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Reviews

ANALGESIC EFFECT OF PRE-EMPTIVE ORAL NSAIDS ON POST-ENDODONTIC PAIN LEVELS IN SINGLE VISIT ENDODONTICS -A SYSTEMATIC REVIEW

ABSTRACT

Pre-emptive analgesia is an anti-nociceptive treatment that reduces postoperative pain by preventing altered afferent input. As most of the patients present with pain preoperatively have higher levels of released local inflammatory mediators. Thus, pretreatment analgesia decreases the establishment of central sensitization, a mechanism by which spinal neurons increase their response to the peripheral nociceptive impulse. This systematic review aims to compare and evaluate the postoperative pain levels and analgesic intake on NSAIDs' preoperative oral administration in single visit root canal treatment. According to PRISMA guidelines, the present review was done and was registered in the PROSPERO (Centre for Reviews and Dissemination University of York.). Registration number-CRD42020195775. The research question was formulated based on the PICO strategy. A comprehensive electronic literature search was conducted across PubMed/Medline, Scopus and Cochrane Database independently by two reviewers. Articles published from January 1990 to May 2019 that focused on pre-emptive strategies in single visit root canal treatment were included in the present review. Based on specified inclusion and exclusion criteria's, the selected articles were subjected to quality assessment, and the risk of bias was evaluated. A total of 6 articles were included, out of which three were hand searched. The overall risk of bias of included studies was moderate, and the study limitations were high. Among the studies included, Ibuprofen was considered as the best drug of choice in single visit endodontics.

Keywords: Diagnosis, Permanent Tooth, Root Canal.

Kavalipurapu Venkata Teja[1]
*Sindhu Ramesh[1]
Kaligotla Apoorva Vasundhara[2]

ORCID IDs of the authors:
K.V.T. 0000-0003-0123-8873
S.R. 0000-0003-2617-6592
K.A.V. 0000-0003-0088-0098

[1] Department of Conservative Dentistry& Endodontics, Saveetha Dental College& Hospitals, Saveetha Institute of Medical& Technical Sciences, Chennai, TamilNadu, India.
[2] Department Prosthodontist & Implantologist, AndhraPradesh, India.

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***Corresponding Author:**
Department of Conservative Dentistry& Endodontics, Saveetha Dental College& Hospitals, Saveetha Institute of Medical&Technical Sciences, Chennai, TamilNadu, India
Phone: +919840136353 **E-mail:** drsinsushil@gmail.com

INTRODUCTION

The pain is the primary reason for which most of the patients seek endodontic treatment frequently.[1] Endodontic procedures help to restore a tooth affected irreversibly by bacterial invasion and infection.[2] The therapy aims at complete debridement of the inflamed and necrotic pulp tissue from the root canal space and sealing it from the external environment.[2,3] There is a significant relief in pain, preceding an appropriate and flawless endodontic procedure.[1,4,5,6] However, the pain relief may not be immediate and absolute.[1] Although it is diminished to some extent, immediately following the root canal treatment in most patients, 30% of them still experience moderate to severe postoperative pain due to the residual effects of inflammation.[4] So, an endodontic procedure should consider both primary concerns of the patient and long-term complications such as postoperative pain. Postoperative pain is usually at its worst in the first 24 hours after an endodontic procedure. Gradually the levels decrease in the subsequent 3 to 7 days.[4]

Mechanical, thermal, chemical and immunological stimulation of afferent nociceptors, which synapse in the dorsal horn of spinal cord lead to direct sensation of thalamus and presents as pulpal and periapical pain.[5] Nocicieptors are stimulated by the endogenous inflammatory mediators such as bradykinin, calcitonin-gene related peptide, substance p, growth factors, cytokines, chemokines and arachidonic acid.[6] These substances are generated as part of the innate immune response following a tissue injury or destruction. The arachidonic acid metabolite is converted to prostaglandin by enzymes such as cyclooxygenase enzyme 1 and 2 (COX-1, COX-2). The converted prostaglandins in turn cause the sensitization of afferent nociceptors leading to the decreased pain threshold.[6] Therefore, pharmacologic interventions mainly aim to target cyclooxygenases, limiting prostaglandin production and limiting nerve fibres' sensitization.[7]

Perception of pain is a highly subjective and variable experience. It is not only influenced by the performed treatment procedure, but multiple physical and psychological factors also play a role in perceiving pain.[8] Conventional dental procedures are associated with pain postoperatively, but the incidence and severity are highest with root canal therapy.[9] The post endodontic pain is mainly due to the extrusion of canal contents, debris and microbes from root canal space to the periapical area. These conditions lead to an intense inflammatory response and infection.[10] Various non-narcotic analgesics like Non-Steroidal Anti-inflammatory Drugs NSAID'S are used in treating endodontic pain. The mechanism of action is mainly by inhibiting prostaglandin synthesis at the sites of inflammation.[11] Several clinical studies have evaluated NSAID'S use to treat postoperative pain in endodontics with conflicting results. Some studies state conclude the beneficial effect in administering non-narcotic analgesics, whereas others claim no efficient results.[12,13] Various other drugs that are used along with NSAID'S include opioids and combination of medications for treating endodontic pain.[14]

