidence of publication bias at the earlier time points. The overall effect estimates are still

fairly strong for the earlier time points, although they are more susceptible to the individual studies at 72 h. Detailed results of the Begg's test and Egger's test are provided in the Supplementary Materials (Figure S2).

Discussion

Overview of study and key findings

This meta-analysis was conducted to summarize the evidence regarding the effectiveness and safety of postoperative medications for pain relief following nonsurgical endodontic treatment. Our results demonstrate that corticosteroids significantly reduce pain in all follow-ups, NSAIDs reduce PEP at any time point, and combination therapies showed promising results. The results of this meta-analysis also highlight the potential of optimizing pain management strategies in clinical practice.

1. Most effective pain reduction after 8 hours was by Dexamethasone tabs which were used immediately after treatment and 2 after 4 hours (4 mg each tab). 2. Most effective pain reduction after 12 hours was by Betamethasone tabs which were used 1 capsule immediately after treatment and then three times a day for 48 hours (2 mg each tab). 3. Most effective pain reduction after 24 hours was by Dexamethasone tabs which were used 3 tablets immediately after endodontic treatment, then 4 tablets each every 3 h (0.75 mg each tab). 4. Most effective pain reduction after 48 hours was by Dexamethasone tabs which were used immediately after treatment and 2 after 4 hours (4 mg each tab). 5. Most effective pain reduction after 12 hours was by Betamethasone tabs which were used 1 capsule immediately after treatment and then three times a day for 48 hours (2 mg each tab). 6. Most effective pain reduction after 72 hours was by Long acting Betamethasone submucosal injection (0.7 mg).

NSAIDs

Our analysis showed that NSAIDs were significantly effective in reducing PEP at almost all time points and among them Ibuprofen and Indomethacin were more prominent. Ibuprofen showed a reduction in pain at 8, 12, 24, 48, and 72 hours after treatment. The greatest effect also occurred in the early postoperative period, which may be a consequence of the pharmacokinetics and mechanism of action of known NSAIDs in modulating the acute inflammatory response.

These results are supported by Gopikrishna and Parameswaran (2003), who conducted a similar study on the ameliorative effect of rofecoxib 50 mg and ibuprofen 600 mg on postendodontic pain compared to placebo. The results showed that both medications significantly reduced pain at 4 and 8 h after treatment. The results of a significantly higher effectiveness of rofecoxib compared to ibuprofen 12 and 24 h after treatment correspond, in particular, to our results in the meta-analysis on the prolonged analgesic effect of some NSAIDs [14].

Arslan et al. (2011) studied tenoxicam (20 mg) and ibuprofen (200 mg) compared to placebo in the treatment of early PEP. Both drugs were effective as analgesics 6 h after treatment, but no significant difference was observed between the drugs and placebo. Their effectiveness in treating early pain is consistent with our previous findings on the significant analgesia produced by NSAIDs in the first few hours of the postoperative period by both tenoxicam and ibuprofen [15].

Combination therapies

Notably, combination treatments, particularly those involving the concomitant use of NSAIDs and acetaminophen or opioids, have shown superior efficacy to monotherapies. This added value must be attributed to synergy when more than one agent is administered together, as combinations tend to have a more comprehensive effect on pain management by simultaneously targeting different pain pathways.

Elzaki et al. (2016) also noted something that supported our findings regarding the enhanced effectiveness of NSAIDs with acetaminophen. The authors reported that a combination of ibuprofen and acetaminophen was more effective for pain relief than either drug alone, confirming our results [21]. Bahrololoomi and Amrollahi (2019) also examined paracetamol (650 mg) and ibuprofen (400 mg) for pulp anesthesia. Ibuprofen was significantly more effective in reducing pain at 2, 4, and 6 h after treatment. The combination provided better

pain relief than either medication alone [22]. Thus, the consensus appears to be that the combination of the two NSAIDs and acetaminophen actually results in superior pain relief by utilizing the complementary mechanisms of action of both medications [21].

In 1999, Doroschak et al. conducted a study comparing flurbiprofen (100 mg) and tramadol (100 mg), individually and in combination. In this case, the combination significantly reduced pain at 6 and 24 h compared to placebo and showed greater effectiveness than either drug alone. Again, this is fully supported by our analysis showing increased effectiveness of combination therapies [23]. This synergistic effect was observed in both studies, confirming the idea of targeting multiple pain pathways to achieve better pain management.

