Review Article

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Effect of premedication on postoperative pain after root canal therapy in patients with irreversible pulpitis: a systematic review and meta-analysis

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This systematic review aimed to assess the effect of premedication on postoperative pain after root canal treatment in vital teeth. Five electronic databases were searched for randomized clinical trials, and two independent reviewers selected eligible studies, extracted data, and assessed the quality of studies using the Cochrane Risk of Bias tool. Meta-analysis was conducted using the random-effects model, and the pooled effect estimate of the standardized mean difference (SMD) between premedication and placebo was calculated. Subgroup analysis was conducted based on the class and route of the drug. Studies with a high risk of bias were excluded from the sensitivity analysis. Ten trials satisfied the inclusion criteria, of which eight were included in the meta-analysis. Premedication was more effective in reducing postoperative pain than placebo at 6 hours (SMD = -1.00; 95% confidence interval [CI] = -1.33 to -0.66), 12 hours (SMD = -0.80; 95% CI = -1.05 to -0.56), and 24 hours (SMD = -0.72; 95% CI = -1.02 to -0.43). The results of the sensitivity analysis confirmed the findings of the primary analysis. Based on these results, it can be concluded that premedication is effective in reducing postoperative pain in teeth with irreversible pulpitis. However, additional quality studies are required for further validation.

Keywords: Meta-Analysis; Postoperative Pain; Premedication; Root Canal Therapy; Systematic Review.

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INTRODUCTION

Pain elimination is one of the primary therapeutic goals of endodontic interventions [1,2]. Studies have reported varying incidences of postoperative pain after root canal treatment. This wide range may be attributed to differences in study design and patient factors [3,4]. However, there is a consensus that the occurrence of pain after treatment is an unavoidable and unpleasant phenomenon for both clinicians and patients [5,6]. Preoperative variables, such as age, sex, and pulp status, as well as intraoperative factors, such as anesthetic agents, instrumentation techniques, irrigants, and intracanal medicaments used, may affect the incidence of postoperative pain [3,7].

The use of preemptive analgesics are a common strategy employed to prevent postoperative pain, as they may control the inflammatory cascade following endodontic treatment [8]. Studies have utilized different nonsteroidal anti-inflammatory drugs [NSAIDs], such as ibuprofen [9-13], tenoxicam [11], piroxicam [14], rofecoxib [9], indomethacin [13] and ketorolac [15,16], as prophylactic agents in controlling post-endodontic

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pain. Similarly, different corticosteroids, such as dexamethasone [14,17-21], betamethasone [21], and prednisolone [16,22], have been assessed for the prevention of pain after root canal treatment. Despite the large number of studies, post-endodontic pain continues to be a major clinical problem. Meta-analyses [1,2] on the topic and a recent network meta-analysis [8] reported favorable effects of pre-treatment administration of anti-inflammatory drugs on the prevention of postoperative pain.

There is a higher incidence and intensity of postoperative pain in teeth with vital inflamed pulp than in teeth with necrotic pulp [23]. Although the exact mechanism of postoperative pain in vital teeth is not clear, the production of prostaglandin metabolites along with other inflammatory mediators in irreversible pulpitis may accentuate pain by increasing peripheral and central sensitization [24]. In addition, mechanical and chemical irritation to the pulp and contiguous tissues during root canal instrumentation may lead to increased postoperative discomfort in patients with vital pulp [25]. Consolidation of studies involving similar pulp diagnoses is required to improve endodontic treatment planning. There is a lack of evidence-based guidelines for the administration of premedication before root canal treatment in patients with vital inflamed pulp. Only one meta-analysis evaluated the benefit of premedication exclusively in patients with vital pulp [2]. However, the authors evaluated studies using only corticosteroids. This leaves the role of preoperative administration of NSAIDs unexplored in cases of irreversible pulpitis. The NSAID class of drugs is preferred in clinical practice because of their easy availability, good efficacy, and fewer side effects [1]. Keeping this in mind and the fact that more studies have been published since the last meta-analysis on the topic, an updated review was planned by including both classes of anti-inflammatory drugs. The purpose of this systematic review and meta-analysis was to assess the effectiveness of premedication in preventing post-treatment pain following root canal treatment in patients with irreversible pulpitis.

METHODS

This systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines [26]. Before that, the review proposal was drafted and registered on the PROSPERO public registry of a systematic review (CRD42020184445).

1. Research question

The research question framed for the review using the PICOS format was as follows:

P – Patients with irreversible pulpitis in mature permanent teeth

I – Prophylactic premedication before root canal treatment

C – Compared to control/placebo

O – Postoperative pain

S – Randomized controlled trial

The primary outcome of this review was to assess the effect of premedication with anti-inflammatory drugs on postoperative pain after non-surgical root canal therapy in teeth with irreversible pulpitis at 6, 12, and 24 hours postoperatively. The secondary outcome was the number of required analgesics.

2. Literature search

PubMed, Cochrane Library, TRIP, LILACS, and Google Scholar electronic databases were searched for articles published from inception to June 2021 (Table 1). Clinicaltrials.gov was accessed for the identification of relevant unpublished trials. Reference lists of studies selected for review, systematic reviews on the topic, and standard endodontics textbooks were manually searched. Studies in English were assessed according to a predefined set of eligibility criteria. The authors were contacted to obtain missing data.