Previous studies showed conflicting results when the drugs were prescribed preoperatively and postoperatively to reduce the endodontic pain.[13,15] Pre-emptive analgesia is an anti-nociceptive treatment that reduces postoperative pain by preventing altered afferent input processing.[16] As most of the patients present with pain preoperatively have higher levels of released local inflammatory mediators. Thus, pretreatment analgesia decreases the establishment of central sensitization, a mechanism by which spinal neurons increase their response to the peripheral nociceptive impulse.[13]

METHODS

The present review aims at evaluating the postoperative pain levels and analgesic intake on preoperative oral administration of Non-Steroidal Anti-inflammatory Drugs in single visit root canal treatment.

Objectives:

The systematic review mainly concentrated on the pretreatment analgesia on post endodontic pain levels in patients undergoing single visit root canal treatment. The present review gives a comprehensive idea on analgesics used and the

regimen preferred in single visit root canal treatment.

PICO Question:
Is there any variation in the postoperative pain levels and postoperative analgesic intake on preoperative administration of NSAIDs in single visit root canal treatment?

PICO analysis:
Population: Teeth undergoing single visit root canal treatment.

Intervention: Oral preoperative administration of NSAIDs.

Comparison: Experimental group compared to placebo, a different NSAID, an extra dose of the experimental NSAID.

Outcome:
Primary outcome: Postoperative pain levels.

Secondary outcome: Postoperative analgesic intake.

Protocol for registration:
According to PRISMA guidelines, the present review was done and was registered in the PROSPERO (Centre for Reviews and Dissemination University of York; http://www.crd.york.ac.uk/PROSPERO). Registration number - CRD42020195775.

Source
To identify studies included or considered for this review, detailed search strategies were developed for the database searched. The MEDLINE search used the combination of controlled vocabulary and free text terms.

Searched Data Bases
- PubMed (January 1990 to May 2019)
- PubMed Advanced Search
- MEDLINE
- Cochrane Database of Systematic Reviews

Full-text articles in English were only applied during the electronic search to include all the possible clinical trials in the systematic review's potentially relevant article search phase. No time restriction was applied. Reference list of the reviews and identified randomized controlled trials were also checked for possible additional studies.

Hand Searching:
The following journals were hand-searched:

- Journal of Endodontics
- International Endodontic Journal
- Journal of Conservative Dentistry
- Indian Journal of Dental Research
- Journal of International and Oral Health
- Journal of Dental School
- Caspian Journal of Dental Research

Language

Full-text articles in English were only selected.

Inclusion Criteria

Criteria for considering studies for this review

Types of studies

- Randomized controlled trials
- Clinical trials
- Prospective Invivo studies

Types of Participants

- Patients under the age group of 18 years to 65 years undergoing single visit root canal treatment.

Types of Interventions

- Patients prescribed preoperatively with oral NSAIDs before a single visit root canal treatment.

Types of Comparisons
- Compared to placebo, the experimental group, a different NSAID, or a different experimental NSAID dose.

Types of Outcome Measures
1. Primary Outcome: Postoperative pain levels
2. Secondary Outcome: Postoperative analgesic intake

Exclusion Criteria
The following studies were excluded

1. Case reports/Case series
2. Invitro Studies

3. Animal studies
4. Review articles
5. Absence of baseline pain
6. Invivo studies comparing NSAIDs in multiple visit root canal treatment
7. Invivo studies comparing corticosteroids and opioids in single visit root canal treatment
8. Studies not mentioned in the inclusion criteria

Search

A search was carried out in an electronic database (i.e.,) PubMed Central, Cochrane, Lilac, Science Direct, Google Scholar) using the following search terms alone employing PUBMED search builder from January 1990 up to May 2018. Various "search terms" or "keywords" were used to execute the PubMed search. The searched terms were: "Teeth", "permanent teeth", "Pain", "Endodontic pain", "Pre-emptive", "Preoperative", "Analgesics", "NSAIDS", "Analgesic intake", "Post endodontic pain", "Single visit root canal treatment".

Description of Studies

Duplicates were excluded, and 392 articles were identified. Out of those 373 articles were excluded looking title and abstract. The remaining 19 articles were assessed fully by two independent examiners according to the inclusion criteria. Out of which 16 articles were excluded with reason (Table 1).

