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Sodium Hypochlorite Concentration and Post-Endodontic Pain - Unveiling the Optimal Balance: A Systematic Review and Meta-analysis

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Abstract:	Introduction: This study systematically reviewed literature regarding the effect of different concentrations of sodium hypochlorite (NaOCl) used during root canal treatment (RCT) on post-endodontic pain (PEP) and rescue analgesia. Methods: Following registration with PROSPERO (CRD42023388916), a search was conducted using PubMed, Scopus, Web of Science, and Embase databases. Randomized controlled trials (RaCTs) of patients receiving RCT which assessed PEP at different time intervals were included. Following data extraction and Cochrane risk of bias assessment 2, meta-analyses were performed to evaluate PEP during the first 48h along with rescue analgesic intake. The certainty of the evidence was evaluated using the Grading of Recommendations, Assessment, Development and Evaluation approach. Results: Five RaCTs with 674 patients were included. One study exhibited a low risk of bias, while four raised some concerns. Patients treated with low concentrations of NaOCl (£3%) were significantly less likely to report PEP at 24h (OR=2.32; [95%CI, 1.63-3.31]; P<0.05) and 48h (OR=2.49; [95% CI,1.73-3.59]; P<0.05) as compared with high concentrations of NaOCl (³5%). Furthermore, with low concentrations of NaOCl, significantly lesser moderate-severe PEP was reported at 24h (OR=2.32; [95%CI, 1.47-3.62]; P<0.05) and 48h (OR=2.35; [95%CI, 1.32-4.16]; P<0.05) and lesser analgesia was needed (OR=2.43; [95%CI, 1.48-4.00]; P<0.05). Conclusions: While PEP can be influenced by several factors, low certainty evidence suggests that when NaOCl is used as an irrigant during RCT, PEP may be less likely with lower concentrations of NaOCl. Moderate certainty evidence indicates that lesser analgesia may be required with lower concentrations of NaOCl. These results should be cautiously interpreted.

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ABSTRACT

Introduction: This study systematically reviewed literature regarding the effect of different concentrations of sodium hypochlorite (NaOCl) used during root canal treatment (RCT) on post-endodontic pain (PEP) and rescue analgesia.

Methods: Following registration with PROSPERO (CRD42023388916), a search was conducted using PubMed, Scopus, Web of Science, and Embase databases. Randomized controlled trials (RaCTs) of patients receiving RCT which assessed PEP at different time intervals were included. Following data extraction and Cochrane risk of bias assessment 2, meta-analyses were performed to evaluate PEP during the first 48h along with rescue analgesic intake. The certainty of the evidence was evaluated using the Grading of Recommendations, Assessment, Development and Evaluation approach.

Results: Five RaCTs with 674 patients were included. One study exhibited a low risk of bias, while four raised some concerns. Patients treated with low concentrations of NaOCl (≤3%) were significantly less likely to report PEP at 24h (OR=2.32; [95%CI, 1.63-3.31]; P<0.05) and 48h (OR=2.49; [95% CI,1.73-3.59]; P<0.05) as compared with high concentrations of NaOCl (≥5%). Furthermore, with low concentrations of NaOCl, significantly lesser moderate-severe PEP was reported at 24h (OR=2.32; [95%CI, 1.47-3.62]; P<0.05) and 48h (OR=2.35; [95%CI, 1.32-4.16]; P<0.05) and lesser analgesia was needed (OR=2.43; [95%CI, 1.48-4.00]; P<0.05).

Conclusions: While PEP can be influenced by several factors, low certainty evidence suggests that when NaOCl is used as an irrigant during RCT, PEP may be less likely with lower concentrations of NaOCl. Moderate certainty evidence indicates that lesser analgesia may be required with lower concentrations of NaOCl. These results should be cautiously interpreted.

Keywords: Sodium hypochlorite; post-endodontic pain; rescue analgesia; root canal treatment; systematic review

INTRODUCTION

The resolution of pulpal and periapical disease can be achieved by reducing the microbial bioburden from the root canal system through endodontic treatment[1]. Instrumentation of infected root canals during root canal treatment (RCT) is only able to remove microbial biofilms in part since root canal instruments do not touch and shape all surfaces of the root canal system uniformly[2]. Biofilms may therefore persist, leading to persistent periapical disease or emergent post-treatment disease. Irrigation is therefore important and complements the shaping process, especially in areas such as the isthmus and fins. Sodium hypochlorite (NaOCl) is the most widely preferred irrigant in endodontics[3,4]. Its concentration can range from 0.5% to above 6%, yet consensus on the optimal concentration has not been achieved [5,6]. Higher concentrations are associated with superior tissue dissolution and antimicrobial efficacy[7]. Nevertheless, research indicates that lower concentrations, when coupled with increased volume, can be equally effective[8].

From a patient's perspective, the purpose of an RCT is to increase overall quality of life by alleviating pain and/or preventing its recurrence[9]. Consequently, experiencing pain after RCT is uncomfortable for the patient and may require an emergency appointment at the dental office. The occurrence of post-endodontic pain (PEP) ranges from 3% to 58%[6,10]. PEP may be caused by several factors, including irrigation[11,12]. Sodium hypochlorite (NaOCl) is a caustic chemical known to have adverse effects, particularly when extruded into the peri-radicular region. A higher concentration may therefore influence PEP[13].

Several studies have explored the impact of the NaOCl concentration on PEP; however, an association in this context has not yet been established[6,13,14]. Thus, the objective of this study was to conduct a systematic review of the existing literature to ascertain whether *in vivo* evidence indicates differences in the incidence of PEP after primary RCT when using high (≥5%) or low (≤3%) concentrations of NaOCl. The null hypothesis asserts that the incidence of PEP does not vary based on the concentration of sodium hypochlorite employed.