3. Inclusion and exclusion criteria

Two review authors (G. K. and P. S.) independently

Table 1. Search strategy for the literature search in the electronic database

Database	Search strategy
PubMed	#1 ((((((("irreversible pulpitis"[All Fields]) OR ("pulpitis"[All Fields])) OR ("pulpitis"[MeSH Terms])) OR (pulpitis[Title/Abstract])) OR ("irreversible pulpitis"[Title/Abstract])) OR ("root canal therapy"[MeSH Terms])) OR ("root canal treatment"[All Fields])) OR ("endodontics"[All Fields])) OR ("endodontics"[MeSH Terms]) #2 (((((("postoperative pain"[All Fields]) OR ("pain, postoperative"[MeSH Terms])) OR ("postoperative pain"[Title/Abstract])) OR ("pain"[Title/Abstract])) OR ("pain"[MeSH Terms])) OR (pain) #3 (((((((("premedication"[All Fields]) OR (premedication[MeSH Terms])) OR ("premedication"[Title/Abstract])) OR ("anti inflammatory agents"[Title/Abstract])))) OR ("anti inflammatory agents"[All Fields])) OR ("anti inflammatory agents"[Title/Abstract])) OR ("anti-inflammatory agents"[MeSH Terms]) #1 AND #2 AND #3 Filters: **Randomized Controlled Trial**
Cochrane	#1 "pulpitis" in All Text OR "root canal therapy" in All Text OR "root-canal treatment" in All Text OR endodontics in All Text (Word variations have been searched) #2 (postoperative pain) OR (pain) #3 (premedication) OR (anti-inflammatory agents) #1 AND #2 AND #3
TRIP	(((((((("irreversible pulpitis"[All Fields] OR "pulpitis"[All Fields]) OR "pulpitis"[MeSH Terms]) OR "pulpitis"[Title/Abstract]) OR "irreversible pulpitis"[Title/Abstract]) OR "root canal therapy"[MeSH Terms]) OR "root canal treatment"[All Fields]) OR "endodontics"[All Fields]) OR "endodontics"[MeSH Terms]) AND (((((("postoperative pain"[All Fields] OR "pain, postoperative"[MeSH Terms]) OR "postoperative pain"[Title/Abstract]) OR "pain"[Title/Abstract]) OR "pain"[MeSH Terms]) OR ("pain"[MeSH Terms] OR "pain"[All Fields]))) AND ((((((("premedication"[All Fields] OR "premedication"[MeSH Terms]) OR "premedication"[Title/Abstract]) OR "anti-inflammatory agents"[Title/Abstract]) OR "anti-inflammatory agents"[All Fields]) OR "anti-inflammatory agents"[Title/Abstract]) OR "anti-inflammatory agents"[MeSH Terms])
LILACS	(mh:("Root Canal Therapy" OR "Premedication" OR "Endodontics" OR "Pain, Postoperative" OR "Anti-Inflammatory Agents" OR "Pulpitis") AND db:("LILACS") AND type_of_study:("clinical_trials") AND la:("en"))

assessed the titles and abstracts identified after a full literature search. Full-text articles that satisfied the following inclusion criteria were included in the review. In case of disagreement between the two reviewers, an acceptable decision was made after mutual discussion and with the help of a third reviewer (S. T.).

The inclusion criteria of our study were:

1. Randomized controlled trials (RCTs) evaluating the effect of various anti-inflammatory agents administered before non-surgical root canal treatment on post-treatment pain
2. Permanent teeth with irreversible pulpitis
3. Comparison with placebo/control
4. Pain measurement at least until 24 hours after root canal therapy
5. Pain measurement using a visual analog scale (VAS)
6. Studies published in the English language only

The exclusion criteria of our study were non-randomized cross-sectional studies and review articles.

4. Data extraction

Data were extracted from all included studies using the predefined data extraction form. The information retrieved from the study included details about the study, such as the last name of the first author; year of publication; country of the trial; demographic details, such as the total sample, age and sex of the patients; dropouts; preoperative diagnosis; randomization; number of groups; type and name of drug; dose and route of drug administration; measurement scale; pain values; additional analgesic intake; adverse effects; and conclusion.

5. Risk of bias

The Cochrane Collaboration's Risk of Bias tool was used to assess the risk of bias in individual studies. Each included study was graded by two review authors independently as having a high, low, or unclear bias based on seven parameters: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete

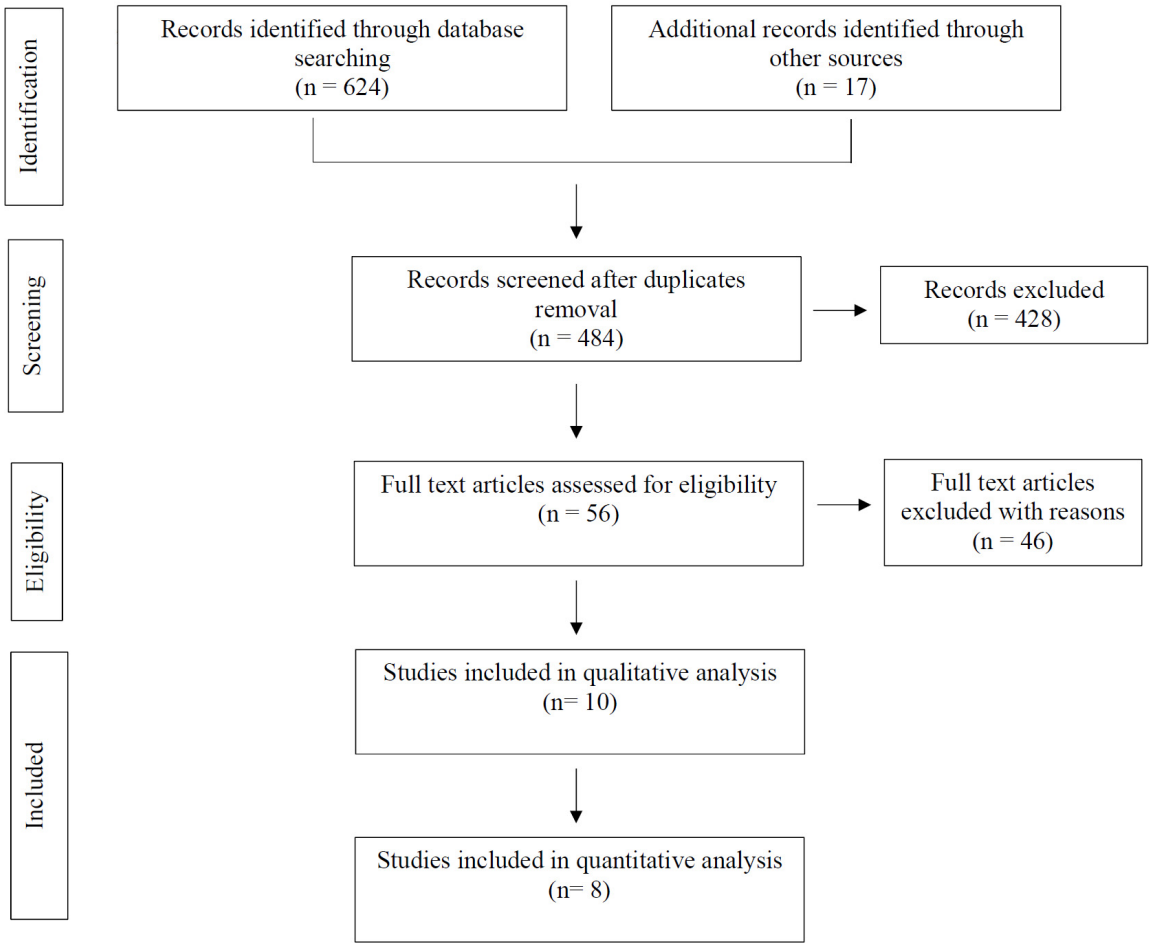

Fig. 1. The Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) flow diagram

data, selective reporting, and other bias. The overall quality of the study was judged to be at a high risk of bias when any one of the domains had a high risk of bias.

6. Data synthesis and meta-analysis

Meta-analysis was performed using Review Manager 5.3 software (The Cochrane Collaboration, Copenhagen, Denmark) [27]. The random effects model of the meta-analysis was selected, as there were differences in study design and intervention type. The pooled effect estimates of the standardized mean difference (SMD) in postoperative pain in the premedication and control groups were calculated at 6, 12, and 24 hours. Means and standard deviations, if not given, were calculated using the median, range, and p-value or derived from the graphs using WebPlotDigitizer (Ankit Rohatgi Austin, TX). Different pain scales were converted to a 100 mm VAS to homogenize the outcomes of different studies. In the case of three-arm trials, the placebo/control group was split into two halves, or the two groups were combined. The heterogeneity between studies was evaluated using I^2 statistics, with significance set at P = 0.1. A funnel plot to assess publication bias was not used because of the inadequate number of studies. Sensitivity analyses for the primary outcome were performed by excluding studies with a high risk of bias. The GRADE PRO tool (McMaster University, 2020) was used to assess the quality of evidence [28].

RESULTS

1. Study selection

The outline of the search is shown in Fig. 1. Electronic searches in the PubMed, Cochrane Library, LILACS, Trip, and Google Scholar, along with a search in clinicaltrials.gov, yielded 624 citations. A manual search yielded 17 other trials. Title and abstract screening after removal of duplicates yielded 56 potentially eligible studies. After reading the full text of these 56 studies, 10 studies were finally included in this review, of which eight studies were included in quantitative analysis.

2. Characteristics of the included studies

The characteristics of the included studies are summarized in Table 2. Of the 10 studies that were included in this review, six were from Iran [12,13,15,20, 22,29], two were from Egypt [30,31], and there was one each from India [16] and Turkey [32]. All studies were conducted between 2010-2020. A total of 946 patients were evaluated. The enrolled patients belonged to the age range of 14-65 years. All studies, except those by Praveen et al. [16] and Jalalzadeh et al. [22], were conducted exclusively on molars. One study did not mention preoperative pain level [31]. Single-visit endodontics were performed in all the studies.

Table 2. Characteristics of the included studies

Author (y)	Country	Population				Premedication		Control	Outcome		Conclusion
		Total sample	Age	Tooth	Gender	Drug	Route		Pain scale	Time	
Akhlagi (2019) [15]	Iran	60	18-65 years	Mand molar	M – 25 F – 35	Ketorolac (30 mg/ml)	Buccal Infiltration	Saline	170 mm HPVAS	2, 4, 6, 24 hours	Ketorolac significantly reduced postoperative pain at all observed time interval.
Aksoy (2020) [32]	Turkey	90	18-65 years	Mand molar	M – 45 F – 45	Dexamethasone (8 mg / 2 ml)	Submucosal	Saline	170 mm HPVAS	6, 12, 24, 48, 72 hours	Pain level was significantly lower in dexamethasone group than control at each time interval.
Al-Rawhani (2020) [30]	Egypt	68	18-60 years	Mand molar	M – 15 F – 55	Diclofenac potassium 50 mg	Oral	Placebo	170 mm HPVAS	6, 12, 24, 48 hours	Significant difference in pain was observed only at 48 hours.
Atbaei (2010) [29]	Iran	65	14-65 years	Molar	M – 36 F – 29	Piroxicam (0.4 ml of 20 mg/ml)	Intraliga-mentary	0.4 ml of 2% lidocaine	10 cm VAS	4, 8, 12, 24, 48 hours	Significant reduction of pain with piroxicam was observed at all time interval.
Elkhadem (2018) [31]	Egypt	398	18-35 years	Mand molar	M – 141 F – 259	Prednisolone (40 mg)	Oral	Placebo	100 mm VAS	6, 12, 24 hours	Prednisolone group had significantly less pain than placebo at all time interval.
Jalalzadeh (2010) [22]	Iran	25	18-59 years	Multi rooted	-	Prednisolone (30 mg)	Oral	Placebo	10 cm VAS	6, 12, 24 hours	Significant difference in pain at 6, 12 and 24 hours was observed.
Mehrvarzfar (2016) [20]	Iran	60	18-65 years	Molar	M – 27 F – 33	Dexamethasone (0.2 ml / 4 mg/ml)	Intraliga-mentary	2% Lidocaine (0.2 ml), control	170 mm VAS	6, 12, 24, 48 hours	Significant difference between dexamethasone and control at all time interval was reported.
Mokhtari (2016) [13]	Iran	66	19-30 year	Mand molar	M – 29 F – 37	Indomethacin (25 mg), Ibuprofen (400 mg)	Oral	Placebo	100 mm VAS	8, 12, 24 hours	Significant difference between premedication and placebo was observed only at 8 hours.
Praveen (2017) [16]	India	42	18-50 years	Singe rooted	M – 24 F –18	Ketorolac (20 mg), Prednisolone (30 mg)	Oral	Placebo	10 cm VAS	6, 12, 24, 48 hours	Significant difference between premedication and placebo at all observed time interval.
Ramazani (2013) [12]	Iran	72	18-65 years	Mand molar	M – 38 F – 34	Ibuprofen (400 mg)	Oral	Placebo	170 mm HPVAS	4, 8, 12, 24, 48, 72 hours	Ibuprofen compared to placebo significantly reduced pain at all interval.