However, other studies have reported different results. Gong et al. (2019) showed no significant difference in pain reduction with ibuprofen alone compared to its combination with paracetamol in patients with symptomatic necrotic pulps [24]. These discrepancies may be explained by differences in the study design, patient populations, or the specific pain disorder being treated. Differences in the dosage and time of administration are other potential causes of these inconsistencies.

Corticosteroids

Corticosteroids, particularly when administered submucosally, exert pronounced analgesic effects, including dexamethasone, with superior short-term effects, and betamethasone with long-term effects. Our results demonstrate the potential of targeted corticosteroid administration in the treatment of life-threatening PEP.

These findings are consistent with those of Salarpoor et al. (2014), who compared the use of betamethasone (2 mg), indomethacin (75 mg), and ibuprofen (400 mg) for the treatment of PEP. After 6 and 12 h, betamethasone and indomethacin performed better than ibuprofen and placebo, respectively. All drugs worked better than the placebo at 24 and 48 h, but no significant difference was found between the groups that received the drugs [25]. This alignment suggests that betamethasone and indomethacin are effective in the early postoperative period, which is similar to our findings.

Yavari et al. (2019) examined the effects of submucosal corticosteroid, dexamethasone, and long-acting betamethasone injections on PEP. Both corticosteroids demonstrated significant pain relief compared to placebo at all measured time points; dexamethasone was more effective within the first 24 h, while long-acting betamethasone demonstrated sustained pain relief for up to 7 days [6]. These results are consistent with our findings and highlight the effectiveness of dexamethasone for short-term pain relief and betamethasone for long-term pain management. The consistency between our results and those of Yavari et al. (2019) enhances the potential of corticosteroids for the treatment of severe PEP.

Strengths and limitations

A key strength of this meta-analysis is its comprehensive approach, which includes a variety of studies and interventions.

The addition of a strong methodology, quality assessment of the included studies, and sensitivity analysis significantly increased the accuracy of our results. The study pool was extensive, with a sample size of 2,122 participants, which further contributed to the robustness of the results.

However, several limitations must be taken into account. The high heterogeneity between studies (I^2 values) ranged from 73.1% to 100%, suggesting significant variation in study designs, populations, and outcome measures. This heterogeneity could affect the generalizability of some of these results, although it reflects true clinical diversity. Therefore, large sample and well-designed RCTs are needed in order to validate the results of this meta-analysis in the future.

Furthermore, the vast majority of studies from specific geographical areas could introduce potential biases and further limitations in generalizing the results on a global scale. Another challenge to a clear conclusion regarding the preferred treatment regimen is the variability in dosing regimens between different studies and the timing of drug administration.

The results presented here highlight the differences in the effectiveness of endodontic pain management strategies. While medica-

tions and approaches are highly effective, others may have limitations or, in some cases, even side effects. This means that pain management plans should be more tailored to the needs and response of each individual patient.

Future research directions

While this meta-analysis provides valuable insights, several areas warrant further investigation:

1. Further meta-analyses on medications that are used during dental procedure and pre-operation should be done separately. 2. The optimal drug combination and dosage for PEP should be based on a study in a large, randomized, controlled, multicenter trial that includes at least two arms comparing combination therapies. 3. Further research into the long-term effects of corticosteroids and side effects from their use in the management of endodontic pain are indicated as useful in formulating guidelines for their application. 4. Prospective studies evaluating the effectiveness of alternative interventions such as PDT and laser disinfection in different patient populations and endodontic diseases are needed to determine their place in routine clinical practice. 5. From personal differences in pain thresholds to genetic variability in drug metabolism, research into the mechanisms of pain perception will lead to much more targeted and therefore effective treatment strategies. 6. Economic analyzeses comparing the cost-effectiveness of different pain management strategies in the context of endodontics would be relevant and useful for clinical decision-making at all levels and for resource allocation.

Conclusion

This meta-analysis provides strong evidence for the effectiveness of corticosteroids, NSAIDs and combination therapies in postoperative pain management after nonsurgical endodontic treatment. Such findings underpin evidence-based pain management strategies in endodontics but highlight fundamental areas for further research to better treat patients and achieve better outcomes.

Key implications of the findings from this meta-analysis for clinical practice regarding endodontics are as follows:

NSAIDs: NSAIDs should be a drug of choice for the treatment of PEP following nonsurgical endodontic procedures due to their regular effectiveness. Indomethacin and ibuprofen were highly effective in pain management.