Table 1. Table Depicting the List of studies excluded based on the criteria

S.No	Author	Year	Reason for Exclusion
1.	Menhinick *et al.*[17]	2004	Discussed on pain intensity of the patient following Pulpectomy on using ibuprofen or a combination of ibuprofen
2.	Rogers *et al.*[19]	1999	The study discussed on efficacy of dexamethasone and ketorolac tromethamine when used as an intracanal medication, with oral ibuprofen and placebo on post-treatment endodontic pain
3.	Mehrvarzfar *et al.*[15]	2011	The study compared the efficacy of tramadol, novafen and in pain reduction after root canal preparation
4.	Modaresi *et al.*[19]	2006	The study compared the efficacy of ibuprofen, acetaminophen-codeine and placebo premedication therapy on the depth of anesthesia during the treatment of inflamed teeth
5.	D.R. Mehlish *et al.*[20]	2010	The study compared the analgesic efficacy of concurrent ibuprofen and paracetamol with ibuprofen and paracetamol alone in the management of moderate to severe acute postoperative pain after removal of impacted teeth
6.	Wells *et al.*[21]	2011	The study compared the efficacy of ibuprofen and ibuprofen combined with acetaminophen on post-treatment pain after emergency debridement of teeth in symptomatic patients with a pulpal diagnosis of necrosis
7.	Elazaki *et al.*[22]	2016	The study the compared efficacy of non-steroidal anti-inflammatory drugs in controlling post-endodontic pain after root canal preparation
8.	Metri M *et al.*[23]	2016	The study results were reported as a change in the intensity of the pain rather than absolute pain on pretreatment with diclofenac sodium on post endodontic pain in single visit root canal treatment
9.	S. Jenarthanan *et al.*[24]	2018	The study compared the efficacy of diclofenac sodium administered using different delivery routes in the management of endodontic pain
10.	Taggar *et al.*[25]	2017	The study compared two ibuprofen formulations in the reduction of spontaneous pain and mechanical allodynia measured using a bite force transducer
11.	Nabi *et al.*[26]	2018	The study compared the analgesic effect of preoperative ibuprofen in controlling the post endodontic pain with or without low-level laser therapy in single visit root canal treatment
12.	Joshi *et al.*[27]	2016	The study compared the efficacy of oral and intraligamentary Piroxicam for the management of post endodontic pain after a single visit root canal treatment
13.	Ramazani *et al.*[28]	2013	The study compared the prophylactic effects of oral zintoma and ibuprofen on post endodontic pain after a single visit root canal treatment
14.	Praveen *et al.*[29]	2017	The study evaluated the premedication of ketorolac and prednisolone on post endodontic pain in single visit root canal treatment
15	Torabinajed *et al.*[12]	1994	The study evaluated the effectiveness of various medications on post endodontic pain after instrumentation
16.	Sethi *et al.*[30]	2014	The study compared the effect of single-dose pretreatment analgesia with different analgesics on postoperative endodontic pain after root canal preparation

Finally, six studies obtained from hand and electronic search matching the inclusion criteria were assessed for systematic review (Figure 1), (Figure 2).

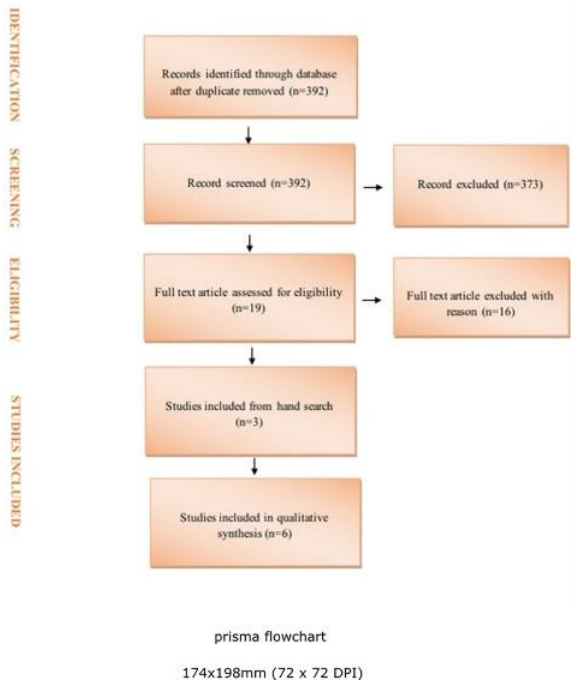

Figure 1. PRISMA Flow Chart Depicting the Search Stratergy

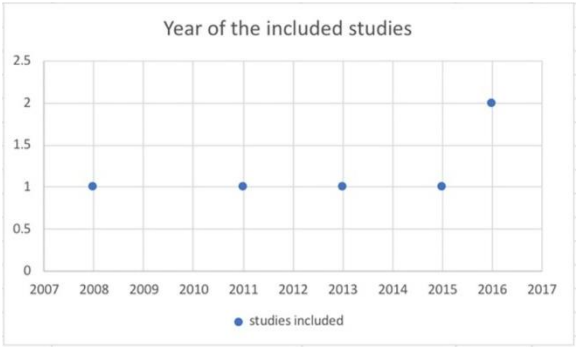

Figure 2. Graph Depicting the Year of the Included Studies

Two independent reviewers did the above analysis, and in case of disagreement, a consensus was reached after discussion with a third reviewer.

The checklist's methodology was followed based on the Quality Assessment of Diagnostic Accuracy Studies Tool (QUADAS). Only clinical trials were included for this systematic review.