HPVAS, Heft-Parker visual analog scale; Mand, mandibular; VAS, visual analog scale.

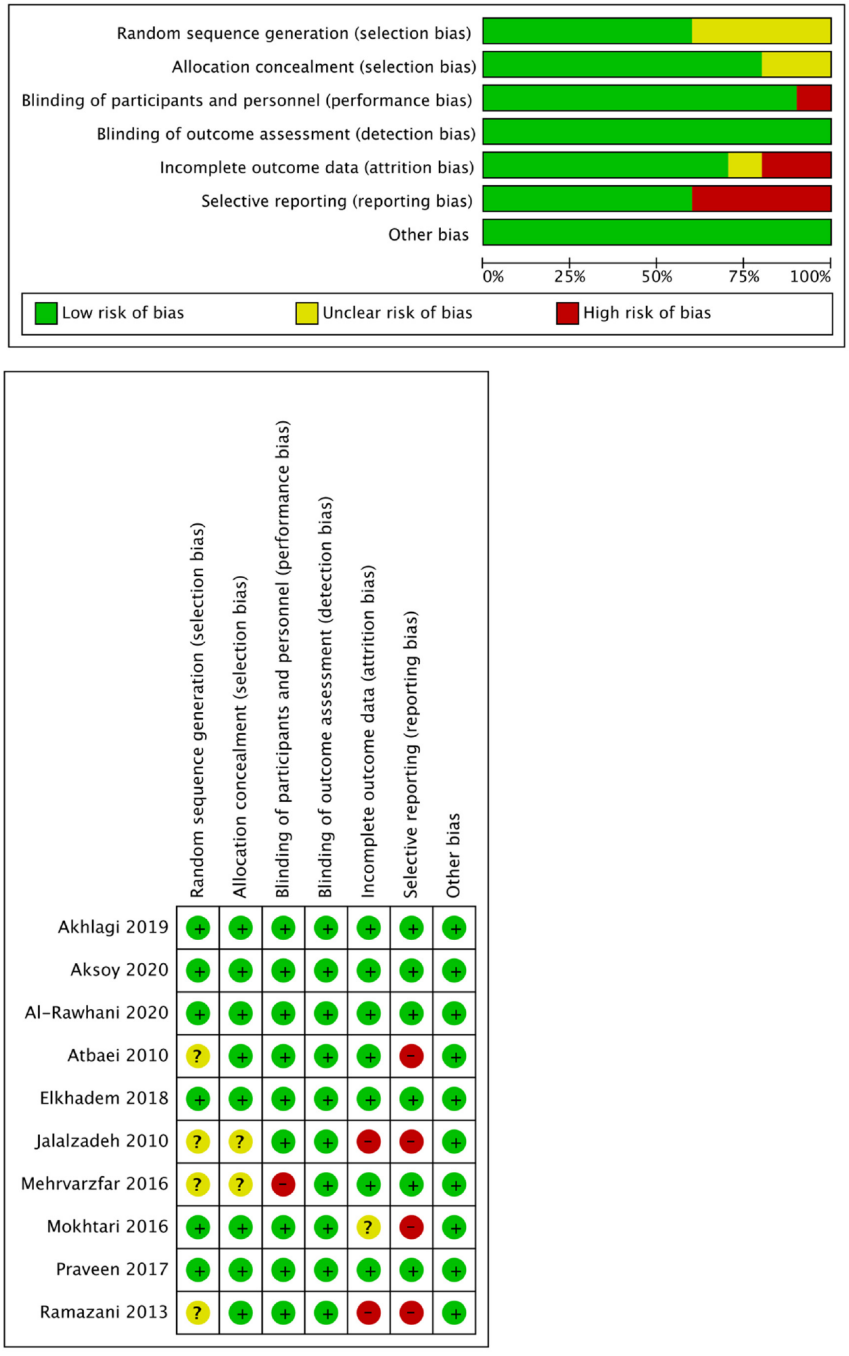

Fig. 2. Summary of the Risk of Bias assessment of the included studies

Corticosteroids and NSAIDs were used in four [20,22,33,34] and five studies [12,13,15,29,32], respectively. In one study, both were used as premedications [16]. Among corticosteroids, dexamethasone was administered through submucosal [32] and intraligamentary [20] routes, while prednisolone was administered orally [16,22,31]. In NSAIDs, piroxicam was administered via the intraligamentary route [29], and diclofenac potassium [30], ibuprofen [12,13], and indomethacin [13] were administered orally. Ketorolac was administered via both oral [16] and intraligamentary [15] routes.

