ECRONICON OPEN ACCESS

EC DENTAL SCIENCE
Research Article

Management of Endodontic Pain: A Systematic Review of Randomized Controlled Trials

Montaser Omar Ezmirly[1]*, Tasnim Abdulkhaleq Bageri[2], Bayan Mohamed Babatin[2], Reem Bakur Natto[2], Watin Abid Shaikh[2], Alaa Ali Mufti[2]

[1]*Department of Endodontic, King Fahd Hospital of Armed Forces, Jeddah, Saudi Arabia*

[2]*College of Dentistry, Ibn Sina National College, Jeddah, Saudi Arabia*

***Corresponding Author:** Montaser Omar Ezmirly, Department of Endodontic, King Fahd Hospital of Armed Forces, Jeddah, Saudi Arabia

Received: June 24, 2019; **Published:** July 04, 2019

Abstract

Objective: To evaluate different strategies used for management of endodontic pain to choose the best therapeutic approach.

Methods: Twelve databases were searched systematically for RCTs discussing management of endodontic pain. In addition, manual search with different methods was performed to retrieve all possible studies. Three independent reviewers scanned retrieved references for possible inclusion.

Results: A total of 24 randomized controlled trials were finally included in the qualitative synthesis of this review. The studies were divided into two groups: preoperative and postoperative analgesic treatments. Steroid therapy has been shown to be effective for short-term management of the endodontic pain. Also, NSAIDs has shown to be effective in both preoperative and postoperative settings with a combination therapy showing superiority to an individual one. Both LLLT and cryotherapy have shown a limited evidence for being effective in reducing post-endodontic pain.

Conclusions: NSAIDs are better considered as the first line of treatment of post-endodontic pain either pre or postoperative (individually or in combination) followed by the combination of NSAIDs and other pain medications. Moreover, Dexamethasone can be considered for the short-term treatment of post-endodontic pain with minimal adverse effects.

Keywords: *Endodontics; Pain; Analgesics; Randomized Controlled Trials*

Introduction

Individuals with low socioeconomic status and low education level are associated with more dental service utilization [1]. Therefore, healthy lifestyle and regular dental care visits can prevent negative consequences stems from various diseases affecting teeth and gums that required special care and treatment [2]. Pre-operative, operative, and post-operative pain originates from damaged teeth and its covering mucosa constitutes a major problem affecting both the dentists and patients. The good therapeutic approach starts from diminishing pain for those patients to allow good tissue healing. Root canal pathology and tissue damage by instrumentation stimulate inflammatory mediators such as kinins and prostaglandins which induce vascular leakage in addition to activation of nociceptors to cause pain [3].

Several therapeutic approaches emerged for decreasing post-endodontic pain. Non-steroid anti-inflammatory drugs (NSAIDs) such as rofecoxib showed a significant effect in reducing post-endodontic pain compared to ibuprofen and placebo after 24 hours of patients undergoing root canal removal, however, the comparison was only significant compared to placebo after 4 and 8 of root canal removal [4]. Moreover, a combination of NSAIDs can be beneficial in reducing postoperative pain. The combination of ibuprofen/paracetamol was categorized as the best intervention for pain relief following endodontic therapy compared to other groups [5]. Furthermore, dexamethasone can provide an alternative option for physicians, the drug acts by decreasing the level of prostaglandin and leukotriene synthesis. Pochapski., *et al.* demonstrated a significant effect of dexamethasone in reducing of post-endodontic pain at 4 and 8 hours following post-endodontic treatment; meanwhile, the significance was lost at 24, 48 hours compared to placebo [6]. Recently, laser was used to control inflammation, reduce pain and avoid steroid side effects. Patients allocated to the laser group had a significant reduction

of edema in addition to better wound healing in 1st, 3th and 7th day, meanwhile the trend was significant for 3th and 7th day for ecchymosis reduction [7]. Low-level laser therapy reduced significantly postoperative pain following root canal therapy compared to the control group supporting the favorable effect of adding laser as an adjuvant therapy for better healing and diminishing pain sensation. We aim to systematically review previous literature discussing several strategies on endodontic pain management which will enable physicians to choose the best therapeutic approach.

Method and Materials

Search strategy and study selection

The study was conducted following the accepted methodology recommendations of PRISMA's checklist for systematic reviews. We conducted a systematic electronic database search for suitable studies from inception till 8th February 2019 in twelve databases including Google Scholar, Popline, WHO health library (GHL), System for Information on Grey Literature in Europe (SIGLE), Scopus, Web of Science (ISI), PubMed, Virtual Health Library (VHL), The New York Academy of Medicine (NYAM), clinical trials.gov, metaRegister of Controlled Trials (mRCT) and the WHO International Clinical Trials Registry Platform (ICTRP) using the following search term: (endodontics) AND (root canal treatments OR analgesics) AND (randomized controlled clinical studies). A manual search was conducted by searching for relevant publications from references of included articles, relevant papers in PubMed and Google Scholar and primary studies that had cited the included papers. We also hand searched using each keyword to avoid missing any relevant publications. Three independent reviewers scanned the titles and abstracts against our inclusion and exclusion criteria to select potential articles. We included all randomized controlled trials (RCTs) reporting management of endodontic pain. There were no restrictions on country, language or publication date. Papers were excluded if one of the following exclusion criteria was met: i) *in vitro* or animal studies; ii) data duplication, overlapping or unreliably extracted or incomplete data; iii) not a RCT including; abstract only articles, reviews, thesis, books, conference papers or articles without available full texts (editorials, author response, letters, and comments) along with any previous systematic reviews, meta-analyses and literature reviews on our topic of interest. Three reviewers independently performed an initial eligibility assessment on the retrieved titles and abstracts. Full texts of eligible articles were then retrieved and reviewed for inclusion in the systematic. In both steps of the screening, inclusion or exclusion of a study by all three reviewers was considered conclusive. Controversies during the process were resolved by discussion and consensus. When necessary, disagreements and discrepancies were resolved by consensus with senior reviewers.