Data extraction and statistical analysis:

The extracted included the type of treatment, protocol followed, drugs and controls used in each study, the time drugs administered, the time points at which the pain was measured, and the outcome variables used to measure pain, and postoperative analgesic intake. Information on the pre and postoperative pain at measured time points were gathered from each of the treatment arms of the included articles were derived, and the graphs were plotted. The included six eligible studies used various pain assessment scales, including Heft-Parker visual analogue scale, modified visual analogue scale (VAS) and categorical pain scales. All data was converted to standardize 170mm Heft-Parker VAS scoring for interpreting the results. A meta-analysis can yield a more precise overall estimate of the treatment effect. However, it was not possible in the present study due to the heterogeneity among the included studies such as differences in the sample sizes and follow up periods. Hence, only a descriptive evaluation of data has been performed.

RESULTS

Summary of included studies

The electronic and manual search identified 392 studies after de-duplication. Three other records were identified through hand searching and were included in the present study. Three hundred ninety-two records were screened out of which 373 studies were excluded, and 19 full-text articles were assessed for eligibility. Sixteen studies were excluded with reason. Finally, after assessing full texts, six articles from manual and electronic search on postoperative endodontic pain management with NSAIDs in single visit endodontics were identified and included in the study.[13,31-35] The drugs that were studied included ibuprofen 200mg tablet, tenoxicam 20mg table, ketorolac 10mg tablet, celecoxib 400mg capsule, gelofen 400mg capsule (ibuprofen 400mg capsule), novafen 200mg capsule (ibuprofen 200mg capsule), tenoxicam 20mg capsule, ibuprofen liquigel capsule, ibuprofen 600mg tablet, ibuprofen 600mg liquigel capsule, ibuprofen 400mg tablet and indomethacin 25mg tablet. All the included studies provided baseline demographic data. Ethnicity was not reported in any of the included studies.[13,31-35] The mean baseline pain for the selected studies was 73.217 on a 170mm Heft parker VAS, ranging from 52 to 150. The study by Mokhtari *et al.*[35] Categorized the treated tooth and arch type and reported the tooth's specific diagnosis. Bali *et al.*[31] specified the diagnosis, but the treated tooth and arch type was not specified. Ashraf *et al.*, specified the arch and the tooth type, but the diagnosis was unclear. The time of evaluating the postoperative pain levels was different, and the disparity was observed in all

the included studies.[13.31-35] Characteristics of included studies are found in (Table 2).