3. Risk of bias assessment

Five studies were assessed as having a low risk of bias,

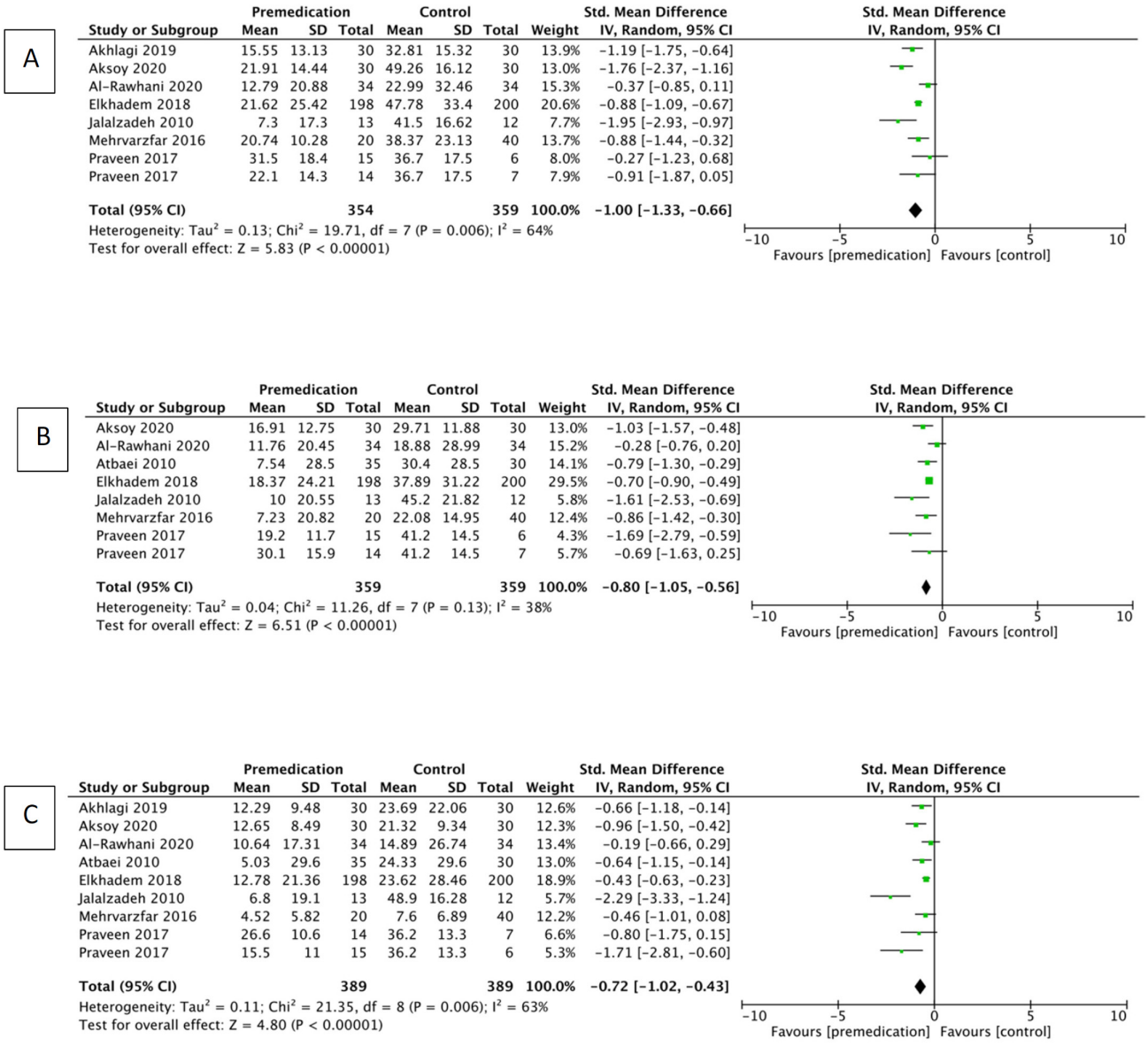

Fig. 3. Forest plot of postoperative pain between premedication and control groups at (A) 6 hours (B), 12 hours, and (C) 24 hours

and the other five studies were graded as having a high risk of bias (Fig. 2). Random sequence generation was unclear in four studies [13,20,22,29]. Allocation concealment was unclear in two studies [20,22]. Blinding of participants and operators was not possible in one study because of the performance of mock intraligamentary injection [20]. A high dropout rate was reported in two studies [12,22], whereas one study did not mention any drop-out [13]. Selective reporting was graded as high risk in four studies [12,13,22,29].

4. Meta-analysis

A total of eight studies were included in the meta-analysis. Two studies were excluded because of the unobtainable mean and SD [12,13]. Forest plot comparisons were performed for 6, 12, and 24 h.

5. Postoperative pain at 6 h

Data from seven out of eight studies were available for comparison of pain at 6 h. A total of 354 and 359