METHODOLOGY

This review was performed and reported in accordance with PRISMA guidelines[15,] and the protocol was registered at PROSPERO (CRD42023388916) *a priori*.

Research question: Following the Population-Intervention-Comparator- Outcomes-Time-Study Design (PICOTS) framework, the following research question was developed: "In adult patients undergoing non-surgical root canal treatment (P), does irrigation with higher concentrations of sodium hypochlorite (≥5%) (I) compared with irrigation with lower concentrations (≤3%) (C) result in differences in the incidence of PEP (O) within the first 48 hours (T) in randomized controlled trials (S)?"

The secondary outcome was to assess the potential efficacy of rescue analgesics in alleviating PEP.

Eligibility criteria: This systematic review comprised *in vivo* studies involving patients who underwent non-surgical endodontic treatment using a low concentration of sodium hypochlorite (≤3%) and compared them with patients treated with a high concentration of sodium hypochlorite (≥5%) to assess the relationship between the incidence of postoperative endodontic pain (PEP) and the concentration of sodium hypochlorite applied. Articles published in English, with no restrictions on publication date, were considered for inclusion.

Publications were excluded if the inclusion criteria were not met. Articles such as *in vivo* studies not meeting the criteria of randomized controlled trials (RCTs), conference abstracts, case reports and case series were also excluded from this review.

Information sources and search strategy: The electronic database search for this systematic review was conducted across four databases, i.e., PubMed, Scopus, Web of Science (WOS), and Embase. The search was independently conducted by two authors (N.P. and M.S.T.) and lasted until 25th July 2023. Medical subject headings (MeSH) and their synonyms related to post-endodontic pain were utilized to develop the literature search strategy for the initial search, as described below: ("Pain, postoperative [MeSH]" or "Postoperative pain" OR "post-endodontic pain") AND ("pulpitis [MeSH]" OR "endodontics [MeSH]" OR "endodontic treatment" OR "root

canal therapy[MeSH]" OR "endodontic therapy") AND ("sodium hypochlorite [MeSH]" OR "hypochlorite sodium" OR "NaOCl" OR "Irrigating agent" OR "sodium hypochlorite solution").

The authors conducted a manual search of the references of the included articles. The detailed search strategy adopted across each database, including the search terms and entry terms, is provided in Supplementary Table 1.

Selection process: Rayyan software (http://rayyan.qcri.org) was utilized for organizing and managing the articles included in this systematic review[16]. Following the initial search and removal of duplicates, two authors (N.P. and M.S.T.) independently screened the identified publications based on their titles and abstracts. Articles that failed to meet the predetermined inclusion criteria were excluded. Subsequently, two authors (N.P. and M.S.T.) evaluated the full texts of the selected studies to assess their eligibility in accordance with the predefined criteria. In the event of any disagreement between the two authors, a third author (P.D.B.) with expertise in systematic review methodology was consulted to assist in reaching a resolution. If further clarification regarding the methodology or findings of a specific study was needed, the authors of those studies were contacted for additional information.

Data extraction: Following the selection of eligible articles, two authors (N.P. and M.S.T.) independently extracted the data from the selected studies. The study characteristics and outcome data are presented in Tables 1-3. In cases where discrepancies or disagreements arose during data extraction, they were resolved through open discussion. Furthermore, to ensure completeness of the data, the corresponding authors were contacted via email, with up to three attempts made over a two-week period, in instances where relevant information was missing or unclear. Despite efforts to contact Farzaneh *et al*. and Verma *et al*. for data on the incidence of pain, these efforts proved unsuccessful[14,17]. Consequently, the incidence of PEP at different time intervals was extracted from bar graphs as an alternative data source[18]. For this purpose, figures on the incidence of pain from both articles were converted into JPEG files by exporting each page through Adobe Acrobat 9. Subsequently, these JPEG images were imported into ImageJ software version 1.92 (Wayne Rasband, National Institute of Health, USA). The y-axis scale was calibrated using the graduations on the images[19]. A line tool was then employed to measure the actual length of each bar, and these measurements were used to derive the final dataset.

Risk of bias assessment: The Cochrane risk of bias (RoB)-2 tool was utilized to assess the risk of bias in the selected studies in this systematic review[20]. According to RoB-2, the risk of bias assessment was performed across five domains, and for each domain, the risk of bias was categorized as high (x), low (+), or some concern (-). A study was deemed to be at low risk of bias if it was labeled as having a low risk of bias for all domains and as a study with some concerns if it was labeled as having some concerns in at least one domain but was not labeled as having a high risk for any domain. A study was considered to have a high risk of bias if it was labeled high risk in any one domain or had some concerns in multiple domains. The risk of bias assessment was performed by two authors (N.P. and P.D.B.) independently, and in case of any disagreement, a third author (M.S.T.) was consulted to reach a consensus through discussion.

Quantitative synthesis and certainty of evidence: The incidence of pain was reported differently across the selected studies; some employed a binary classification of pain as absent or present, while others provided the incidence on an ordinal scale as no/mild/moderate/severe pain. For the purpose of analyzing the overall incidence of pain across low and high concentrations of NaOCl, the incidence of pain was dichotomized as either present or absent, wherein mild/moderate/severe pain on the pain scale was considered together as the presence of pain. These assessments were conducted to determine the incidence of pain at 24- and 48-hour intervals post-treatment. Furthermore, given the greater clinical relevance of moderate and severe pain, which often necessitate the use of analgesics, incidences of pain across these two grades were amalgamated in three selected studies[13,14,17] that reported pain with grades of moderate to severe intensity to draw comparisons between low and high concentrations of NaOCl. Similarly, the secondary outcome, i.e., rescue analgesic usage, was also analyzed in both groups. These comparisons were conducted using the Peto odds ratio with a fixed-effects model and a confidence interval of 95%. The Peto odds ratio was selected for analysis due to the low number of events, which are sometimes even reported as zero[21]. For each considered outcome, the heterogeneity across studies was assessed with the chi-square test and I^2 values.

The Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach was utilized to evaluate the certainty of evidence, which involved analyzing factors such as the risk of bias, inconsistency, imprecision, indirectness, and publication bias[22].

RESULTS

Study Selection: During the initial electronic search, 351 articles were identified. After eliminating duplicates, 199 studies were subjected to title and abstract screening. Subsequently, eleven articles met the eligibility criteria and underwent a thorough full-text review, leading to the final selection of five articles for data extraction and synthesis. The details of the excluded articles are provided in Supplementary Table 2. The PRISMA flow diagram depicting the selection process for this systematic review is presented in Figure 1.

Characteristics of the included studies: The detailed characteristics of the five randomized controlled trials[6,13,14,17,23] included in this systematic review are outlined in Table 1. All the papers included in this review were published between 2018 and 2022, ensuring the incorporation of the latest evidence. A total of 674 subjects were included in this systematic review, with a predominant representation of women and an age range of 18-50 years.

Considering the pulpal diagnoses, two studies within this review concentrated on irreversible pulpitis, where one study solely addressed asymptomatic cases with no spontaneous pain[17] while the second study included both asymptomatic and symptomatic cases of irreversible pulpitis[23]. The remaining studies considered pulpal and periapical diagnoses involving teeth with pulp necrosis accompanied by chronic apical periodontitis[14] and pulpal necrosis associated with asymptomatic or symptomatic apical periodontitis[13]. Notably, one study did not specify any specific diagnoses for consideration[6]. The teeth included in the trials were predominantly first or second mandibular molars[13,14,17]; however, one study did not distinguish between mandibular molars[23], and another study considered all types of teeth[6] for inclusion.

The treatment protocol used varied among the studies included (Table 2). In four studies, a single operator conducted the endodontic treatment[6,14,17,23], while in one study, seven postgraduate residents were involved in providing endodontic treatment[13]. The treatment protocol also differed in terms of the number of visits where the endodontic treatment was delivered during a single visit among the three included studies[6,17,23], whereas in two studies, the treatment was administered over two visits[13,14]. For comparison, the concentrations of NaOCl used in each study were as follows: 1% vs 5% [14], 1.3% vs 5.25%[13], 2.5% vs 5.25%[17], 2.25% vs 5.25% vs 8.25%[6], and 3% vs 5.25%[23].

Risk of bias across the included studies: Figure 2 illustrates the risk of bias scores obtained through the assessment using Cochrane's RoB 2 tool[20] across various domains among the studies included in this systematic review. Among the included studies, one study showed a low risk of bias[17], while in four other studies, assessments raised some concerns regarding the risk of bias[6,13,14,23]. Among these four studies, three appeared to have concerns about reporting the results[13,14,23], whereas in one study, variations in baseline characteristics might have potentially adversely affected the randomization process[6].

Synthesis of Results: The PEP and related outcomes from each study included in this review are detailed in Table 3. While only one study illustrated significantly less PEP within the 1.3% NaOCl group than within the 5.25% group[13], a similar trend emerged in three other studies included in this review, where a lower PEP was evident in the group using a lower concentration of NaOCl (i.e., ≤3%), albeit without statistical significance[6,14,23]. In contrast, one study reported significantly less pain associated with a high concentration of NaOCl (5.25%) for the first three days postoperatively, while no difference was observed from day 4 to day 7 postoperatively[17]. Pain was assessed at different time points in the studies examined in this review, with 24 and 48 hours postoperatively being the commonly used time points. A consistent pattern emerged across the included studies, suggesting that the majority of PEPs occurred within the first 24 hours. Subsequently, the pain levels gradually decreased by 48 hours, and no reported pain was observed at the 7-day mark.

With respect to rescue analgesic intake, the majority of the studies showed that participants in high-concentration groups (≥5%), although not significantly, had greater rescue analgesic usage[6,13,14,23]. Contrary to these findings, Farzaneh *et al.* noted that the mean analgesic intake was significantly greater in patients treated with 2.5% NaOCl[17]. Regarding the incidence of flare-ups, only one participant in the low-concentration group (≤3% NaOCl) reported severe pain even 48 hours postoperatively with swelling, necessitating an emergency visit[23].

Additionally, Demench *et al.* reported that overfilling (OR=8.38 [2.68–26.2]; 95% CI: $P<0.05$) was significantly associated with a greater PEP[6]. Mostafa *et al.* reported that the overall incidence of PEP was significantly associated with preoperative pain (OR=1.788 [1.459, 2.192]; 95% CI:

P<0.05), periapical radiolucency (OR=1.788 [1.049, 1.568]; 95% CI: *P*<0.05) and analgesic intake (OR=2.477 [1.614, 3.803]; 95% CI: *P*<0.05) [13].

A meta-analysis was conducted across the studies considering the availability of data for each outcome. The overall incidence of PEP was higher in patients treated with a high concentration (≥5%) of NaOCl than in those treated with a low concentration (≤3%), as indicated by the odds ratios at 24 hours (OR=2.32; [95%CI-1.63,3.31]: *P*<0.05) and 48 hours (OR=2.49; [95%CI-1.73,3.59]: *P*<0.05). Similar results were observed when moderate and severe PEP were considered for meta-analysis (Figure 3). Notably, considerable heterogeneity was observed in these four meta-analyses based on the I^2 values. Additionally, according to the GRADE approach for certainty of evidence, all four meta-analyses for incidence of pain depicted low certainty of evidence, indicating limited confidence in the effect estimate (Table 4).