Table 2. Table Depicting the Data and Characteristics of the Included Studies

Author and year	**Treatment Groups (n)**	**Time of Delivery**	**Time of Pain Evaluation**	**Outcome Variable**	**Inclusion Criteria**	**Anesthetic agent used, Irrigation Protocol, the file system used, Sealer Used and Obturation Technique Followed**	**Drugs Prescribed Postoperatively**	**Postoperative pain Scores and Analgesic intake**
Bali et al 2016.[31]	Group 1: 200mg of ibuprofen (30) Group 2: 20mg of tenoxicam (30) Group 3: 10mg of ketorolac (30)	Single dose orally half an hour before the procedure	Baseline,0,6, 12,24	Postoperative pain: 10point visual analogue scale	Permanent teeth diagnosed with symptomatic irreversible pulpitis	2ml of xylocaine 2% adrenaline 1:200,000, 5.25% NaOCl and EDTA gel (volume and time of irrigant used was not specified), instrumentation (not specified), Calcium hydroxide based sealer(seal apex), lateral condensation technique	Not mentioned	Pain scores: Group 1: Baseline: 5.32; 0hrs: .72; 6hrs: .85; 12hrs: 0.87; 18 hrs: 0.73; 24hrs: 0.66 Group 2: Baseline: 5.20; 0hrs: .78; 6hrs: .68; 12hrs: 0.56; 18hrs: 0.66; 24hrs: 0.44 Group 3: Baseline : 6.02; 0hrs: .75; 6hrs: .69; 12hrs: 0.55; 18hrs: 0.40; 24hrs: 0.42 Analgesic intake: Not specified.
Ashraf et al 2013.[32]	Group 1: 400mg of Celecoxib capsules (15) Group 2: Placebo capsules (15)	Group 1 received single dose orally half an hour before the procedure. Group 2 received two placebo capsules half an hour before the procedure.	Baseline,4,8, 12,24	Postoperative pain: 170mm Heft-Parker VAS	Patients complaining of pain in mandibular first and second molars	2% lidocaine with1/80,000 epinephrine, 2.5% NaOCl(volume and time of irrigant used is not specified), instrumentation (not specified), resin based sealer (AH26 sealer, Dentsply, Konstanz, Germany), lateral condensation technique	Three 325mg acetaminophen tablets prescribed to be taken if required.	Pain scores: Group 1: Baseline: 148.9; 4hrs: 55.2; 8hrs: 55.2; 12hrs: 70.0; 24hrs: 31.4; 48hrs: 15.7 Group 2: Baseline: 150.0; 4hrs: 92.8; 8hrs: 92.8; 12hrs: 100.7; 24hrs: 48.5; 48hrs: 21.07 Analgesic intake: Not specified.
Dejkam et al 2015.[33]	Group 1: 400mg of Gelofen capsule (20) Group 2: 200mg of Novafen capsule (20) Group 3: 500mg of flour and starch placebo capsules (20)	Each participant received two capsules 60 minutes before the treatment.	Baseline,4,8, 12,24,48 hours postoperatively	Postoperative pain: 10point Visual Analogue Scale	Permanent teeth with pulpal diagnosis not specified	2%Lidocaine with 1/80,000 epinephrine, irrigation protocol and instrumentation not specified, resin based sealer(AH26 sealer), lateral condensation technique.	Acetaminophen codeine as and when required.	Pain scores: Group 1: Baseline: 5.55; 4hrs: 2.7; 8hrs: 1.75; 12hrs: 2.55; 24 hrs: 1.75; 48hrs: 1.0 Group 2: Baseline: 5.95; 4hrs: 3.25; 8hrs: 2.45; 12hrs: 2.8; 24hrs: 1.65; 48hrs: 0.7 Group 3: Baseline: 5.15; 4hrs: 2.35; 8hrs: 2.5; 12hrs: 3.4; 24hrs: 1.8; 48hrs: 1.0 Analgesic intake: Placebo: 7 patients: 3 tablets 3 patients: 2 tablets Celecoxib group: 3 patients: 3 tablets 2 patients: 2 tablets 1 patient: 1 tablet
Arslan et al 2011[34]	Group 1: 20mg of tenoxicam capsule (16) Group 2: 200mg of liquigel ibuprofen capsule (16) Group 3: Sugar placebo (16)	The Single-dose prescribed orally before root canal treatment	Baseline,6,12,24,48,72 hours postoperatively	Postoperative pain: 100mm Visual Analogue Scale	Pain originating from a tooth >=50mm of VAS included pulpal and periapical diagnosis not specified	4% Articaine HCl with 1:100,000 epinephrine(ultracaine D-S forte), 5.25% NaOCl, EDTA gel (volume and time of irrigant used was not specified), final irrigation with 1ml of 15% liquid EDTA for 1 minute, followed by 3ml of 5.25% NaOCl, instrumentation (not specified), calcium hydroxide based sealer(seal apex), lateral compaction technique.	Instructed to take extra dosage of test medication(dosage not specified)	Pain scores: Group 1: Baseline: 82.6; 6hrs: 7.92; 12hrs: 9.62; 24hrs: 4.09; 48hrs: 4.80; 72hrs: 1.8 Group 2: Baseline: 83.2; 6hrs: 2.83; 12hrs: 15.3; 24hrs: 3.49; 48hrs: 2.34; 72hrs: 0.0 Group 3: Baseline: 83.2; 6hrs: 35.1; 12hrs: 19.8; 24hrs: 16.4; 48hrs: 13.6; 72hrs: 8.86 Analgesic intake: Not specified.

Attar et al 2008[13]	Placebo (12) 600mg Ibuprofen tablets (14) 600mg Ibuprofen liquigel (13)	Single dose orally before the treatment	Baseline, during treatment, 6,12,18,24 hours postoperatively	100mm VAS, 170mm HP-Categorial VAS, Categorial	Pain >=30 on VAS included pulpal and periapical diagnosis not specified.	Long acting anesthetic was administred (agent not specified), 3% or 6% NaOCl (volume and time of irrigant used was not specified), Flexofiles (Dentsply, Mallifier, Tulsa), Size 2 to 4 gates gidden burs (Dentsply, Mallifier), GT nickel-titanium rotary files (Dentsply, Mallifier), Roth's 801 or ZOE or AH Plus resin seler was used. Obturation by down packing with system-B (SybronEndo Corp, Orange, CA) and backfilling using obtura (Obtura Spartan, Fenton, MO)	Tylenol ES (500mg) was prescribed as escape medication	Pain scores: Group 1: Baseline: 65.6; 6hrs: 17.9; 12hrs: 20.4; 24hrs: 11.9 Group 2: Baseline: 64.7; 6hrs: 26.2; 12hrs: 24; 24hrs: 23.5 Group 3: Baseline: 65.9; 6hrs: 28.1; 12hrs: 31.8; 24hrs: 21.6 Analgesic intake: Not specified.
Mokhtari et al 2016[35]	Group A: 400mg of ibuprofen tablet (22) Group B: 25mg of indomethacin tablet (22) Group C: Placebo (22)	Single-dose orally one hour before the procedure	Baseline, during treatment ,8,12 and 24 hours postoperatively	Postoperative pain: 100mm VAS	First and second mandibular molars with irreversible pulpitis	1.8ml of 2% lidocaine with 1:80000 epinephrine, 2.5% NaOCl and saline (volume and the time of irrigant used was not specified), instrumentation (not specified), AH-26 sealer (Dentsply,Tulsa), lateral condensation technique.	Postoperative medication not specified	Pain scores: Group 1: Baseline: 54.6; 8hrs: 4.2; 12hrs: 17.2; 24hrs: 8.4 Group 2: Baseline: 57.4; 8hrs: 8.6; 12hrs: 17.6; 24hrs: 14.4 Group 3: Baseline: 57.4; 8hrs: 24.2; 12hrs: 18.6; 24hrs: 9.2 Analgesic intake: patients were asked to record the analgesic intake, but the number of drugs taken were not specified.