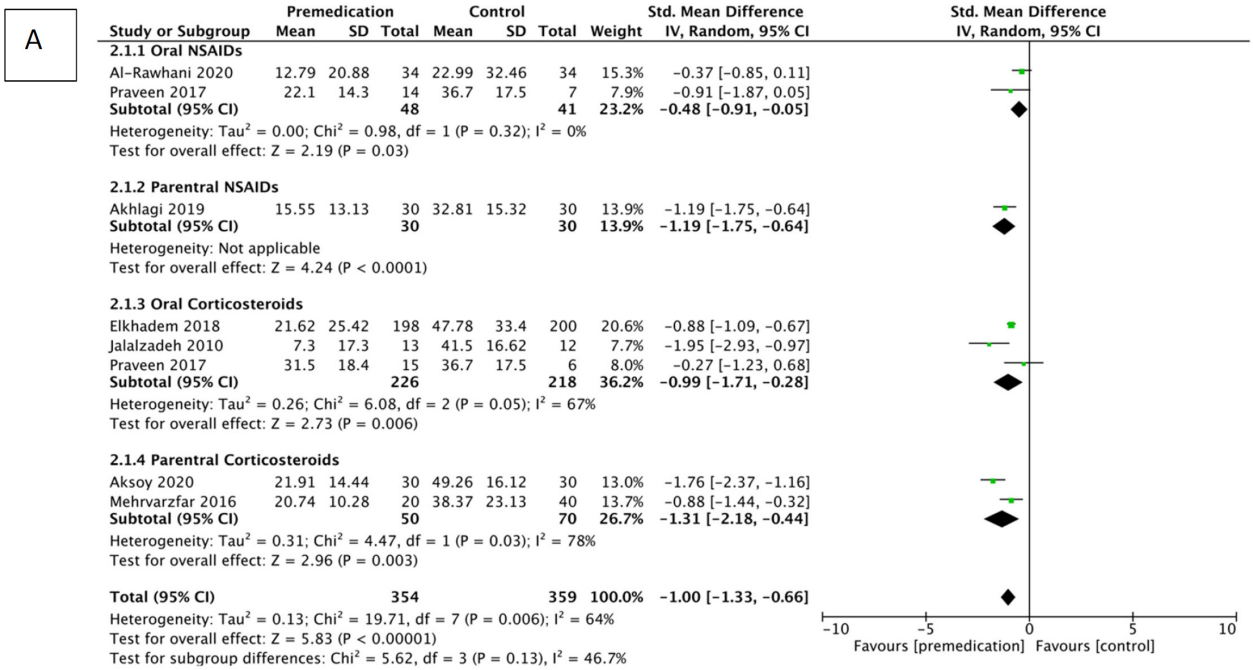

Fig. 4. Subgroup analysis of postoperative pain at (A) 6 hours and (B) 12 hours

patients in the premedication and control groups, respectively, were included in the analysis. The overall effect estimate was in favor of premedication (SMD = -1.00; 95% CI = -1.33 to −0.66) (Fig. 3). Moderate heterogeneity was observed in the data (I^2 = 64%). Subgroup analysis revealed a statistically significant effect size in all subgroups, with the highest estimate for parenteral corticosteroids (SMD = -1.31, 95% CI = -2.18 to -0.44). The test for subgroup differences suggested that there was a statistically non-significant subgroup effect

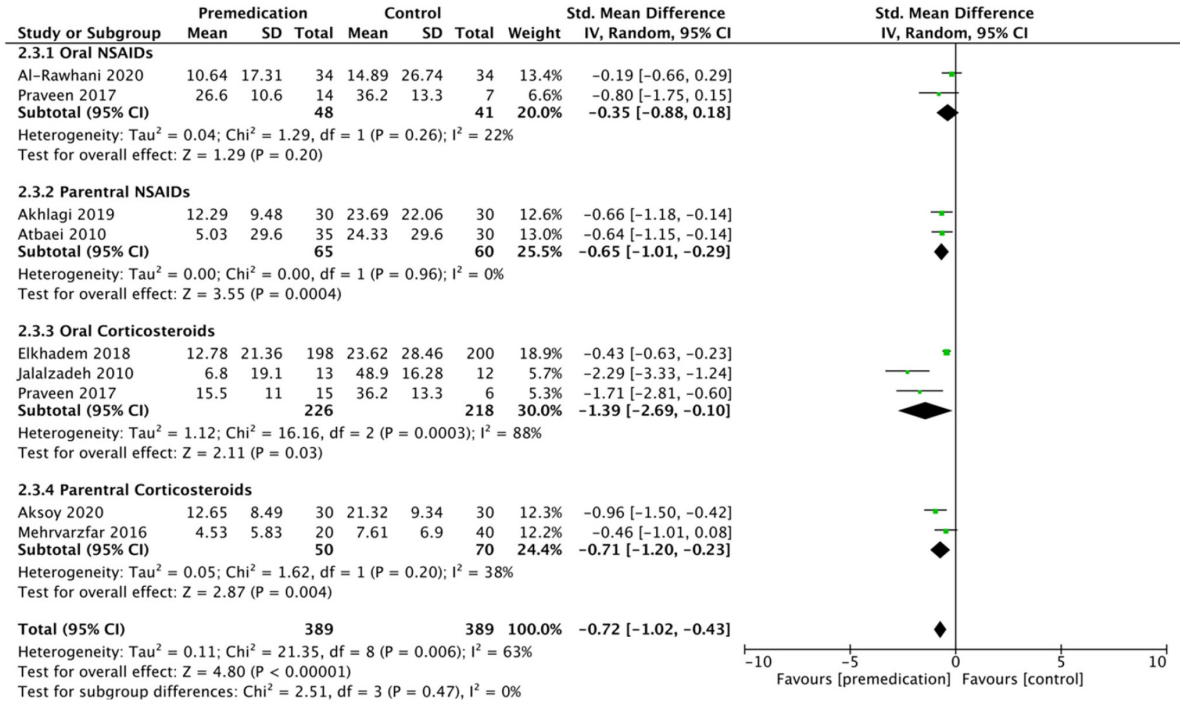

Fig. 5. Subgroup analysis of postoperative pain at 24 hours

(P = 0.13), implying that the route of administration or class of drug did not significantly modify the effect of premedication in comparison to placebo (Fig. 4). However, a small number of trials and participants contributing to the data and substantial unexplained heterogeneity between trials in oral (I^2 = 67%) and parenteral (I^2 = 78%) corticosteroid subgroups indicated that the analyses might not have been able to detect the subgroup difference.

6. Postoperative pain at 12 h

The data of 359 patients in both the premedication and control groups were analyzed at a 12-hour interval. Although less than the 6-hour interval, the overall effect estimate was significantly in favor of premedication (SMD = -0.80; 95% CI = -1.05 to −0.56) (Fig. 3). Heterogeneity in the data was "not clinically important" (I^2 = 38%). Subgroup analysis revealed that oral corticosteroids contributed the most to heterogeneity (I^2 = 55%) (Fig. 4). During subgroup analysis, all subgroups showed a statistically significant reduction in post-operative pain. The maximum effect size was observed with oral corticosteroids (SMD = -1.19, 95% CI = -1.95 to -0.44). The test for subgroup differences revealed a non-significant effect (P = 0.14). However, the results must be interpreted with caution due to limited trials in the subgroups and substantial unexplained heterogeneity between trials in oral corticosteroids (I^2 = 68%).

