Research Article

Effectiveness of Intracanal Cryotherapy using Different Irrigants on Reduction of Post Endodontic Pain – A Systematic Review and Meta-analysis

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Received: 03-11-2021; **Revised:** 24-01-2022; **Accepted:** 05-02-2022; **Published on:** 15-02-2022.

ABSTRACT

Introduction: Recently the non-pharmacological management of post endodontic pain has been extensively studied. The aim of this systematic review was to evaluate the effectiveness of intracanal cryotherapy in reducing postoperative endodontic pain. A comprehensive search was conducted by accessing electronic databases like PubMed, Google Scholar, Google and EBSCO. Articles evaluating the effect of intracanal cryotherapy in reducing postoperative pain using different irrigating agents which were published till November 2020 were included in the study. Risk of bias was assessed using the Cochrane risk of bias criteria. Meta-analysis was performed for ten studies and tested the heterogeneity using I2 index. Qualitative and quantitative analysis was done for thirteen and ten studies respectively. Intracanal cryotherapy was found to be effective in reducing post-operative pain at 6 hours and 24 hours. Within the limitations of the study, it can be concluded that intracanal cryotherapy using cold saline or 17% EDTA at a temperature range of 2.5°C to 6°C as final irrigating agent helps in reducing postoperative pain at 6 hrs and 24 hrs following single-visit or multi visit root canal treatment in teeth diagnosed with irreversible pulpitis with apical periodontitis.

Keywords: Intracanal cryotherapy, cold saline, postoperative pain.

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DOI: 10.47583/ijpsrr.2022.v72i02.022

DOI link: http://dx.doi.org/10.47583/ijpsrr.2022.v72i02.022

INTRODUCTION

Postendodontic pain is multifactorial[1] and is linked to periapical inflammatory response which could be secondary to anatomical, mechanical, chemical and/or microbial factors associated with the tooth or the periradicular tissues[2–5]. The non-pharmacological methods used to mitigate postoperative pain include counselling, preoperative patient-calming approaches and explanations[6], occlusal reductions[7], verbal anesthesia, music therapy, medication to more specific counselling and operative procedures like cryotherapy. The pharmacologic methods include, long-acting anesthesia, medication using antihistamines[8], nonsteroidal anti-inflammatory drugs[9], narcotic analgesics, and steroidal anti-inflammatory drugs[10]. Moreover, the use of medications to relieve pain is associated with an increased risk of harm, including gastrointestinal irritation and other systemic adverse effects[11]. Thus, alternative techniques such as cryotherapy are being evaluated for management of postoperative pain.

Cryotherapy is a relatively new form of treatment which involves applying cold through various methods which may decrease the conduction velocity of nerve signals, reduces the local blood flow by vasoconstriction and hence reduce hemorrhage, edema and local inflammation [11,12] in order to promote healing and other therapeutic results. One way to apply cryotherapy to the inflamed periradicular tissues is by intracanal irrigation with a cold substance after the endodontic cleaning and shaping procedure. Number of studies[13–15] have been performed to evaluate the effectiveness of intracanal cryotherapy in reducing the postoperative pain, however, a systematic analysis of the quality of these randomized controlled trials needs to be evaluated using well defined criterias like those used in a systematic review. Thus, the aim of this systematic review was to evaluate the effectiveness of intracanal cryotherapy in reducing postoperative endodontic pain.

MATERIALS AND METHODS

Protocol and registration

The research protocol is designed according to the PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analyses) guidelines 2009. The protocol of this systematic review was registered with the International Prospective Register of Systematic Review (PROSPERO CRD42021229572).

Focused question

Is intracanal cryotherapy (intervention) effective in decreasing the postoperative pain (outcome) as compared to the use of irrigants at room temperature (comparator) after cleaning and shaping in endodontic treatment in adult permanent teeth (population)?

PICOS criteria

POPULATION: Adults permanent teeth undergoing endodontic treatment

INTERVENTION: Cryotherapy

COMPARISON: Saline at room temperature

OUTCOME: Post-operative pain

STUDY DESIGN: RCTs

Eligibility criteria

Inclusion Criteria

The inclusion criteria included studies which employed the following:

- patients of varied age groups requiring endodontic treatment of permanent teeth
- irrigants at different temperatures as treatment modalities for endodontic pain reduction
- minimum follow up of up to 24 hours
- multiple techniques of irrigation for control and study group of cryotherapy
- Publications in English, with full text available in either soft or hard copy.

Exclusion Criteria

The exclusion criteria included the studies which employed the following:

- use of different techniques to reduce post endodontic pain
- multiple dependent variables besides post endodontic pain
- multiple independent variables besides cryotherapy
- Non clinical treatment (eg, studies on cell cultures or animal study).
- Publications were in the form of letters, commentaries, or narratives.
- No specified criteria provided for evaluating the outcome of treatment, or no mention of how to determine the healing outcome.