Qualitative review

Significant differences between the studies selected included the treatment drugs, the dose of the medication, sample size and population type, time of the outcome variable measurement. The quality of evidence was average as most of the studies included had a moderate risk of bias as measured using a quality assessment tool. Sequence generation was specified only in the study reported by Arslan *et al.*[32] Allocation concealment was set in Ashraf *et al.*[32], and Mokthari *et al.*[35], study. The information about the blinding of patients and the care provider and assessor, the information about the other sources of bias were clearly specified by Ashraf *et al.*, Arslan *et al.*, and Mokhtari *et al.* studies.[32,34,35] The quality assessment and risk of bias is found in (Table 3).

Table 3. Table Depicting the Quality Analysis and Risk of Bias Assessment of Included Studies using Cochrane Quality Assessment Tool

Author, year	**Sequence generation adequate?**	**Allocation adequately concealed?**	**Blinding of participants?**	**Blinding of care providers?**	**Blinding of outcome assessors?**	**Incomplete outcome data adequately addressed? Was the overall attrition sufficiently low/differential attrition sufficiently low?**	**Was the study free of selective outcome reporting?**	**Were there other sources of bias? Were there important baseline differences in prognostic factors?**	**Risk of bias**
	Acceptable methods must be truly random; randomized table, computer-generated random numbers, etc. patients should be accepted sequentially.	**The group selection must be hidden from patients, personel and assesors until treatment is rendered; otherwise randomization may be tampered with bias increased.**				**How many people dropped out of the study? <20% is good, <15% is better for smaller studies. This avoids the risk of bias in the population sample.**	**Did they not report the data you know they observed? This is not especially relevant to these papers.**	**Were the groups similar at baseline? For any of the baseline groups, a difference of <10% is acceptable**	
Bali, 2016.[31]	Unclear-methods of randomisation not described	Unclear	Unclear	Yes	Unclear	Unclear	Yes	Yes	High

Ashraf, 2013.[32]	Unclear-methods of randomisation not described	Yes-sequentially numbered containers	Yes	Yes	No	Yes/Yes- 6.6% patients lost	Yes	Yes	Moderate
Dejkam, 2015.[33]	Unclear-methods of randomisation not described	Unclear	Yes	Yes	No	Unclear	Yes	Yes	Moderate
Arslan, 2011.[34]	Yes- block randomisation	Unclear	Yes	Yes	Yes	Yes/Yes	Yes	Yes	Moderate
Attar, 2008.[13]	Unclear-methods of randomisation not described	Unclear	Unclear	Unclear	Unclear	Yes/No-13% patients lost to follow up	Yes	Yes-differences in gender and diagnosis distribution	High
Mokhtari, 2016.[35]	Unclear-methods of randomisation not described	Yes- table of random numbers	Yes	Yes	No	Unclear	Yes	Yes	Moderate

The data obtained was reorganized into bar graphs (Graph 1), which illustrates the VAS scores at 4, 6, 8, 12, 24, 48 and 72 hours. At 4 hours, only two studies compared the pain reduction out of which gelofen 400mg capsule (Ibuprofen 400mg capsule) proved better than celecoxib 400mg capsule and Ibuprofen 200mg capsule.[32,33] At 6 hours' time interval, three studies analyzed the outcome of all the drugs compared. Ibuprofen 200mg liquigel capsule seemed to have the highest VAS score reduction, followed by tenoxicam 20mg tablet and ketorolac 10mg tablets.[31,35] Three studies compared postoperative pain reduction at 8 hours' time interval. Ibuprofen 400mg tablet had least VAS scores followed by indomethacin 25mg tablet compared with celecoxib 500mg and 200mg and 400mg novafen and gelofen capsules.[32.33,35]

All the six studies[13,31-35], compared the postoperative pain scores at 12 and 24 hours' time interval, there were varied reduction scores obtained. However, Bali *et al.*[32] seemed to have least VAS scores among the drugs compared; ketorolac 10mg tablet had least scores followed by tenoxicam 20mg tablet and Ibuprofen 200mg tablet. At 24 hours' time interval, VAS score reduction was evident in Arslan *et al.*, study. Ibuprofen 200mg liquigel capsule had least VAS scores of 3.49, followed by tenoxicam 20mg capsule and ketorolac 10mg tablet.[33]

Three studies[32,33,34], compared the outcome at 48 hours out of which, the VAS point reduction at 48 and 72 hours was observed in Arslan *et al.*[33], study, where the least VAS scores were reported with Ibuprofen 200mg liquigel capsule both at 24 and 72 hours, as compared to Indomethacin 25mg and placebo. At 48hour interval, the VAS point reduction with Ibuprofen liquigel capsule was 2.[36] Whereas at 72 hours it was reported to be nil or 0. General observations of the included studies showed a gradual trend of increased pain scores from 8 to 12 hours in all the groups, representing the peak pain levels experienced by the patient postoperatively. The pain scores tapered gradually at 48hour interval, and the reported pain levels were almost nil at 72hour intervals. Thereby it can be justified that the pain after a single visit root canal treatment may last for 24 to 72hour intervals after which the pain experienced by the patient is almost nil.