7. Postoperative pain at 24 h

A total of nine comparisons yielded 389 patients each in the premedication and control groups for the analysis of pain score at 24 h. The overall effect estimate was in favor of premedication (SMD = -0.72; 95% CI = -1.02 to −0.43) (Fig. 3). Moderate heterogeneity was found in the data (I^2 = 63%). Subgroup analysis revealed that the maximum effect size was observed with oral corticosteroids (SMD = -1.39; 95% CI = -2.69, -0.10), albeit with the highest heterogeneity (I^2 = 88%) (Fig. 5). Of the subgroups, only oral NSAIDs had a statistically non-significant effect. The test for subgroup differences revealed a non-significant effect (P = 0.47).

Certainty assessment							Summary of findings				
							№ of patients		Effect		
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Premedication	Control	Relative (95% CI)	Absolute (95% CI)	Certainty
Postoperative pain 6h											
7	randomised trials	serious [a]	serious [b]	serious [c]	not serious	none	354	359	-	SMD **0.99 lower** (1.33 lower to 0.66 lower)	⨁◯◯◯ VERY LOW
Postoperative pain 12h											
7	randomised trials	serious [a]	not serious [d]	serious [c]	not serious	none	359	359	-	SMD **0.76 lower** (0.98 lower to 0.54 lower)	⨁⨁◯◯ LOW
Postoperative pain 24h											
8	randomised trials	serious [a]	serious [b]	serious [c]	not serious	none	389	389	-	SMD **0.72 lower** (1.02 lower to 0.43 lower)	⨁◯◯◯ VERY LOW

a : inclusion of high risk of bias studies, b: high heterogeneity, c: difference in intervention

Fig. 6. Level of certainty assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Profiler tool

8. Sensitivity analysis

Sensitivity analysis was performed for the primary outcome at 6, 12, and 24 h intervals. The effect size was not substantially altered, indicating the robustness of the results.

9. Quality of evidence

The quality of evidence generated by the meta-analysis was assessed using the GRADE approach using GRADEpro. The GRADE evidence for reduction of postoperative pain by premedication compared to placebo was "very low" at 6 and 24 hours, and "low" at 12 hours (Fig. 6).

10. Secondary outcome

Additional analgesic intake: Ibuprofen in four [15,16, 22,32], acetaminophen in three [12,15,22], diclofenac potassium in two [30,31], and no specific drug was prescribed as rescue medication in three studies [13,20,29]. Additional analgesic intake was significantly higher in the control group than in the premedication group in three studies [15,31,32], while no significant difference was observed in three studies [12,20,29]. Two studies failed to mention the analysis of rescue medication intake, while two studies excluded patients who used rescue medication. Because of the paucity of data, a meta-analysis was not planned.

DISCUSSION

Postoperative pain following root canal treatment has been widely reported [2,5]. Preemptive administration of anti-inflammatory drugs is advocated as an effective method to prevent its occurrence [8]. It may inhibit the release of inflammatory mediators and thereby help reduce postoperative pain. Both NSAID and cortico-steroid groups of drugs were included for comparison with placebo or control in relieving pain after endodontic therapy. NSAIDs act by inhibiting prostaglandin synthase enzymes or cyclooxygenases, resulting in antipyretic, analgesic, and anti-inflammatory actions [1]. Cortico-steroids have broader anti-inflammatory actions that involve the inhibition of pro-inflammatory cytokines and inhibition of T-lymphocytes [31]. While previous systematic reviews have evaluated their effect on vital and non-vital teeth [8], the present study focused only on trials involving teeth with irreversible pulpitis to assess and provide conclusive evidence regarding the benefit of

premedication in this particular subset of pulpal pathology. It also helped eliminate the heterogeneity observed in other analyses in terms of dental pulp status.

An extensive literature search was performed to identify potentially eligible studies. A total of 56 studies were identified after the literature search for full-text reading, of which ten studies were included in this review. Inclusion of patients with variable pulp diagnosis, presentation of results in incompatible form, and a non-prophylactic mode of administration were the most common reasons for exclusion of the studies (Supplemental Table S1). Efforts were made to contact the authors if and when required. However, after three electronic requests via e-mail, only one author responded to our query, and clarifications regarding the other studies were not received.

Sample size calculation was not reported in three out of ten trials [12,22,29]. According to a report assessing the quality of randomized controlled trials in Endodontology, approximately 45% of studies either did not report or had inadequate sample size estimation. Underestimation of sample size seriously affects the validity of the results as the probability of detecting a true effect diminishes with a smaller sample size [35] and may lead to type II errors [33]. Providing a priori sample size estimation is also an integral part of the Consolidated Standards of Reporting Trials guidelines [34].

Manual [12,13,20,22,29] and rotary instrumentation [15,16,30-32] were used in five studies each. Majority of the studies used NaOCl as an irrigant, with only two studies [20,29] employing saline for intracanal irrigation. The cold lateral condensation technique was the preferred method of obturation, which was used in eight out of ten studies, with epoxy resin-based sealer used in all but one study [29]. Nine studies provided temporary coronal restoration after completion of root canal treatment, while only one study permanently restored teeth with composite resin [32]. The occlusal reduction was distinctly mentioned in three studies [15,16,22].