Combination therapies: The use of combination therapies consisting of an NSAID and paracetamol is only likely to be useful in moderate to severe PEP and could be considered if a trial of monotherapy has failed. Among the various NSAID combinations studied, the combination of ibuprofen and paracetamol is superior to the other NSAID combinations in terms of pain relief.

Corticosteroids for severe PEP: Corticosteroids, particularly submucosal corticosteroids, have been found to be of great benefit in the treatment of severe PEP. Dexamethasone was used in pathologies where a short-term palliative effect was required, and conversely, betamethasone retained its analgesic effect. Dexamethasone and betamethasone relieve pain and improve a patient's quality of life.

Consideration of individual patient factors: With this in mind, pain management strategies must be individualized by a clinician based on patient factors, expected severity of pain, and specific endodontic procedures. Therefore, it is important to have personalized pain management plans in place to optimize pain relief and improve patient outcomes.

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Disclosure of conflict of interest

None.

Abbreviations

PEP, postoperative endodontic pain; NSAID, non-steroidal anti-inflammatory drugs; RCT, randomized controlled trials; PDT, photodynamic therapy; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-analyses; MeSH, Medical Subject Headings.

Address correspondence to: Sina Ahmadi, Xian Jiaotong University, No. 28, Xianning West Road, Xi'an 710049, Shaanxi, China. Tel: +86-298-

530-1004; E-mail: sinaahmadiwu@stu.xjtu.edu.cn; Alireza Mokhtari Sakhvidi, Dental Faculty, Tehran Medical Sciences, Islamic Azad University, Shariati St, Tehran 19395-1495, Iran. Tel: +98-21-226-18515; ORCID: 0000-0003-1274-558X; E-mail: Dralirezamokhtari95@gmail.com