The study by Attar *et al.* had varied results in which placebo proved beneficial compared to the other tested drugs at all-time intervals. The study was determined to be dissimilar compared to the other included studies. The reason could be the smaller sample size, different timing of the treatment dose, and the placebo group's behaviour. The study was categorized into two sessions where partial treatments were temporized and completed treatments were obturated in single visit. Because the treatments were not stated to be identical, the placebo group may have perceived their treatment to be more effective, and the patients may be more suggestible to placebo.[13]

However, these comparisons' major disadvantage is the difference in the study designs and a significant difference in the baseline VAS scores. The study by Ashraf *et al.* reported that the baseline VAS score was 148.9 for celecoxib group, which was reduced to 15.7 at 48 hours. The mean

VAS score reduction for celecoxib was 133.3.[32] Whereas, the Ibuprofen 200mg liquigel capsule, which has the least VAS score of 2.34 at 48 hours, showed a mean VAS reduction of only 80.86.[34] Hence, the baseline pain scores should also be taken into consideration before concluding. Future trails have to concentrate more on other groups of NSAIDs. COX-2 and NSAID therapy combination have to be explored more in patients with moderate to severe baseline VAS scores.

As far as the analgesic intake is concerned, (Table 4) study by Ashraf *et al.*, has specified the amount of postoperative analgesic consumption where the amount of analgesic intake in the placebo group was higher celecoxib group.[32]

Table 4. Table Depicting the Data of Analgesic Intake, Rescue Medication and Incidence of adverse events

Author, year	Treatment groups (n)	Rescue medication	# Patients withdrawn	Adverse events
Bali, 2016.[31]	Ibuprofen 200mg (30) Tenoxicam 20mg (30) Ketorolac 10mg (30)	Not specified.	No patients took extra medication for pain control.	The patients reported no additional side effects.
Ashraf, 2013.[32]	Celecoxib 400mg capsules (15) Placebo capsules (15)	Three 325mg acetaminophen tablets prescribed to be taken if required.	Two patients were excluded from the study as one underwent third molar surgery, and the other was not able to answer the questions. Rescue medication: Placebo: 7 patients: 3 tablets 3 patients: 2 tablets Celecoxib group: 3 patients: 3 tablets 2 patients: 2 tablets 1 patient: 1 tablet	The patients reported no side effects.
Dejkam, 2015.[33]	Gelofen capsule 400mg (20) Novafen 200mg capsule (20) Placebo 20mg capsule (20)	Acetaminophen codeine as and when required.	Not specified.	The patients reported no side effects.
Arslan, 2011.[34]	Placebo (16) Tenoxicam 20mg (16) Ibuprofen 200mg (16)	Extra dose of treatment medication	No patients took the rescue medication.	The patients reported no side effects.
Attar, 2008.[13]	Placebo (12) Ibuprofen 600mg tablet (14) Ibuprofen 600mg liquigel (13)	Tylenol ES (500mg)	6 patients lost the follow-up by not returning questionnaires. No patients took the escape medication.	The patients reported no side effects.
Mokhtari, 2016.[35]	Ibuprofen 400mg tablet (22) Indomethacin 25mg tablet (22) Placebo (22)	Additional analgesics not specified.	Not specified.	The patients reported no side effects.

Although the patients were prescribed with rescue medication, the intake was not specified in Mokhtari and Dejkam *et al.*[33,35], studies. None of the included studies reported any adverse events or side effects noted on the intake of a placebo, or any experimental NSAID prescribed[13,31-35] except in the Bali *et al.*[31], study all the other studies specified on the type of rescue medication prescribed.[13,32-35] None of the included studies reported any adverse events or side effects[31,32-35] except for Attar *et al.*[11], study, where the data was not reported. Only 2 included studies[13,32] reported on patients withdrawal, which is specified in (Table 3).

Quantitative Review

All the studies included a measure of variance in the form of data tables, like graphs and p-value.[13,31-35] However, these studies cannot be considered for meta-analysis due to the heterogenicity among the included studies such as differences in the sample sizes and follow up periods. Hence, only a descriptive evaluation of data has been performed.

Strength of Evidence

The strength of evidence of the included studies was graded based on the AHRQ EPC methodology. The study limitations were high. Although the study designs were randomized controlled trials, the risk of bias was higher. The studies were direct; the interventions and comparisons were similar as specified in the review question. The studies seem to be unrestrained by using VAS to measure outcomes, which aligns with the review question's outcome. The studies were inconsistent in that they had varying

effect sizes and in different directions. The studies were imprecise, as they have inadequate power given the amount of difference predicted between the placebo and experimental groups (Table 5).