Data extraction

Based on a pilot review and extraction, a data extraction form was developed by two authors, using Microsoft Excel file. Three reviewers independently extracted data from included studies using the excel sheet. Data rechecking was carried out by at least two different authors and re-checked by a third reviewer for accuracy. All the disagreements and discrepancies were resolved by discussion and consensus. Papers published by the same research group and studying the same factors were checked for potential duplicate data based on the year of patient recruitment and the hospital where the patients were recruited and confirmation from study authors.

Quality assessment

Three independent reviewers evaluated the risk of bias in included studies. Methodological quality assessment was done using the Cochrane quality assessment tool to determine the quality of the included studies. Any discrepancy between the reviewers was solved by consensus.

Results

Results of the search

After performing a full search of twelve electronic databases since inception till February 8th, 2019, we identified a total of 1050 studies. When duplicated studies were removed, 793 studies remained for further selection and investigation. After a thorough screening of titles, abstracts, and keywords, 272 articles were selected for further screening. The full texts of those articles were retrieved. After that, 252 articles were excluded based on the pre-specified exclusion criteria. Manual search resulted in the identification of 4 more relevant studies. Eventually, a total of 24 randomized controlled trials were included in the qualitative synthesis of this review. A flow chart illustrating the systematic review process of identifying and selecting trials based on the widely accepted PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines is presented in figure 1 [8].

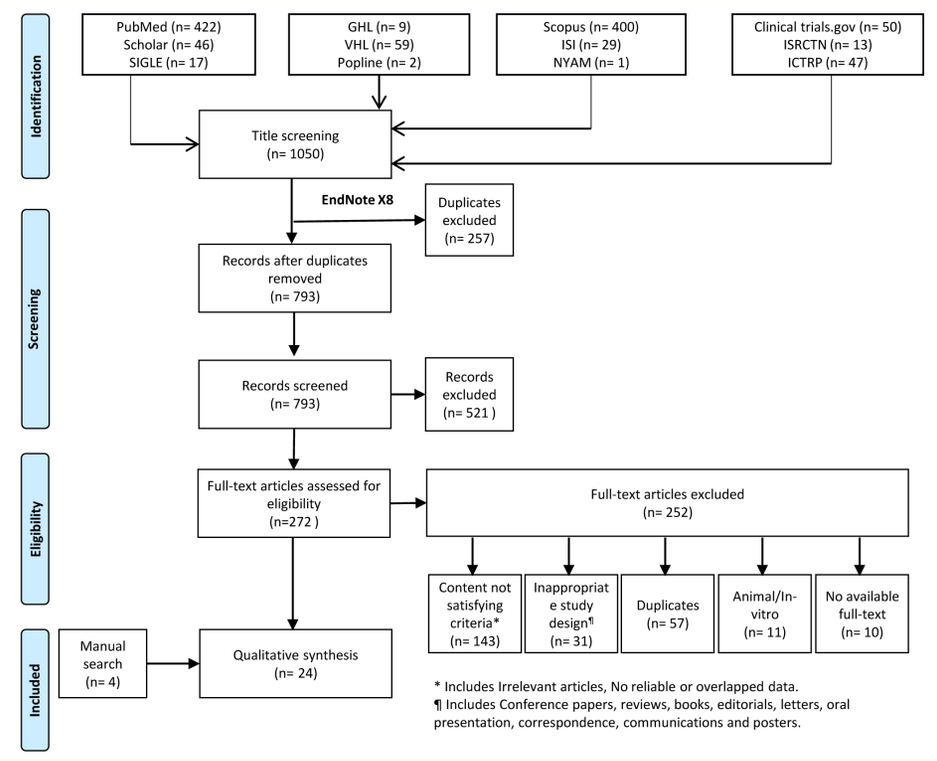

Figure 1: *Flow chart of the data used according to PRISMA guideline.*

Data synthesis could not be performed due to the high variability in methodological approaches of included trials as well as the differences in interventions, evaluation metrics, designs, and outcomes discusses in each trial. Therefore, a meta-analysis pooling the results of all trials in order to determine the efficacy of all approaches for managing the pain of endodontic origin could not be performed.

Included trials

After a thorough review of the included trials, we found that all of these trials were conducted to determine the efficacy of various medications in treating pain following the endodontic treatment. In this review, our main focus was on 2 clinical situations involving the use of various pain medications. The first was the preoperative administration of pain medication prior to endodontic treatment (e.g. root canal treatment or retreatment). While the second one was the postoperative administration of various pain medications and laser therapy following endodontic treatment in order to prevent or manage pulpal or periapical pain. In comparison to the previous systematic review conducted in 2016 to assess the efficacy of oral analgesics only in treating the pain of endodontic origin [9], we included all trials reporting the use or oral medications, injections (intramuscular, intraoral, extraoral, intracanal), laser therapy and cryotherapy for management of post-endodontic pain.

Effects of interventions

Preoperative administration of medication

A total of 9 randomized controlled trials reported the outcomes of preoperative administration of various pain management regimens on post-endodontic pain (Table 1 and 2) [4,6,10-16]. Two trials investigated the effect of preoperative low-level laser therapy (LLLT) on post-endodontic pain [10,12]. One trial showed that LLLT significantly reduced post-endodontic pain from the 1st day post-treatment till the 4th day [10]. On the other hand, the other trial reported that no significant reduction in pain was noted at any time point of evaluation after LLLT [12]. Interestingly, dexamethasone has been reported to significantly reduce pain levels following endodontic treatment as compared to placebo across all trials investigating dexamethasone [6,14,15]. However, a single trial reported that dexamethasone (single-oral dose; 4 mg) was effective in reducing pain levels at 4 and 12 hours after treatment, but no significant difference from placebo was

noted at 24 and 48 hours [6]. Preoperative administration of ibuprofen has been reported to significantly reduce post-endodontic pain as compared to placebo [4,14,16]. Ibuprofen (600 mg) has been shown to be superior to etodolac (400 mg) in reducing pain 4 and 8 hours after endodontic treatment [16]. However, it was inferior to rofecoxib (50 mg) at 12 and 24 hour points [4]. Noteworthy, a single trial investigated the efficacy of intraosseous injection of Depo Medrol (40 mg) and reported that it significantly reduced pain post-treatment till the 7th day of evaluation, where none of the patients reported moderate to severe pain in the 2nd till the end of follow-up [13].