The intake of rescue analgesia was evaluated as a secondary outcome. Moderate certainty evidence (Table 4) indicated that analgesics were more likely to be used by patients who were treated with higher concentrations of NaOCl (OR=2.43; [95%CI-1.48,4.00]; *P*<0.05) (Figure 4). There was low statistical heterogeneity observed for this secondary outcome (I^2=0).

DISCUSSION

The present systematic review assessed the development of PEP in relation to the concentration of sodium hypochlorite, which is a commonly used endodontic irrigant. Among the five randomized controlled trials included in this review, three showed no significant difference in PEP between the high (≥5%) and low (≤3%) concentration groups treated with NaOCl[4,9,186,14,23] but favored the low concentration group with lower pain values. Calcium hydroxide (CH) was used as an intracanal medicament between appointments in one study[14] which might explain the lack of significant difference between the higher and lower concentration groups since CH helps reduce PEP[24,25]. Moreover, one study reported significantly less pain in the low-concentration group than in the high-concentration group[13], while another study observed significantly less pain in the high-concentration group than in the high-concentration group[17]. While the evidence has a low level of certainty, the meta-analysis indicated that, considering both the overall incidence and the incidence of moderate and severe pain, PEP was twice as likely to occur with high concentrations of NaOCl than with low concentrations.

There is a lack of consensus on the optimal concentration of NaOCl used for endodontic procedures. Recent trends, however, indicate a shift toward higher concentrations of NaOCl, driven by its enhanced tissue dissolving and antimicrobial capabilities. It is essential to recognize the associated risks of cytotoxicity and extrusion, which contribute to increased PEP[26–30]. This observation aligns with the prevailing pattern identified in this systematic review, where a higher incidence of PEP was noted in the group utilizing higher concentrations of NaOCl. However, less PEP has also been recognized with the use of high-concentration NaOCl[17]. This maybe attributed to the inclusion of cases without periapical radiolucencies which could have prevented the extrusion of irrigant and debris. In addition, the greater dissolution capacity of 5.25% NaOCl may effectively breakdown pulpal tissues, thereby preventing the release of signaling molecules that could otherwise upregulate inflammation in periapical tissues[17]. It is also important to highlight that all participants in this trial received analgesics immediately after the procedure, potentially contributing to the observed differences. All the individuals enrolled in this trial did not report spontaneous pain[17], and pre-operative pain significantly influenced PEP, as indicated by previous research[31–33] and another study[13] included in this review. This distinction is noteworthy, as the remaining four studies in this review included both symptomatic and asymptomatic cases[6,13,14,23].

In the present systematic review, it was observed that the incidence of PEP was highest in the first 24 hours post-treatment, which corroborates existing evidence suggesting that the incidence of PEP can also increase to 65% within the first 24 hours[34]. However, this trend tended to decrease within the first 48 hours. This finding aligns with the findings of a prior systematic review that examined pain following RCT[35]. With a reasonable level of confidence, it was also found that patients in the high-concentration group were twice as likely to consume analgesics for PEP than patients in the low-concentration group. It should be noted that in one study included in this review[13], a placebo capsule was administered initially to differentiate between patients with no or mild pain who did not require analgesics and patients with moderate to severe pain who needed rescue analgesics, based on existing literature[36].

Limitations and Future Directions

Although the randomized controlled trials included in this systematic review shared similarities, inherent variations were present concerning pulpal diagnosis, periapical status, and treatment

protocols, including the use of intracanal medicament[14] and a sham analgesic[13]. A factor that may significantly affect the incidence of PEP, over-extended root filling, was not accounted for in this systematic review[6]. Therefore, the evidence derived from this review should be interpreted cautiously in the clinical context. Recent literature highlights the importance of standardizing research methods within the acknowledged limitations when investigating irrigants to enhance the reliability of findings in this area of research through future clinical trials[37].

CONCLUSIONS

Based on low certainty evidence, the findings indicated that the likelihood of PEP maybe significantly lesser and of lower intensity when lower concentrations of NaOCl are used during RCT as compared with higher concentrations of NaOCl. Similarly, significantly lesser analgesia was required in patients treated with lower concentrations of NaOCl based on moderate certainty of evidence. These findings should be treated with caution as several other patient and operative factors may also contribute to the heterogenous nature of the data.

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TABLE LEGENDS

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Table 2: Treatment protocol of the included studies

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Figure 3: Forest plot for the incidence of postoperative pain associated with high and low concentrations of NaOCl A. Overall incidence of pain at 24 hours post-treatment B. Overall incidence of pain at 48 hours post-treatment C. Incidence of moderate/severe pain at 24 hours D. Incidence of moderate/severe pain at 48 hours

Figure 4: Forest plot for rescue analgesic intake with high and low concentrations of NaOCl