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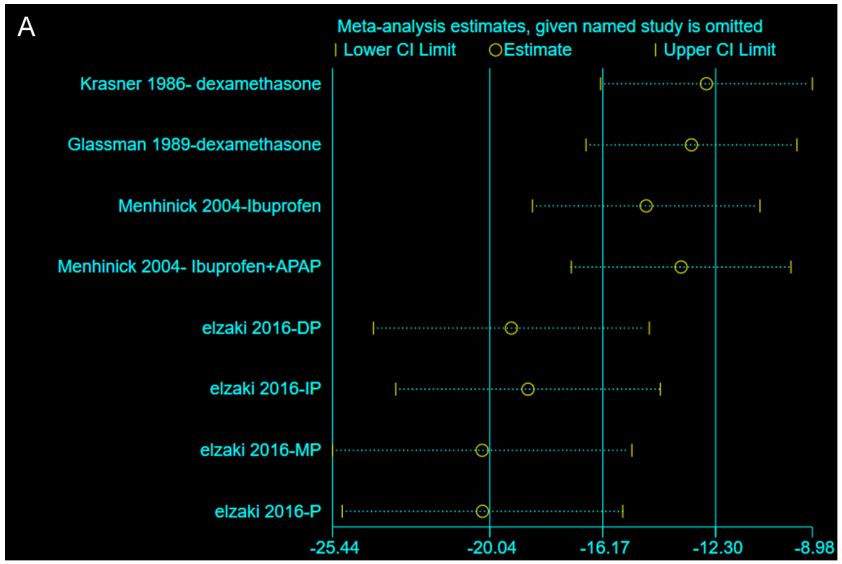
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Estimate
Upper CI Limit
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Glassman 1989-dexamethasone
Menhinick 2004-Ibuprofen
Menhinick 2004- Ibuprofen+APAP
elzaki 2016-DP
elzaki 2016-IP
elzaki 2016-MP
elzaki 2016-P
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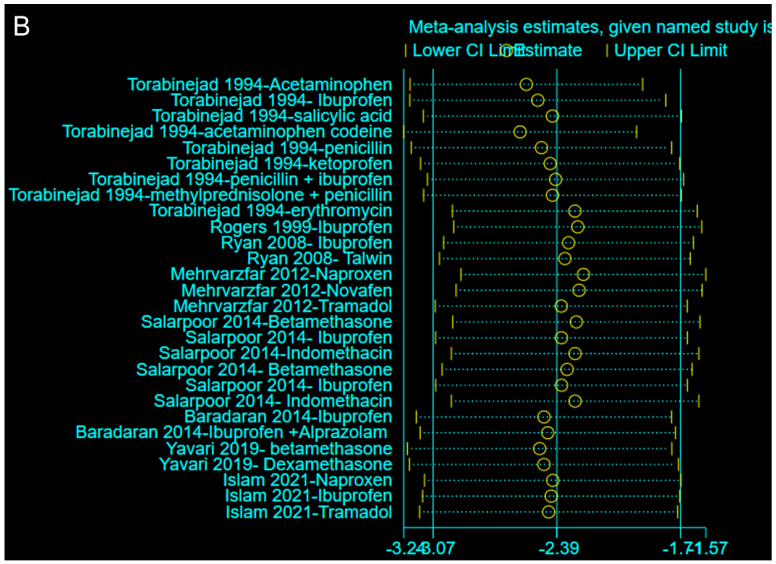
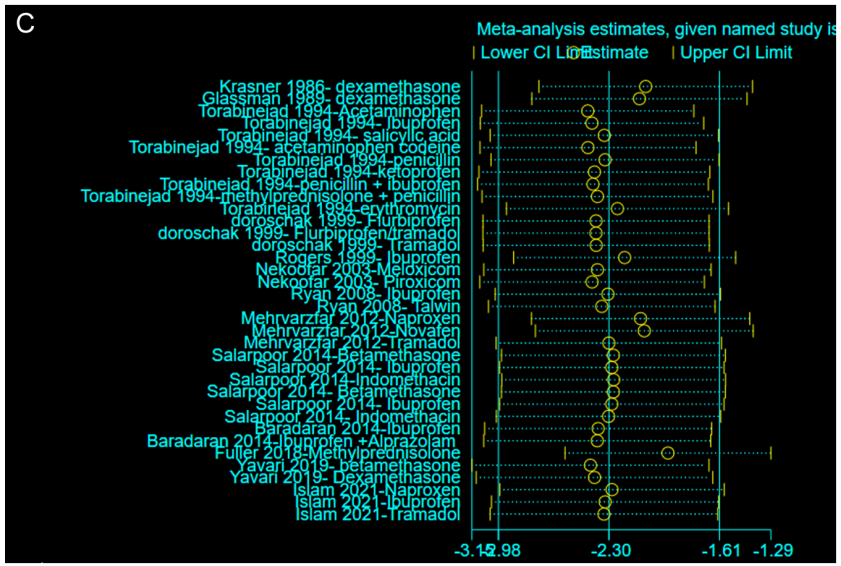
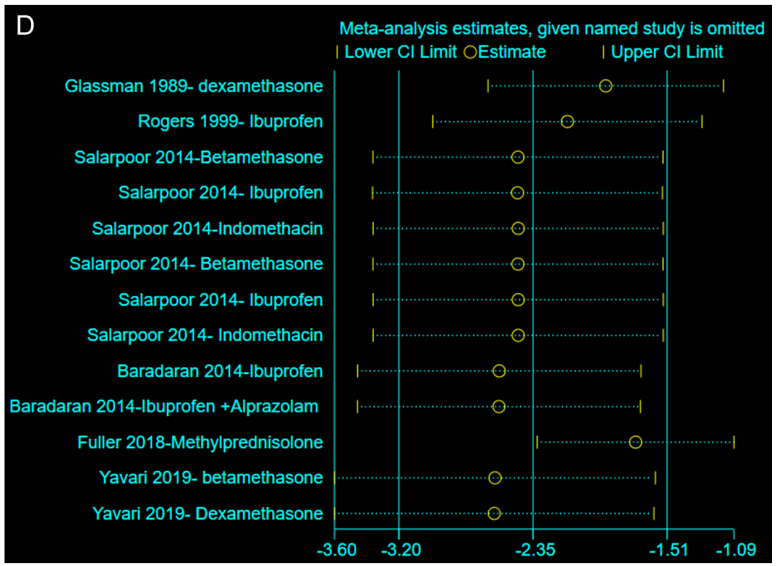
-16.17
-12.30
-8.98