Characteristics and outcome profile of included studies for preoperative pain treatment modalities							
Study	**Sample Size**	**Study Type**	**Diagnosis**	**Pain Assessment Tool**	**Intervention**	**Evaluation Points (Follow up)**	**Outcome**
Gopikrishna/ 2003	45	Randomized; DB	Symptomatic cases (spontaneous pain of at least 30 (0–100) in VAS).	VAS	Rofecoxib (50 mg); single-dose or ibuprofen (600 mg)	4, 8, 12, 24, 48, and 72 after endodontic treatment	At 4- and 8-h periods, both rofecoxib and ibuprofen provided significantly better pain relief than placebo. At the 12- and 24-h periods, rofecoxib demonstrated significantly better pain management than both ibuprofen and placebo.
Gallatin/ 2000	40	Randomized; DB	Emergency cases (with moderate or severe pain).	0 to 3-point self-designed pain scale (0= no pain; 1= mild pain; 2= moderate pain; 3= severe pain)	Depo-Medrol (40 mg); intraosseous injection	each day after endodontic treatment till 7 days	Over the 7-day observation period, subjects who were given Depo-Medrol injection reported significantly ($p < 0.05$) less pain while taking significantly ($p < 0.05$) fewer pain medications. For the Depo-Medrol group, by day 1, only 10% of the patients reported moderate to severe pain. By day 2 none of the patients reported moderate or severe pain, and this continued through day 7.
Menke/ 2000	36	Randomized; SB	NCS	VAS	Etodolac (400 mg) or ibuprofen (600mg)	Immediately postoperative, 4, 8, 12, 24, 48, and 72 h after endodontic treatment	Ibuprofen was superior to both etodolac and placebo in significantly reducing postendodontic pain at 4 and 8 hours after treatment.
Pochapski/ 2009	47	Randomized; DB	NCS	NRS	Dexamethasone (4mg); single-dose; oral	4, 12, 24, 48 hours after endodontic treatment	Oral dexamethasne resulted in a significant reduction in postendodontic pain at 4 and 12 hours ($P< .05$). However, no statistical difference ($P> .05$) was observed at 24 and 48 hours. The placebo group exhibited higher rescue medication intake (3 tablets of acetaminophen 750 mg).

Camargo/ 2018	56	Randomized; DB	Asymptomatic and Symptomatic cases	NRS	Single-dose ibuprofen (400 mg) or dexamethasone (8mg)	4, 8, 12, 24, and 48 hours after endodontic treatment	Preoperative administration of Ibuprofen or dexamethasone reduced post-endodontic pain as compared to placebo.
Arslan/ 2017	36	Randomized; TB	Symptomatic cases (<50 mm score on VAS).	VAS	LLLT	1st, 2nd, 3rd, 4th, 5th, 6th, and 7th day after intervention	LLLT significantly reduced pain in the 1st 4 days after intervention, however on the 5th and 7th day, no significant difference was noted. No patient reported pain in the LLLT. Number of patients who needed analgesics was much lower in the LLLT than placebo
Lin/ 2006	90	Randomized; DB	not reported	1 to 10=point pain scale	Single-dose of oral dexamethasone (8 mg) preoperatively and 2 single doses (4 mg) 1 and 2 days postoperatively; or a single dose of etodolac (600 mg) and 2 single doses (600 mg) 1 and 2 days postoperatively.	8, 24, 48 hours, and 7 days after endodontic treatment	Both etodolac and dexamethasone had a significant effect of reducing postoperative pain in patients who had surgical endodontic procedure compared with placebo (P= .001).
Attar/ 2008	39	Randomized; DB	emergent cases	3 pain scales (VAS, category, and HeftParker)	Single-dose ibuprofen; tablet or liquigels	6, 12, 18, 24 hours after endodontic treatment	Single-dose pretreatment analgesia (ibuprofen) alone in endodontic pain patients did not significantly reduce postoperative pain below the reduction in pain from endodontic treatment.
Yoshinari/ 2019	10	Randomized; SB	asymptomatic patients	Self-adapted VAS (no pain: 0 to 4 mm; mild pain: 5 to 44 mm; moderate pain: 45 to 74 mm; severe pain: 75 to 100 mm)	photodynamic therapy (LLLT)	6, 12, 24, 36, 48, and 72 hours after endodontic treatment	No statistically significant differences in postoperative pain between the groups at any observation times (p<0.05) was noted.

Table 1: *Characteristics and outcome profile of included studies for preoperative pain treatment modalities.*

SB: Single-Blinded; DB: Double-Blinded; TB: Triple-Blinded; VAS: Visual Analogue Scale; NRS: Numeric Rating Scale; NCS: Not Clearly Specified.