Table 1: Characteristics of the included studies

Author/year	Country	No. of participants	Sex and age	Tooth type	Pre-op. Pain	Pulpal/periapical diagnosis	Excluded
Farzaneh *et al*[17] (2018)	Iran	Total included: 122 Finally, included for data analysis:110	F 71, M= 39, Mean age of approximately 28±8yrs	Permanent mandibular 1st and 2nd molars	Recorded with VAS from 0-9	Irreversible pulpitis with no spontaneous pre-op pain	Non-restorable teeth, teeth where rubber dam isolation not possible, over instrumentation and overfilling, pregnancy and lactation, severe periodontal disease. Pain medication at least 6 hours before treatment visit.
Verma *et al*[14] (2019)	India	Total included: 100 Finally, included for pain analysis: 90	F=? M=? Mean age range: 18-47yrs	Permanent mandibular 1st and 2nd molars	10 cm VAS	Pulpal necrosis with chronic apical periodontitis	Teeth where rubber dam isolation not possible, Periodontally compromised teeth, previously accessed teeth, on analgesics within past 3 days or antibiotics in last month.
Mostafa *et al*[13] (2020)	Egypt	Final included for analysis:308	F= 178, M= 130; Age range of 25-45yrs	Permanent mandibular 1st and 2nd molars	0-10 NRS	Non-vital pulp with symptomatic as well as asymptomatic apical periodontitis	Analgesics taken 12 hours before treatment, severely curved root canal, acute periapical or periodontal abscess, badly decayed crowns, pregnant and lactating, allergies to materials/medications used.
Demenech *et al*[6] (2021)	Brazil	Total included for NaOCl groups: 135 Finally, included for data analysis:126	F=79, M= 47 Mean age 38.1±14.4 yrs.	All	Y/N	Not specified	Complex cases, if on analgesic or anti-inflammatories, patients with non-odontogenic facial pain, or chronic pain.
Thumar *et al*[23] (2022)	India	Included in plain NaOCl group: 56	F=24 M=16 Mean age range: 20-50yrs	Permanent mandibular molars	Y/N	Symptomatic or asymptomatic irreversible pulpitis	Analgesics taken 12 hours before treatment, rubber dam not possible, complex cases, Occlusal discrepancies.

? = not mentioned, VAS= visual analog scale

Table 2: Treatment protocol of the included studies

Author/ year	Instrumentation	Operator	Apical enlargement size	NaOCl conc. used	Needle type	Volume of irrigant used	Other irrigants used	Activation (Y/N)	Patency (Y/N)	Number of appointments	ICM	Obturation technique	Coronal seal
Farzaneh *et al*[17] (2018)	RaCe rotary files	Single practitioner	#30/4%	2.5% and 5.25%	30G; side-perforated used 2 mm short of WL	2 ml between each instrument	17% EDTA (3 ml) and final 5 ml normal saline	N	Y	1	-	Cold Lateral compaction [Gutta percha (GP) and AH26 sealer]	Not mentioned
Verma *et al*[14] (2019)	Mtwo rotary files	Single operator	Not mentioned	1% And 5%	30G, 2 mm short of WL [needle design not specified]	5 ml between each instrument, and to remove smear layer	17% EDTA (5 ml) and final 5 ml of NaOCl in chosen conc.	N	N	2	CH	Interappointment pain assessed [prior to obturation]	Temporary filling (Cavit)
Mostafa *et al*[13] (2020)	Protaper Universal (F2/F3)	7 post-graduate students	#25/30	1.3% and 5.25%	27G, notched tip needle 3 mm short of WL	3 ml between instruments and 5 ml final flush	Lubricant (Glyde File prep) used with each instrument	N	Y	2	No	Interappointment pain assessed post-instrumentation and immediately after root filing [Single cone GP with AH plus sealer technique]	Temporary filling (Cavit)
Demenech *et al*[6] (2021)	WaveOne gold (reciprocating) and ProDesign Logic (rotating)	Single specialist	Not mentioned	2.25, 5.25, and 8.25%	Endo-Eze Tip [gauge and design not specified]	6 ml	17% EDTA, and final rinse 0.9% saline.	N	Y [for necrotic pulp]	1	-	Tagger's hybrid technique	Glass ionomer cement coronal seal
Thumar *et al*[23] (2022)	Hyflex CM	Single post-graduate student	#25, 4%/6%	3% And 5.25%	?	2 ml between instruments and 5 ml final irrigation	Saline	Y	?	1	-	Cold Lateral compaction [GP and Sealapex sealer]	Composite

? = not mentioned; ICM=intracanal medicament; CH= calcium hydroxide; Y= yes; N=no

Table 3: Summary of analyses for post-endodontic pain (PEP) and analgesic usage

Author	Evaluation tool	Symptoms and evaluation period	Pain score in percentage (%) and rescue analgesic intake in various concentration of NaOCl used			Outcome
			Low concentration (LC) (1-3% NaOCl)	High concentration (HC) (5-5.25% NaOCl)	Very HC (8.25%NaOCl)	
Farzaneh *et al*[17] (2018)	Recorded with VAS from 0-9 Categorized as 0: no pain 1-3: mild pain 4-6: moderate pain 7-9: severe pain	PEP at 24 hours	Severe/Mod. pain- 18.2	Severe/Mod. pain- 16.4		Significantly less PEP associated with 5.25% NaOCl during the first 72 hours. Mean analgesic usage was found to be significantly higher in patients treated with 2.5% NaOCl.
			Mild/No pain -81.8	Mild/No pain - 83.6		
		PEP at 48 hours	Severe/Mod. pain- 12.7	Severe/Mod. pain- 3.6		
			Mild/No pain -87.3	Mild/No pain -96.4		
		PEP at 72 hours	Severe/Mod. pain- 1.8	Severe/Mod. pain- 1.8		
			Mild/No pain -98.2	Mild/No pain -98.2		
		Rescue analgesics (Glofen 400 mg)	2.27 (0.25)*	1.64 (0.16)*		
Verma *et al*[14] (2019)	10 cm VAS Categorized as 0: no pain 1-3: mild pain 4-6: moderate pain 7-10: severe pain	PEP at 24 hours	Severe/Mod. pain- 4.4	Severe/Mod. pain- 4.4		No significant difference between groups, although lower values were reported in the low-concentration group.
			Mild/No pain -95.6	Mild/No pain 95.6		
		PEP at 48 hours	Severe/Mod. pain- 0	Severe/Mod. pain- 0		
			Mild No pain-100	Mild No pain-100		
		PEP at 72 hours	Severe/Mod. pain- 0	Severe/Mod. pain- 0		
			Mild No pain-100	Mild No pain-100		
		Rescue analgesics	Needed- 20%	Needed- 24%		
Mostafa *et al*[13] (2020)	0-10 NRS Categorized as 0: no pain 1-3: mild pain 4-6: moderate pain 7-10: severe pain	PEP at 24 hours	Severe/Mod. pain- 12.3	Severe/Mod. pain- 35		Significantly less pain associated with 1.3% than 5.25%, Rescue Analgesic usage was lesser in 1.3% NaOCl group in
			Mild/No pain- 87.7	Mild/No pain- 65		
		PEP at 48 hours	Severe/Mod. pain- 6.4	Severe/Mod. pain- 22.7		
			Mild/No pain- 93.6	Mild/No pain- 77.3		
		Sham analgesics/	Sham use- 14.9	Sham use- 24.0		