B
Meta-analysis estimates, given named study is
Lower CI Limit
Estimate
Upper CI Limit
Torabinejad 1994-Acetaminophen
Torabinejad 1994- Ibuprofen
Torabinejad 1994-salicylic acid
Torabinejad 1994-acetaminophen codeine
Torabinejad 1994-penicillin
Torabinejad 1994-ketoprofen
Torabinejad 1994-penicillin + ibuprofen
Torabinejad 1994-methylprednisolone + penicillin
Torabinejad 1994-erythromycin
Rogers 1999-Ibuprofen
Ryan 2008- Ibuprofen
Ryan 2008- Talwin
Mehrvarzfar 2012-Naproxen
Mehrvarzfar 2012-Novafen
Mehrvarzfar 2012-Tramadol
Salarpoor 2014-Betamethasone
Salarpoor 2014- Ibuprofen
Salarpoor 2014-Indomethacin
Salarpoor 2014- Betamethasone
Salarpoor 2014- Ibuprofen
Salarpoor 2014- Indomethacin
Baradaran 2014-Ibuprofen
Baradaran 2014-Ibuprofen +Alprazolam
Yavari 2019- betamethasone
Yavari 2019- Dexamethasone
Islam 2021-Naproxen
Islam 2021-Ibuprofen
Islam 2021-Tramadol
-3.24
-3.07
-2.39
-1.71
-1.57


C
Meta-analysis estimates, given named study is
Lower CI Limit
Estimate
Upper CI Limit
Krasner 1986- dexamethasone
Glassman 1989- dexamethasone
Torabinejad 1994-Acetaminophen
Torabinejad 1994- Ibuprofen
Torabinejad 1994- salicylic acid
Torabinejad 1994- acetaminophen codeine
Torabinejad 1994-penicillin
Torabinejad 1994-ketoprofen
Torabinejad 1994-penicillin + ibuprofen
Torabinejad 1994-methylprednisolone + penicillin
Torabinejad 1994-erythromycin
doroschak 1999- Flurbiprofen
doroschak 1999- Flurbiprofen/tramadol
doroschak 1999- Tramadol
Rogers 1999- Ibuprofen
Nekoofar 2003-Meloxicom
Nekoofar 2003- Piroxicom
Ryan 2008- Ibuprofen
Ryan 2008- Talwin
Mehrvarzfar 2012-Naproxen
Mehrvarzfar 2012-Novafen
Mehrvarzfar 2012-Tramadol
Salarpoor 2014-Betamethasone
Salarpoor 2014- Ibuprofen
Salarpoor 2014-Indomethacin
Salarpoor 2014- Betamethasone
Salarpoor 2014- Ibuprofen
Salarpoor 2014- Indomethacin
Baradaran 2014-Ibuprofen
Baradaran 2014-Ibuprofen +Alprazolam
Fuller 2018-Methylprednisolone
Yavari 2019- betamethasone
Yavari 2019- Dexamethasone
Islam 2021-Naproxen
Islam 2021-Ibuprofen
Islam 2021-Tramadol
-3.15
-2.98
-2.30
-1.61
-1.29


D
Meta-analysis estimates, given named study is omitted
Lower CI Limit
Estimate
Upper CI Limit
Glassman 1989- dexamethasone
Rogers 1999- Ibuprofen
Salarpoor 2014-Betamethasone
Salarpoor 2014- Ibuprofen
Salarpoor 2014-Indomethacin
Salarpoor 2014- Betamethasone
Salarpoor 2014- Ibuprofen
Salarpoor 2014- Indomethacin
Baradaran 2014-Ibuprofen
Baradaran 2014-Ibuprofen +Alprazolam
Fuller 2018-Methylprednisolone
Yavari 2019- betamethasone
Yavari 2019- Dexamethasone
-3.60
-3.20
-2.35
-1.51
-1.09