Characteristics and outcome profile of included studies for postoperative pain treatment modalities							
Study	**Sample Size**	**Study Type**	**Diagnosis**	**Pain Assessment Tool**	**Intervention**	**Evaluation Points (Follow up)**	**Outcome**
Rowe/ 1980	149	Randomized; DB	NCS	1 to 4-point pain scale (home report form)	Mefenamic acid [loading dose (500 mg); maintenance dose (250 mg)]; 4 tablets/day for 2 days	2 and 4 hours after each dose	Mefenamic acid significantly reduced postendodontic pain as compared to placebo, while aspirin showed no difference from placebo. Mefenamic acid was superior to aspirin at 4 hours post-medication and superior to placebo at 2- and 4-hours time points. Aspirin was not significantly suprior to placebo at both time points, however, it was superior to mefenamic acid at 2 hour- time-point.
Krasner/ 1986	48	Randomized; DB	NCS	0 to 100-point pain scale	Dexamethasone (0.75 mg)	8 and 24 hours following endodontic treatment	Patients who received dexamethasone reported significantly less postoperative pain than those on placebo at 8 and 24 hours. At both 8 hours and 24 hours after treatment, there was not a single dexamethasone subject who reported high pain.
Glassman/ 1989	40	Randomized; DB	Asymptomatic cases	VAS	Dexamethasone (3 tablets 4 mg)	8, 24, 48 hours following endodontic treatment	oral administration of dexamethasone resulted in a significant reduction in postendodontic pain at all evaluation time points (P< 0.01).
Torabinejad/ 1994	588	Randomized; DB	Asymptomatic and symptomatic cases	VAS	Nine medications: a) Aspirin (650 mg); b) acetaminophen (650 mg); c) ibuprofen (400 mg); d) ketoprofen (50 mg); e) acetaminophen (325 mg) + codeine (60 mg); f) penicillin (500 mg); g) erythromycin (500 mg); h) penicillin (500 mg) + ibuprofen (400 mg); i) methylprednisolone (2 mg) + penicillin (500 mg)	6, 12, 18, 24, 30, 36, 42, 48 hours after endodontic treatment	No significant difference between interventions and placebo was noted in patients with no or mild pain. In patients with moderate to severe pain, ibuprofen, ketoprofen, erythromycin base, penicillin, and methylprednisolone plus penicillin were more effective than placebo within the 1st 48 hours after treatment.

Liesinger/ 1993	106	Randomized; DB	Symptomatic cases	0 to 9-point pain scale	Variable doses of dexamethasone (intraoral/ intramuscular injection): either 2 mg/ml, 4 mg/ml, 6 mg/ml, or 8 mg/ml	4, 8, 24, 48, 72 hours after treatment	As a whole, dexamethasone injecton significantly reduced the severity of pain at 4 and 8 hours. 0.07 to 0.09 mg/kg dosage alone were the optimum dosage for reducing pain at 8 hours. Patients who received dexamethasone took significantly fewer post-treatment pain medications than those who received the placebo.
Elzaki/ 2016	170	Randomized; DB	Symptomatic cases (moderate to severe pain of 4-10 score on NRS)	VRS and NRS	Paracetamol alone and in combination with 3 different NSAIDS: 1-(ibuprofen 600 mg + paracetamol 1000 mg); 2-(mefenamic acid 500 mg + paracetamol 1000 mg); 3-(diclofenac K 50 mg + paracetamol 1000 mg)	every hour after medication till 8 hours	Ibuprofen/paracetamol group had the most pain reduction, followed by combined diclofenac K/ paracetamol, then mefenamic acid/paracetamol group, followed by placebo, (P < .05).
Kreisler/ 2003	52	Randomized; DB	NCS	VAS	LLLT	7 days following endodontic treatment	LLLT significantly reduced postendodontic pain in the 1st postoperative day, however, it was of no significant impact in the days after that.
Yıldız/ 2018	42	Randomized; NCS	Symptomatic cases	VAS	LLLT	1st, 3rd, 5th, 7th, and 30th day after endodontic treatment	LLLT resulted in lower pain levels than those noted in the control and placebo groups on days 1 and 3 (P < .05)
Menhinick/ 2004	57	Randomized; DB	Patients experiencing moderate to severe pain	VAS	Single-dose ibuprofen (600mg) alone or in combination with acetaminophen (1000 mg)	1, 2, 3, 4, 6, 8 hours after treatment	The combination of ibuprofen with acetaminophen was shown to be more effective than ibuprofen alone for the management of postoperative endodontic pain.
Doroschak/1999	49	Randomized; DB	Emergency patients (patient reports spontaneous pain of at least 30 (0 to 100 scale)	VAS	1) Flurbiprofen (100 mg loading dose and then 50 mg every 6 h); 2) tramadol (100 mg loading dose and then 100 mg every 6 h); 3) flurbiprofen and tramadol (same dosing)	1, 2, 3, 4 days after medication	Patients treated with flurbiprofen and tramadol reported less pain, compared with placebo treatment at 6 and 24 h (p < 0.01 for both), and also better than the monotherapy of either medication alone.

Gundogdu/2018	84	Randomized; NCS	Symptomatic patients (severe preoperative pain (visual analogue scale [VAS] > 60) and severe percussion pain (VAS > 60)	VAS	Cryotherapy (intracanal, Intraoral, and extraoral)	1st, 3rd, 5th and 7th day after intervention	Compared with the control group, all the cryotherapy groups exhibited less postoperative pain at the first, third, fifth, and seventh days (P < .05). As regarding the use of oral analgesic medications, the intra-oral cryotherapy group showed the least number of patients using analgesics followed by intracanal and extraoral respectively, however this finding remains insignificant.
Mehrvarzfar/2011	100	Randomized; DB	patients with moderate or severe pain	VAS	Dexamethasone (8 mg/2mL); supraperiosteal injection	6, 12, 24 and 48 hours after intervention	Dexamethasone was considerably effective on controlling the severity of pain during the first 24 hours, however, it was of no significant difference from placebo in 48 hours after treatment.
Asnaashari/2017	61	Randomized; NCS	no pain, mild pain, moderate pain, severe and very severe pain were included	VAS	LLLT	prior to, immediately after, and 4,8, 12, 24, and 48 hours after endodontic treatment	Pain scores decreased significantly through time until 48 hours after treatment. However, no significant differences were observed from placebo regarding pain scores at any time. Regression analysis showed that pain severity scores were lower in the laser-irradiated specimens than control groups (OR=5.69); however, this difference was not statistically significant.
Metin/2018	71	Randomized; NCS	NCS	VAS	LLLT	1st, 3rd and 7th day after endodontic treatment	LLLT group showed better results in number of analgesics taken in the 1st, 3rd and 7th day postop days. The patients had significantly lower pain on the 1st and 3rd postop days in the LLLT group.
Praveen/2017	86	Randomized; TB	NCS	VAS	Single-dose of ketorolac (20 mg), or prednisolone (30 mg)	prior to, immediately after, and 6, 12, 24, and 48 hours after endodontic treatment	At the end of 6 hours, the ketorolac group was superior to other groups in reducing pain score. At the end of 12 hours, the prednisolone group significantly reduced the pain scores compared with the other drugs.