		Rescue analgesics (Ibuprofen 600 mg)	Analgesic use- 5.8	Analgesic use-18.8		comparison with 5.25% NaOCl group. PEP was significantly associated with pre-operative pain, periapical radiolucency, and analgesic intake.
Demenech *et al*[6] (2021)	Pain categorized as Yes or No VAS 0-2: absent/mild 3-10: mod/severe	PEP at 24 hours	Yes- 4.7	Yes- 16.7	Yes- 17.1	NaOCl concentration had no significant role in either the presence or intensity of pain, but a higher percentage of PEP was observed in 5.25% NaOCl group followed by 8.25% group and then 2.5% NaOCl group. Treatment time of more than 10 minutes as well as overfilling were significantly related to higher PEP, particularly in the first 24 hours.
			No- 95.3	No- 83.3	No- 82.9	
		PEP at 48 hours	Yes- 0	Yes- 7.1	Yes- 2.4	
			No- 100	No- 92.9	No- 97.6	
		PEP at 72 hours	Yes- 9.3	Yes- 4.8	Yes- 0	
			No- 90.7	No- 95.2	No- 100	
		VAS score	No/Mild- 93.0	No/Mild- 80.9	No/Mild- 90.2	
			Mod/Severe- 7.0	Mod/Severe- 19.1	Mod/Severe- 9.8	
		Rescue analgesics (Nimesulide 100 mg every 12 hrs. for 3 days)	Yes- 4.7	Yes-16.7	Yes- 4.9	
			No- 95.3	No- 83.3	No- 95.1	
Thumar *et al*[23] (2022)	VAS (0–100 mm).	PEP at 24 hours	0.45 (0.76)*	0.95 (1.43)*		Lower concentration showed less pain level though not significant.
		PEP at 48 hours	0.15 (0.37)*	0.4 (0.88)*		
		PEP at 72 hours	0.05 (0.22)*	0.15 (0.49)*		
		Rescue analgesics	Analgesic use- 5	Analgesic use- 15		

*Mean with standard deviation (SD)

Table 4: Assessment of the Certainty of Evidence utilizing the GRADE Approach

Assessment of Certainty of Evidence							No. of Participants			
No. of studies	**Study design (Initial Quality of Evidence)**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**High Conc. NaOCl**	**Low Conc. NaOCl**	**Odds Ratio-High to low (95% CI)**	**Quality of Body of Evidence**
Primary outcome: incidence of PEP after 24 hours of treatment										
4	Randomized Trials ⊕⊕⊕⊕	Not Serious	Serious	Not Serious	Serious	Undetected	182/337	125/297	2.32 (1.63,3.31)	Low ⊕⊕◯◯
Primary outcome: incidence of PEP after 48 hours of treatment										
4	Randomized Trials ⊕⊕⊕⊕	Not Serious	Serious	Not Serious	Serious	Undetected	126/337	72/297	2.49 (1.73,3.59)	Low ⊕⊕◯◯
Primary outcome: incidence of moderate and severe PEP after 24 hours of treatment										
3	Randomized Trials ⊕⊕⊕⊕	Not Serious	Serious	Not Serious	Serious	Undetected	62/254	31/254	2.32 (1.47,3.67)	Low ⊕⊕◯◯
Primary outcome: incidence of moderate and severe PEP after 48 hours of treatment										
3	Randomized Trials ⊕⊕⊕⊕	Not Serious	Serious	Not Serious	Serious	Undetected	37/254	17/254	2.35 (1.32,4.16)	Low ⊕⊕◯◯
Secondary outcome: Rescue Analgesic Usage										
4	Randomized Trials ⊕⊕⊕⊕	Not Serious	Not Serious	Not Serious	Serious	Undetected	52/302	21/262	2.43 (1.48,4.00)	Moderate ⊕⊕⊕◯