Table 5. Table Showing the Strength of evidence of Included Studies

Outcome: post-operative pain reduction						
Domains						
Study set:	**Number of studies and participants**	**Study limitations**	**Directness**	**Consistency**	**Precision**	**Grade for strength of evidence**
Overall data set	6 RCT's N= 333	High	Direct	Inconsistent	Imprecise	Insufficient

DISCUSSION

Findings and conceptual text

The study's goal is to give comprehensive information on the preemptive analgesic efficacy of oral NSAIDs in patients undergoing single visit root canal treatment. The present review aimed to evaluate the effective oral NSAID for reducing postoperative pain levels in single visit root canal treatment. The review question was, Is there any variation in the postoperative pain levels and postoperative analgesic intake on preoperative administration of NSAIDs in single visit root canal treatment? The literature search has shown that Ibuprofen 200mg liquigel capsules and tablets, Tenoxicam 20mg tablets, and capsules and ketorolac 10mg tablets were the most effective drugs in reducing the postoperative pain levels in single visit root canal treatment at 12 and 24 hour time intervals. However, the results cannot be generalized as there was insufficient evidence on outcomes of this present review, based on the Agency for Healthcare Research and Quality (AHRQ) Evidence-based Practice Centers (EPC) strength of evidence methodology.[36]

The present review showed that Ibuprofen 200mg liquigel capsules and tablets, Tenoxicam 20mg capsules and tablets and ketorolac 10mg tablets effectively relieving post-endodontic pain levels in single visit root canal treatment at 12 and 24 hour time intervals. Previously the literature reviews on pain were obtained from an oral surgery or medical pain perspective and applied to the field of endodontics, which may not be an appropriate way to categorize the pain of endodontic origin. The medical research is mainly concerned with acute surgical pain, which may not be relevant to the endodontic pain. A patient undergoing endodontic treatment may have pre-existing pain for an extended time; the pain may have undergone central sensitization and progressed from an acute to chronic stage.[37,38] Analgesic regimens are useful in chronic pain reduction, may not be effective in acute cases. In addition to the quality of presented pain, the studies concerned with oral surgery tend to have different baseline population presenting to the operatory for the extraction of their wisdom teeth and likely to be young and healthy, so they might have mild or no preoperative pain.

In the present review, no studies mentioned the combination therapies for significant postoperative pain reduction and none of the included studies compared or described the combination NSAIDs in postoperative pain reduction.[13,31-35] As far as dosage is concerned, the single prophylactic dose was administered before the procedure with different doses and dosage schedules. No conclusion can be drawn from the studies, about the time of initial dosage that would lead to the most significant reduction in pain for the patient or how long they should maintain the analgesic regimen. Compared to higher dosages of tablets, capsules with lower dosages have proven beneficial in postoperative pain reduction.

Strength and Limitations of the Review

The systematic review's strengths are the sum of research pretreatment analgesia on post endodontic pain levels in patients undergoing single visit root canal treatment. The present review gave a comprehensive idea on analgesics used and the regimen preferred in single visit root canal treatment.

This review's limitations are the small number of included studies and the sample size of the included studies. Other limitations include the significant heterogeneity in the included studies; the trails differed in the drug administration's timing, the dose and the time after the administration when the effect was measured.

Future Research

More research is indicated to elaborate on Ibuprofen's impact on post endodontic pain. Various trials have to be performed using the different combination of NSAID's and the research has to stress on COX-2 inhibitors in single visit root canal treatment. Future trails have to concentrate on studies comparing the fast-acting formulations of various NSAID's which seems to have the highest action in terms of both speeds of pain relief and efficacy of pain relief.

Summary

This systematic review aimed to compare and evaluate the postoperative pain levels and analgesic intake on NSAIDs' preoperative oral administration in single visit root canal treatment. An electronic search was carried out on the PUBMED database for the articles that could be used to evaluate preemptive oral NSAIDs on postoperative pain levels in patients undergoing single visit root canal treatment.

Article search was narrowed down based upon the pre-stated inclusion and exclusion criteria. A total of six articles were included in this systematic review for detailed evaluation (Figure2).

Assessment of postoperative pain levels and postoperative analgesic intake were the variables of interest.

Based on the result of this systematic review, Ibuprofen 200mg liquigel capsules and tablets, Tenoxicam 20mg capsules and tablets, ketorolac 10mg tablets were effective in relieving post endodontic pain levels in single visit root canal treatment at 12 and 24 hour time intervals. Among all the NSAIDs compared in this systematic review, Ibuprofen was the most widely studied and used almost in all the included studies except for Ashraf *et al.*[32], study. Taking its more comprehensive account of comparison, within the limitations of the current systematic review, Ibuprofen was considered the best drug of choice in single visit endodontics.

CONCLUSIONS

Taking into a more comprehensive account of comparison among the studies included in the present systematic review, Ibuprofen was considered as the best drug of choice in single visit endodontics. It can also be justified that the pain after a single visit root canal treatment may last for 24 to 72hour intervals after which the pain experienced by a patient is nil.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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