Table 2: *Characteristics and outcome profile of included studies for postoperative pain treatment modalities.*

SB: Single-Blinded; DB: Double-Blinded; TB: Triple-Blinded; VAS: Visual Analogue Scale; VRS: Verbal Rating Scale; NRS: Numeric Rating Scale; NCS: Not Clearly Specified.

Postoperative administration of medication

Management of post-endodontic pain through postoperative pain medications was addressed and investigated in 15 randomized controlled trials [5,7,17-29]. Postoperative LLLT significantly reduced post-endodontic pain within the 1st day after treatment however its effect was of no statistical significance the days after that [23]. Controversially, two clinical trials showed that LLLT was effective on both 1st and 3rd day post-treatment [7,18]. That being said, LLLT was found be of no statistical significance compared to placebo in reducing post-endodontic pain [17]. Corticosteroids in the form of dexamethasone were significantly effective in reducing pain [20,22,24,25]. The authors of those trials reported that dexamethasone of variable dosages from 0.75 mg to 8 mg was effective in reducing post-endodontic pain. Also, the outcomes of supra-periosteal injection of dexamethasone were comparable to that of oral medication [25]. The combined therapy of two pain medications has been found to be more effective than monotherapy in reducing post-endodontic pain. A combined therapy of ibuprofen (600 mg) and acetaminophen (1000 mg) was more effective than either medication alone in handling pain post-treatment [26]. Whereas, flurbiprofen (100 mg loading dose and maintenance of 50 mg) and tramadol (100 mg loading dose and maintenance dose) were also more effective than either drug alone or placebo in managing pain [19]. Moreover, ibuprofen (600 mg) plus acetaminophen (1000 mg) combination was superior to other combinations of acetaminophen (1000 mg) plus diclofenac potassium (50 mg) and acetaminophen (1000 mg) plus mefenamic acid (500 mg) in treating post-endodontic pain [5]. Interestingly, a single trial reported the efficacy of cryotherapy in reducing pain, and it was found effective in reducing pain at all evaluation points from the 1st day to the 7th day post-treatment [21].

Risk of bias in included trials

Overall, preoperative pain medication studies were of low risk of bias (Table 3). Five trials were of low risk of bias, while 4 trials were of a high risk of bias, where allocation concealment and random sequence generation were not reported as much in those trials. On the other hand, postoperative pain medication studies were of a relatively high risk of bias; 10 trials were of a high risk of bias, while only 5 trials were of low risk (Table 4). Blinding of outcome assessors and/or patients, allocation concealment, and random generation sequence are the most common unclearly reported points in those trials.

Risk of Bias Assessment of Preoperative Pain Medication Studies								
Study ID	**Selection Bias**	**Random sequence generation (selection bias)**	**Allocation concealment (selection bias)**	**Blinding of participants and researchers (performance bias)**	**Blinding of outcome assessment (detection bias)**	**Incomplete outcome data (attrition bias)**	**Other bias**	**Overall risk**
Gopikrishna/ 2003	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Gallatin/ 2000	Low risk	High risk	High risk	High risk	High risk	High risk	Low risk	High risk
Menke/ 2000	Low risk	Low risk	Low risk	High risk	Low risk	Low risk	Low risk	High risk
Pochapski/ 2009	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Camargo/ 2018	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Arslan/ 2017	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Lin/ 2006	Low risk	High risk	High risk	Low risk	Low risk	Low risk	Low risk	High risk
Attar/ 2008	Low risk	High risk	High risk	Low risk	Low risk	Low risk	Low risk	High risk
Praveen/ 2017	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk

Table 3: *Risk of bias assessment of preoperative pain medication studies.*

Risk of Bias Assessment of Postoperative Pain Medication Studies								
Study ID	**Selection Bias**	**Random sequence generation (selection bias)**	**Allocation concealment (selection bias)**	**Blinding of participants and researchers (performance bias)**	**Blinding of outcome assessment (detection bias)**	**Incomplete outcome data (attrition bias)**	**Other bias**	**Overall risk**
Rowe/ 1980	Low risk	Low risk	Low risk	Low risk	Low risk	High risk	Low risk	Low risk
Krasner/ 1986	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Glassman/ 1989	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Torabinejad/ 1994	Low risk	High risk	High risk	High risk	High risk	Low risk	Low risk	High risk
Liesinger/ 1993	Low risk	High risk	High risk	High risk	High risk	Low risk	Low risk	High risk
Elzaki/ 2016	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Kreisler/ 2003	Low risk	High risk	High risk	High risk	High risk	Low risk	Low risk	High risk
Yıldız/ 2018	Low risk	Low risk	Low risk	High risk	High risk	Low risk	Low risk	High risk
Menhinick/ 2004	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Doroschak/ 1999	Low risk	High risk	High risk	Low risk	Low risk	Low risk	Low risk	High risk
Gundogdu/ 2018	Low risk	Low risk	High risk	High risk	High risk	Low risk	Low risk	High risk
Mehrvarz-far/2011	Low risk	High risk	High risk	Low risk	Low risk	Low risk	Low risk	High risk
Asnaas-hari/2017	Low risk	High risk	High risk	High risk	High risk	Low risk	Low risk	High risk
Metin/2018	Low risk	High risk	High risk	High risk	High risk	High risk	High risk	High risk
Yoshinari/2019	Low risk	High risk	High risk	High risk	High risk	High risk	High risk	High risk