Figure 1: PRISMA flow diagram for the systematic review

Click here to access/download;Figure;Fig 1.tiff

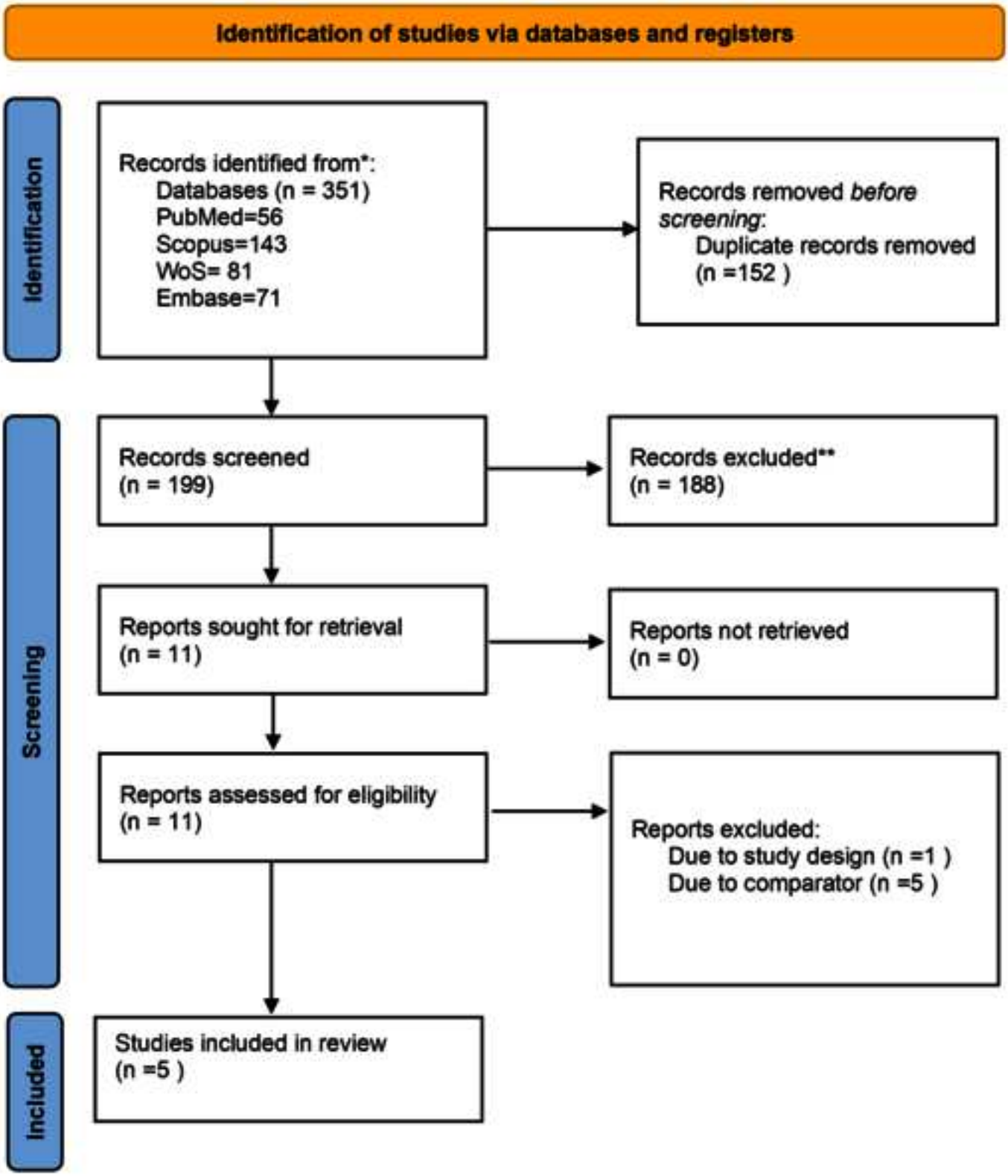

Figure 2: Risk of bias assessment of the included studies

Author/year	Bias from Randomization Process [Selection bias]	Bias due to deviation from intended intervention [Performance bias]	Bias due to missing outcome data [Attrition bias]	Bias in measurement of outcome [Detection bias]	Bias in selection of reported result [Reporting bias]	Overall Risk of Bias
Farzaneh et al., 2018	+	+	+	+	+	+
Verma et al., 2019	+	+	+	+	-	-
Mostafa et al., 2020	+	+	+	+	-	-
Demenech et al., 2021	-	+	+	+	+	-
Thumar et al., 2022	+	+	+	+	-	-

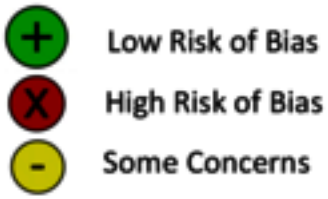

Figure 3: Forest plot for PEP associated with high and low concentrations of NaOCl A. Overall incidence of pain at 24h B.

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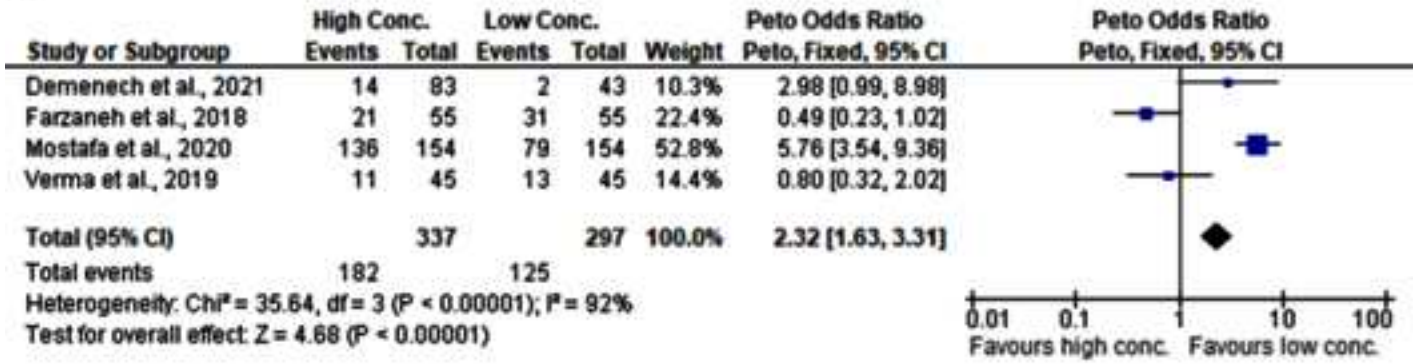
A.