Patients are more likely to experience pain within the first 24 h after root canal treatment [36]. Therefore, the role of premedication may be critical immediately after endodontic treatment; thus, studies assessing pain for a minimum of 24 h were included in the present review. VAS was selected as a primary outcome measure in our review, as it is a valid and reliable tool, and has been used in a previous meta-analysis as an outcome measure [37]. Studies using VAS for pain assessment were included, and different scales were standardized to a 100 mm scale. Evidence in the literature indicates a lower incidence of postoperative pain in a single visit than in multi-visit root canal treatment [38]. Single-visit endodontic treatment was performed in all studies included in this review. Preoperative pain has been suggested as an important factor that can influence postoperative pain. All studies included patients with moderate-to-severe baseline pain. The difference was statistically non-significant between the groups in all but one study, where the pain was recorded as significantly higher in placebo [22].

In the present review, premedication reduced postoperative pain significantly better than placebo or control at all time intervals. Immediate postoperative pain is a consequence of direct insult caused to tissues by root canal treatment procedures [16]. Both NSAIDs and corticosteroids downregulate inflammation by inhibiting the production of pro-inflammatory metabolites [1,22]. As stated earlier, this effect may be directly related to the prevention of central and peripheral sensitization by a single preoperative dose of anti-inflammatory medication [31,39]. Furthermore, the acute inflammatory reaction induced as such decreases over time [40]. Decreased levels of inflammation and consequent pain should reduce the observed benefit of analgesics in later periods. This might explain why the largest effect estimate was observed at 6 h.

Substantial heterogeneity in the data was observed at a 6- and 24-hour period. Subgroup analysis based on the class and route of drug administration was performed. The analysis revealed that studies on oral and parenteral corticosteroids at 6 h, as well as on oral corticosteroids at 12 and 24 h, contributed to majority of the observed

heterogeneity. The effect size for premedication was highest in the parenteral route at 6 h. This may be attributed to the higher and quicker bioavailability through the parenteral route. The maximum effect sizes were observed with oral corticosteroids at 12 and 24 h. This can be explained by the fact that the action of corticosteroids is expected to last longer owing to its interaction with intracellular receptors and its regulation of protein synthesis [41].

Consistent with a previous systematic review [8], corticosteroids were found to be effective in reducing postoperative pain. In contrast, another recent systematic review stated that corticosteroids have a minimal role in reducing postoperative pain [42]. Significant heterogeneity, a small number of included studies, and timing of corticosteroid administration may help explain this contradiction. Their conclusion was based on only two studies, with one involving only asymptomatic vital inflamed pulps [43], and the other with no clear pulp/periapical status [44]. More importantly, the review evaluated the efficacy of drugs administered postoperatively. Any injury produces primary hyperalgesia in the affected tissue and secondary hyperalgesia in the surrounding undamaged tissue [45]. It may be further amplified if the neurons are already sensitized because of a previously ongoing inflammatory process [46,47]. Furthermore, inflammatory mediators have been demonstrated to peak after 3-4 hours of acute tissue injury causing post-treatment pain [48]. Preemptive administration of corticosteroids may decrease the release of mediators responsible for primary and secondary hyperalgesia. Once the inflammatory process has established itself, however, its control using postoperative drugs may be less effective, as corticosteroids may need time to mediate their effect [33].

The GRADE evidence profile aids in understanding the quality of evidence that accompanies the conclusions made in a review. This indicates the confidence with which the asserted conclusion can be stated as correct [49]. Risk of bias and indirectness were downgraded at all observed time intervals because of the inclusion of high-risk bias studies and differences in interventions. Inconsistency was downgraded at 6 and 24 h because of high heterogeneity, while it was judged as not significant at 12 hours. The other factors governing the quality of evidence, such as imprecision, were not found to be significant. This led to the "very low" and "low" quality of final evidence at 6 and 24 hours, and at 12 hours, respectively, indicating a need for further studies exploring the subject.

A limitation of this systematic review was the inclusion of only a limited number of studies, especially in the subgroup analysis. The inclusion of trials published in English only could be considered as another limitation. Mean and standard deviations were derived indirectly in three studies, which also included data extraction from the graph in one study. Despite being a standard practice during the conduct of meta-analysis, doing so may lead to less precise data compared to that obtained directly. Precise figures for primary outcomes must be provided in future studies to avoid any ambiguity, and sole reliance on graphs must be avoided. Pulp status and baseline pain score were reported inconsistently in studies that were analyzed in a previous meta-analysis, and the author conceded that it may have contributed to heterogeneity [8]. Inclusion of studies involving only irreversible pulpitis in the present review may have removed one of the major sources of heterogeneity. However, wide variation was observed in the methodologies of the studies reporting postoperative pain after root canal treatment. These confounders, along with several other unknown preoperative and intraoperative variables inadvertently introduced during the trial, may have been responsible for the observed clinical heterogeneity. In addition, the results may not be generalized to teeth with other pulpal and periapical conditions, as this review was limited to patients with irreversible pulpitis. Therefore, exploration of the efficacy of premedication in necrotic teeth with or without periapical involvement is needed in future studies. Prior sample size estimation was not provided in three studies, and incomplete reporting prevented the inclusion of two additional studies in the meta-analysis. Future studies should adopt a standardized design and

strictly adhere to guidelines specifically designed for randomized controlled trials [38]. Furthermore, certain trials excluded patients taking rescue medication, leading to significant attrition of clinical material and the introduction of bias. It would be better to retain all the recruited individuals until the end of the trial.

CONCLUSION

Despite the limitations of this systematic review and meta-analysis, it shows evidence that the preoperative administration of anti-inflammatory drugs is an effective modality for reducing postoperative pain for up to 24 hours in teeth with irreversible pulpitis. This reduced pain may also help minimize the incidence of adverse effects that may be associated with repeated intake of post-operative analgesics. However, a low level of evidence using the GRADE approach and limited studies indicate that further trials are needed to validate this hypothesis. These trials should adhere to established CONSORT guidelines for randomized controlled trials as well as follow a standardized, replicable methodology and the intention-to-treat analysis.

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