Table 4: *Risk of bias assessment of postoperative pain medication studies.*

Discussion

There is a great difference in protocol assessing endodontic pain from that of oral surgery in various aspects. Those who are in need of endodontic treatment may contract various systemic conditions and may also vary in age or the degree of pulpal pathology. These factors lay the way for introducing bias to a study [4,16]. Periapical anatomy is another major factor, which can lead to various inflammatory processes and responses following root canal treatment or retreatment [22,29]. Subsequently, analgesics and other anti-inflammatory drugs used in oral surgery cannot be extrapolated for use in treating the pain of endodontic origin. Therefore, we carried out a thorough search of the literature of all available data about the use of various pain treatment options.

Steroid medication

Steroid therapy has been shown in the literature to be an effective option for managing the pain of endodontic origin. The use of dexamethasone, in endodontics, is not widely considered for clinical management of post-endodontic pain, maybe due to the fear of

secondary infection. Multiple trials in our review have observed a significant effect of pre- and postoperative dexamethasone on reducing post-endodontic pain, however, it was time-limited and dose-dependent [6,14,15,20,22,24,25]. A positive outcome of the short-term use of dexamethasone, is that it has been reported to be virtually with no side effects at all and unlikely to produce any adverse effects, specifically in the absence of any contraindication to such medication [30].

Preoperative administration of a single oral dose of dexamethasone (4 mg) significantly reduced pain at 4 and 12 hours after treatment but not at 24 or 48 hours [6]. Variable dosage of dexamethasone (2 to 8 mg) resulted in significant reduction in pain at 4 and 8 hours [24]. On the other hand, supra-periosteal injection (8 mg/2 mL) resulted in maintained effect till 24 hours [25]. Moreover, administration of 3 tablets of 4 mg dexamethasone, positively maintained the pain-reducing effect till 48 hours after treatment. Noteworthy, Depo Medrol has shown an excellent effect in reducing the pain of endodontic origin in emergency cases (moderate to severe pain). It significantly reduced post-endodontic pain levels at each day after treatment until the 7th day of follow up. Also, only 10% reported moderate to severe pain in the 1st post-treatment day, while none of the patients reported moderate to severe pain in the days after that [13].

Various routes of administration of dexamethasone have been reported in studied trials. Even though the intramuscular administration of dexamethasone seems clinically effective [31] and beneficial in avoiding multiple repetitive postoperative dosages of oral dexamethasone, patient discomfort, and fear, operator experience, and armamentarium are still limiting factors [32]. Therefore, based on the aforementioned observations, we can conclude that oral administration is more preferable than injections and is more readily given and studied.

Non-steroidal anti-inflammatory drugs (NSAIDs)

Most of the trials studying preoperative and postoperative non-steroidal anti-inflammatory drugs (NSAIDs) reported a positive outcome of NSAIDs in effectively managing post-endodontic pain [4,5,16,19,26,27,28]. Only one trial reported that single dose oral ibuprofen was not effective in reducing pain levels following the endodontic treatment [11]. Even though both ibuprofen (600 mg) and rofecoxib (50 mg) has shown effect in 4 and 8 hours, at 12 and 24 hours after treatment, rofecoxib has shown superior outcome related to post-endodontic pain as compared to ibuprofen [4]. On the other hand, ibuprofen (600 mg) was superior at 4 and 8 hours in reducing pain levels as compared to etodolac (400 mg) [16]. Furthermore, ketorolac (20 mg) has shown superior effects at 6 hours of treatment in comparison to prednisolone (30 mg), however, at 12 hours, its effect was minimal to prednisolone [27]. The latent and prolonged effect of prednisolone may be attributed to its greater anti-inflammatory potency compared to NSAIDs [33], as well as its longer biologic half-life (12 - 36 hours) [34]. Noteworthy, aspirin (600 mg) has shown more pronounced effect in reducing pain levels as compared to mefenamic acid (500 mg) within the 1st two hours of treatment, however, mefenamic acid at 4 hours was superior to aspirin resulting in more pain relief [28]. Basically, mefenamic acid requires slightly longer time in order to reach maximum effectiveness for better pain control which was the case in the previous trial and continued to do so in every hour thereafter.

Interestingly, combined therapy of ibuprofen (600 mg) and acetaminophen (1000 mg) has shown superiority over either medication alone [26] and over other combination of drugs such as acetaminophen (1000 mg) plus diclofenac potassium (50 mg) and acetaminophen (1000 mg) plus mefenamic acid (500 mg) [5]. Furthermore, combined therapy of tramadol (100 mg) and flurbiprofen (100 mg) had better pain relief outcome than either medication alone or placebo [19], which provides superior short-term (24 hours) pain relief. This goes in line with the literature, where a combination of NSAIDs was recommended also by the American College of Rheumatology [35], the American Pain Society [36] and the World Health Organization [37].