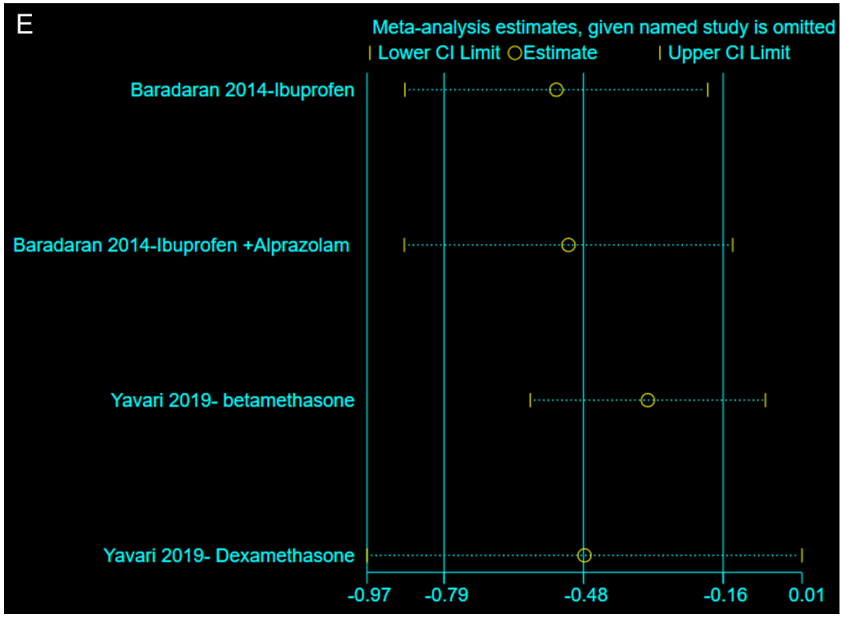


Figure S1. The sensitivity analysis for the effectiveness of medications in managing postoperative endodontic pain: (A) for 8 h, (B) for 12 h, (C) for 24 h, (D) for 48 h, and (E) for 72 h.

A Tests for Publication Bias 8h

Begg's Test

```
adj. Kendall's Score (P-Q) =      9
        Std. Dev. of Score =   8.02 (corrected for ties)
        Number of Studies  =      8
                         z =   1.12
                   Pr > |z| =  0.262
                         z =   1.00 (continuity corrected)
                   Pr > |z| =  0.319 (continuity corrected)
```

Egger's test

Std_Eff	Coefficient	Std. err.	t	P>|t|	[95% conf.	interval]
slope	-5.601167	1.42045	-3.94	0.008	-9.076882	-2.125451
bias	39.25571	33.96345	1.16	0.292	-43.84985	122.3613

B Tests for Publication Bias 12h

Begg's Test

```
adj. Kendall's Score (P-Q) =    -50
        Std. Dev. of Score =  50.61 (corrected for ties)
        Number of Studies  =     28
                         z =  -0.99
                   Pr > |z| =  0.323
                         z =   0.97 (continuity corrected)
                   Pr > |z| =  0.333 (continuity corrected)
```

Egger's test

Std_Eff	Coefficient	Std. err.	t	P>|t|	[95% conf.	interval]
slope	.1451222	.0792913	1.83	0.079	-.0178633	.3081078
bias	-10.91932	2.077634	-5.26	0.000	-15.18996	-6.648684

C Tests for Publication Bias 24h

Begg's Test

```
adj. Kendall's Score (P-Q) =    -122
        Std. Dev. of Score =   73.42 (corrected for ties)
        Number of Studies =      36
                        z =   -1.66
                  Pr > |z| =   0.097
                        z =    1.65 (continuity corrected)
                  Pr > |z| =   0.099 (continuity corrected)
```

Egger's test

Std_Eff	Coefficient	Std. err.	t	P>|t|	[95% conf.	interval]
slope	-.4381001	.3148437	-1.39	0.173	-1.077939	.2017392
bias	-8.074499	8.291908	-0.97	0.337	-24.92568	8.776686

D Tests for Publication Bias 48h

Begg's Test

```
adj. Kendall's Score (P-Q) =       5
        Std. Dev. of Score =   16.40 (corrected for ties)
        Number of Studies =      13
                        z =    0.30
                  Pr > |z| =   0.760
                        z =    0.24 (continuity corrected)
                  Pr > |z| =   0.807 (continuity corrected)
```

Egger's test

Std_Eff	Coefficient	Std. err.	t	P>|t|	[95% conf.	interval]
slope	-.9052549	.225646	-4.01	0.002	-1.401898	-.4086114
bias	-2.807165	4.338905	-0.65	0.531	-12.35703	6.742701

E Tests for Publication Bias 72h

Begg's Test

```
adj. Kendall's Score (P-Q) =       2
        Std. Dev. of Score =    2.94
        Number of Studies =       4
                        z =    0.68
                  Pr > |z| =   0.497
                        z =    0.34 (continuity corrected)
                  Pr > |z| =   0.734 (continuity corrected)
```

Egger's test

Std_Eff	Coefficient	Std. err.	t	P>|t|	[95% conf.	interval]
slope	-3.436577	1.655142	-2.08	0.174	-10.55808	3.684926
bias	8.995081	5.420506	1.66	0.239	-14.32747	32.31763

Figure S2. The Begg's test and Egger's test for the effectiveness of medications in managing postoperative endodontic pain: (A) for 8 h, (B) for 12 h, (C) for 24 h, (D) for 48 h, and (E) for 72 h.