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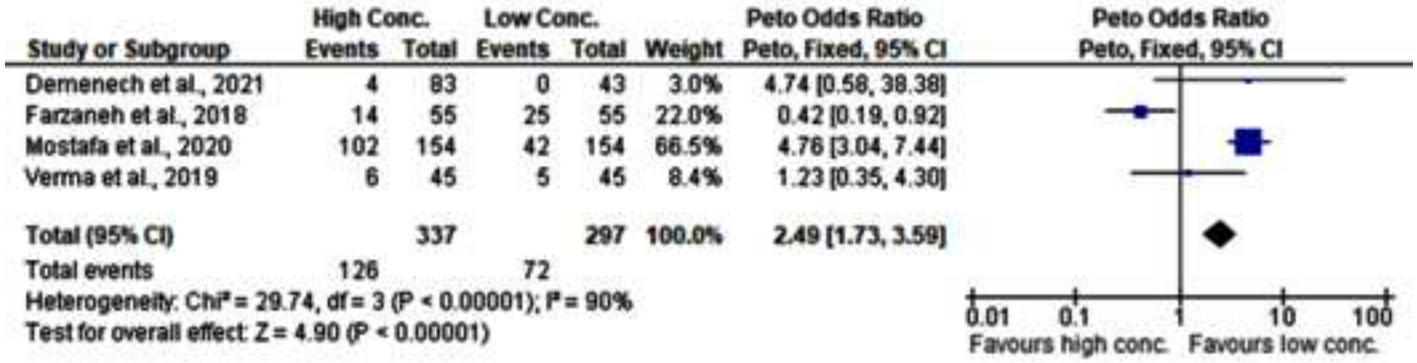

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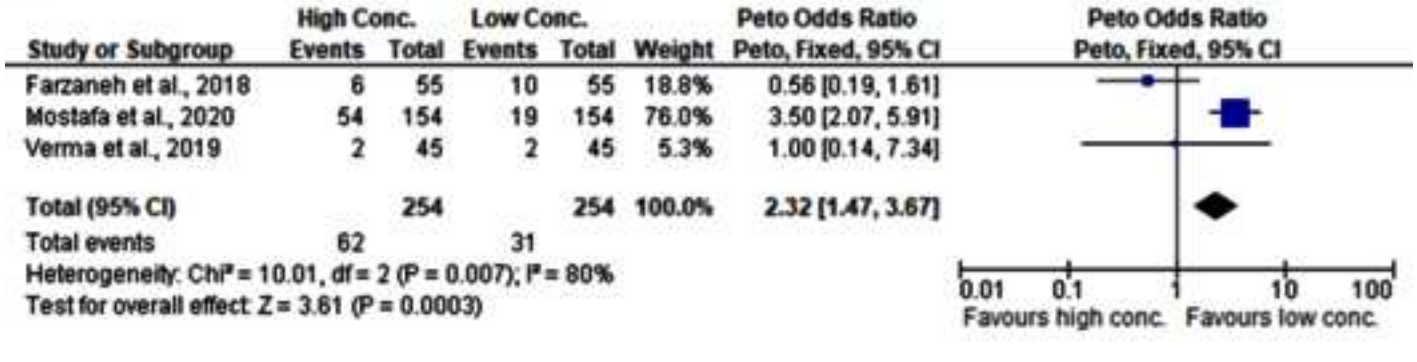

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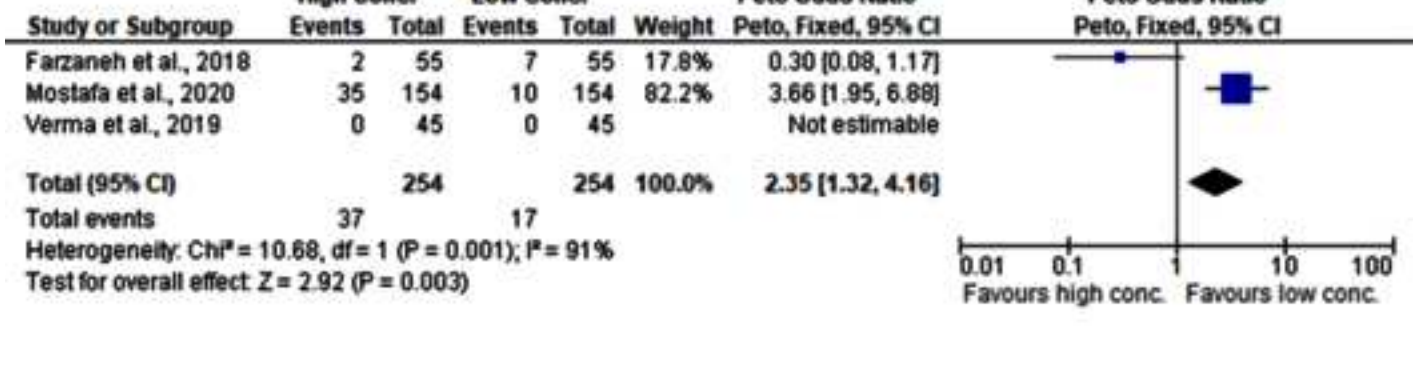

Figure 4: Forest plot for rescue analgesic intake with high and low concentrations of NaOCl

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