Low-level laser therapy (LLLT) and cryotherapy

Both pre- and post-operative LLLT has been shown effective in reducing post-endodontic pain ranging from 1 day to 4 days after treatment [7,10,18,23]. That being said, Asnaashari., *et al*. [17] reported that LLLT was effective in reducing pain after endodontic treatment 5 times higher than the control group, however, it was of no statistical significance. Moreover, Yoshinari., *et al.* [12] found no significant reduction in pain levels in patients treated with LLLT over a period of 7 days. This could be explained by the fact that most of their patients were asymptomatic at baseline and therefore, no significant impact could be detected. The pain reducing the effect of LLLT could be attributed to a reduction in inflammatory processes, firing of nociceptors, increase in lymphatic drainage, and an increase in histamine release [18]. The short term effect of LLLT could be attributed to the number of sessions, where most trials investigated only 1 session of LLLT. Even though repeated LLLT sessions would seem impractical, as most patients tend to self-medicate at home after

endodontic treatment, the effect of prolonged laser treatment or higher total energy application should be investigated to observe any change in pain reduction levels or duration of effectiveness of treatment.

Only one trial has been found in the literature examining the effect of cryotherapy in managing post-endodontic pain and it was reported that all cryotherapy groups (intracanal, extracanal, and intraoral) exhibited less postoperative pain, even on the 5th and 7th day after endodontic treatment [21]. That being said, the application of such treatment modality still requires further investigation for the best long-term success of root canal treatment outcomes.

Pain measurement tools

Measurement of pain level, in endodontics, was carried out through variable scales. Among the scales used in our included trials were visual analogue scale (VAS), numeric rating scale (NRS), verbal rating scale (VRS), Heftparker, and other self-designed pain scales. Even though VAS was the most commonly used pain scale in included trials [4,7,10-12,16-21,23,25-27,29], however there was wide variability in pain rating scales used in the literature and no standardized scale was form was used in all trials or reported in the literature. VAS is considered to be more sensitive in comparison to other pain scales due to its ability to discriminate even the smallest of variations in the intensity of pain [38-42]. On the other hand, only a handful of trials used the NRS [5,6,14] because of its practicality and ease to be understood by most individuals [43].

To the best of our knowledge, this is the first systematic review to discuss various pain treatment options of endodontic origin in order to estimate the efficacy of each treatment option, unlike the previous systematic review conducted in 2016 which only addressed oral analgesic medications in the treatment of endodontic pain [9]. However, there were several limitations encountered upon reviewing the current literature. First, the high variability in the designs and methodologies and outcomes in current trials made it difficult to pool these studies in a quantitative synthesis in order to compare various pain medications in a statistical model. Second, there was no standardization of pain measurement scale among included trials and this could have affected the outcomes discussed in our review. Finally, some trials included symptomatic patients or emergent cases while others included patients who were asymptomatic at baseline which obviously affected and confounded the pain outcomes in some treatment options.

Conclusion

Aside from the limitations of our review, NSAIDs are better considered as the first line of treatment of post-endodontic pain either pre or postoperative (individually or in combination) followed by the combination of NSAIDs and other pain medications. Moreover, Dexamethasone can be considered for the short-term treatment of post-endodontic pain with minimal adverse effects. In the same context, LLLT can be considered postoperatively for patients with severe endodontic pain. Treatment of pain of endodontic origin still warrants further investigation.

Funding

None.

Conflict of Interest

The authors declare no conflict of interest.

Bibliography

1. Duncan RP., *et al*. "The Dynamics of Toothache Pain and Dental Services Utilization: 24-Month Incidence". *Journal of Public Health Dentistry* 63.4 (2003): 227-234.
2. Holt R., *et al*. "ABC of oral health. Dental damage, sequelae, and prevention". *BMJ (Clinical Research Edition)* 320.7251 (2000): 1717-1719.
3. Dray A. "Inflammatory mediators of pain". *British Journal of Anaesthesia* 75.2 (1995): 125-131.
4. Gopikrishna V and Parameswaran A. "Effectiveness of Prophylactic Use of Rofecoxib in Comparison with Ibuprofen on Postendodontic Pain". *Journal of Endodontics* 29.1 (2003): 62-64.

5. Elzaki WM., *et al*. "Double-blind Randomized Placebo-controlled Clinical Trial of Efficiency of Nonsteroidal Anti-inflammatory Drugs in the Control of Post-endodontic Pain". *Journal of Endodontics* 42.6 (2016): 835-842.

6. Pochapski MT., *et al*. "Effect of pretreatment dexamethasone on postendodontic pain". *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontology* 108.5 (2009): 790-795.

7. Metin R., *et al*. "Effects of low-level laser therapy on soft and hard tissue healing after endodontic surgery". *Lasers in Medical Science* 33.8 (2018): 1699-1706.

8. Moher D., *et al*. "Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement". *Annals of Internal Medicine* 151.4 (2009): 264-269.

9. Aminoshariae A., *et al*. "Evidence-based recommendations for analgesic efficacy to treat pain of endodontic origin: A systematic review of randomized controlled trials". *Journal of the American Dental Association (1939)* 147.10 (2016): 826-839.

10. Arslan H., *et al*. "Effect of Low-level Laser Therapy on Postoperative Pain after Root Canal Retreatment: A Preliminary Placebo-controlled, Triple-blind, Randomized Clinical Trial". *Journal of Endodontics* 43.11 (2017): 1765-1769.

11. Attar S., *et al*. "Evaluation of pretreatment analgesia and endodontic treatment for postoperative endodontic pain". *Journal of Endodontics* 34.6 (2008): 652-655.

12. Yoshinari Franciely PK., *et al*. "Influence of Photodynamic Therapy in the Control of Postoperative Pain in Endodontic Treatment: A Cross-Sectional Randomized Clinical Trial". *Pesquisa Brasileira em Odontopediatria e Clínica Integrada* 19.1 (2019).

13. Gallatin E., *et al*. "Pain reduction in untreated irreversible pulpitis using an intraosseous injection of Depo-Medrol". *Journal of Endodontics* 26.11 (2000): 633-638.

14. Jorge-Araujo ACA., *et al*. "Effect of Premedication with Anti-inflammatory Drugs on Post-Endodontic Pain: A Randomized Clinical Trial". *Brazilian Dental Journal* 29.3 (2018): 254-260.

15. Lin S., *et al*. "Etodolac versus dexamethasone effect in reduction of postoperative symptoms following surgical endodontic treatment: a double-blind study". *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontics* 101.6 (2006): 814-817.

16. Menke ER., *et al*. "The effectiveness of prophylactic etodolac on postendodontic pain". *Journal of Endodontics* 26.12 (2000): 712-715.

17. Asnaashari M., *et al*. "Management of Post Endodontic Retreatment Pain With Low Level Laser Therapy". *Journal of Lasers in Medical Sciences* 8.3 (2017): 128-131.

18. Doganay Yildiz E and Arslan H. "Effect of Low-level Laser Therapy on Postoperative Pain in Molars with Symptomatic Apical Periodontitis: A Randomized Placebo-controlled Clinical Trial". *Journal of Endodontics* 44.11 (2018): 1610-1615.

19. Doroschak AM., *et al*. "Evaluation of the combination of flurbiprofen and tramadol for management of endodontic pain". *Journal of Endodontics* 25.10 (1999): 660-663.

20. Glassman G., *et al*. "A prospective randomized double-blind trial on efficacy of dexamethasone for endodontic interappointment pain in teeth with asymptomatic inflamed pulps". *Oral Surgery, Oral Medicine, and Oral Pathology* 67.1 (1989): 96-100.

21. Gundogdu EC and Arslan H. "Effects of Various Cryotherapy Applications on Postoperative Pain in Molar Teeth with Symptomatic Apical Periodontitis: A Preliminary Randomized Prospective Clinical Trial". *Journal of Endodontics* 44.3 (2018): 349-354.

22. Krasner P and Jackson E. "Management of posttreatment endodontic pain with oral dexamethasone: a double-blind study". *Oral Surgery, Oral Medicine, and Oral Pathology* 62.2 (1986): 187-190.

23. Kreisler MB., *et al*. "Efficacy of low level laser therapy in reducing postoperative pain after endodontic surgery-- a randomized double blind clinical study". *International Journal of Oral and Maxillofacial Surgery* 33.1 (2004): 38-41.

24. Liesinger A., *et al*. "Effect of variable doses of dexamethasone on posttreatment endodontic pain". *Journal of Endodontics* 19.1 (1993): 35-39.

25. Mehrvarzfar P., *et al*. "Effect of supraperiosteal injection of dexamethasone on postoperative pain". *Australian Endodontic Journal* 34.1 (2008): 25-29.

26. Menhinick KA., *et al*. "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". *International Endodontic Journal* 37.8 (2004): 531-541.

27. Praveen R., *et al*. "Comparative Evaluation of Premedication with Ketorolac and Prednisolone on Postendodontic Pain: A Double-blind Randomized Controlled Trial". *Journal of Endodontics* 43.5 (2017): 667-673.

28. Rowe NH., *et al*. "Control of pain resulting from endodontic therapy: a double-blind, placebo-controlled study". *Oral Surgery, Oral Medicine, and Oral Pathology* 50.3 (1980): 257-263.

29. Torabinejad M., *et al*. "Effectiveness of various medications on postoperative pain following complete instrumentation". *Journal of Endodontics* 20.7 (1994): 345-354.

30. Maddox DL., *et al*. "Incidence of posttreatment endodontic pain related to medicaments and other factors". *Journal of Endodontics* 3.12 (1977): 447-457.

31. Marshall JG and Walton RE. "The effect of intramuscular injection of steroid on posttreatment endodontic pain". *Journal of Endodontics* 10.12 (1984): 584-588.

32. Patten JR., *et al*. "Adjunct use of dexamethasone in postoperative dental pain control". *Compendium (Newtown, Pa)* 13.7 (1992): 580-584.

33. Marshall JG. "Consideration of steroids for endodontic pain". *Endodontic Topics* 3 (2002): 41-51.

34. Goodman LS. "Goodman and Gilman's the pharmacological basis of therapeutics". McGraw-Hill New York (1996).

35. Altman R., *et al*. "Recommendations for the medical management of osteoarthritis of the hip and knee: 2000 update". *Arthritis and Rheumatology* 43.9 (2000): 1905-1915.

36. Gordon DB., *et al*. "American pain society recommendations for improving the quality of acute and cancer pain management: American Pain Society Quality of Care Task Force". *Archives of Internal Medicine* 165.14 (2005): 1574-1580.

37. Schug SA., *et al*. "Cancer pain management according to WHO analgesic guidelines". *Journal of Pain and Symptom Management* 5.1 (1990): 27-32.

38. dos Santos Calderon P., *et al*. "Concordance among different pain scales in patients with dental pain". *Journal of Orofacial Pain* 26.2 (2012): 126-131.

39. Jamison RN., *et al*. "Comparative study of electronic vs. paper VAS ratings: a randomized, crossover trial using healthy volunteers". *Pain* 99.1-2 (2002): 341-347.

40. Jensen MP., *et al*. "What is the maximum number of levels needed in pain intensity measurement?" *Pain* 58.3 (1994): 387-392.

41. Lara-Munoz C., *et al*. "Comparison of three rating scales for measuring subjective phenomena in clinical research. I. Use of experimentally controlled auditory stimuli". *Archives of Medical Research* 35.1 (2004): 434-438.

42. Ohnhaus EE and Adler R. "Methodological problems in the measurement of pain: a comparison between the verbal rating scale and the visual analogue scale". *Pain* 1.4 (1975): 379-384.

43. Breivik H., *et al*. "Assessment of pain". *BJA: British Journal of Anaesthesia* 101.1 (2008): 17-24.

Volume 18 Issue 7 July 2019