Literature search

A comprehensive search was conducted by accessing electronic databases, along with a manual search, to identify all relevant studies associated with intracanal cryotherapy. Electronic databases, like PubMed, Google Scholar, Google and EBSCO were consulted by looking for the MeSH terms and key words like post endodontic pain, postoperative pain, root canal, irrigation for root canal, cold irrigation, endodontic irrigation, cryotherapy, and intracanal cryotherapy with appropriate Boolean characters.

The search lined all articles printed from 1990 to 2020. Articles from 2016 to 2020 were selected for the study. Duplicate records were removed. Each prospective and retrospective clinical study printed in English language were enclosed. The workflow followed the PRISMA checklist.

All studies known were screened by reading the title and the abstract by two independent reviewers and by applying the inclusion and exclusion criteria. Then full texts of these studies were obtained. Inter-reviewer reliability was assessed with Cohen kappa (0.80). Any possible discrepancies encountered during this process, were resolved by discussion between the reviewers and if a disagreement persisted, the judgment of a third reviewer was considered decisive.

Data collection

Characteristics of included trials and numerical data were extracted by two reviewers using predetermined and piloted extraction forms. During the protocol stage piloting of the forms was performed until over 90% agreement was reached.

Data extraction and data items

Information on authors' names, year of publications, study design, sample size, number of visits, preoperative pulpal and periapical diagnosis, type of teeth included, groups of intervention, follow-up period, method of irrigation, volume of irrigation, temperature of the irrigant, method of pain assessment and the result was independently extracted by two reviewers. Data regarding the included studies was also independently extracted by the reviewers based on a previously defined protocol in a specific form in the Microsoft Office Excel 2007 software (Microsoft Corporation, Redmond, WA, USA) [Table 1].

Table 1: PICOS Data Extraction Chart

Sr No	Author (Year)	Sample size	No. of visit	Type of tooth /Diagnosis	method of irrigation used	Final irrigation regimen in experimental group	Final irrigation regimen in Control group	Results	follow up (time interval)
1	Al-Nahlawi et al. (2016)[13]	75	single visit	Single-rooted - single canal teeth with Vital teeth with irreversible pulpitis or pulp exposure	Endovac microcannula	**Group II**: 20 mL of room temperature saline was irrigated for 5 minutes using EndoVac	**Group I** - No additional irrigation was applied (control).	Pain levels were high ingroups I and II after 6 hours that decreased with time to almostdiminish after 1 week, and on the other hand,	6, 12, 24, 48 hours, and 7 days

Sr No	Author (Year)	Sample size	No. of visit	Type of tooth /Diagnosis	method of irrigation used	Final irrigation regimen in experimental group	Final irrigation regimen in Control group	Results	follow up (time interval)
						Group III: A 20 mL of 2 to 4°C cold saline was irrigated for 5 minutes using EndoVac		group III showedno pain among different monitoring periods. Also pain levels in groups II were lower compared with group I after only 6 hours	
2	Keskin et al. (2016)[14]	170	single visit	incisors, premolars, molars with asymptomatic or symptomatic irreversible pulpitis with either normal apical tissues or symptomatic apical periodontitis	31 G Navi-Tip needle inserted 2 mm short of the WL	**Cryotherapy group** - 5ml of 0.9% physiological saline solution at 2.5°C was used for 5 mins	**Control group** - 5ml of 0.9% physiological saline solution at room temperature was used for 5 min	2.5°C cold saline irrigation as final irrigant can result in significant reduction of post-operative pain as compared to control group	24 and 48 h
3	Vera et al. (2018)[15]	210	multiple visits	uniradicular teeth with a single canal with necrotic pulp and symptomatic apical periodontitis	Endovac microcannula	**Cryotherapy group** - 20 mL sterile cold (2.5°C) saline solution is delivered to the working length with a sterile, cold (2.5°C) Endovac microcannula for 5 mins	**Control group** - 20 mL sterile room temp saline solution delivered to the working length with a sterile microcannula attached to Endovac for 5 mins	Patients in the cryotherapy group suffered significantly less pain after 6, 24, and 72 hours and needed fewer analgesics postoperatively .Patients in the control group presented a significantly higher incidence of postoperative pain, intensity,and need for medication intake	6, 24, and 72 hours
4	Jaiswal et al. (2020)[16]	30	multiple visits	symptomatic apical periodontitis and pulp necrosis	not mentioned	**Group B (cryotherapy group)** - 20ml cold saline (2.5°C) is used for 5mins	**Group A (control group)** - 20ml saline at room temperature is used for 5mins	No statistical difference between the two groups was seen	6 hours and 24 hours
5	Gundogdu et al. (2018)[17]	100	single visit	maxillary or mandibular molar with vital pulp and symptomatic apical periodontitis	needle and syringe	**Intracanal cryotherapy group** - 20 mL of cold saline solution (2.5°C) was used for 5 minutes. **Intraoral cryotherapy group** - 20 mL of room temperature saline solution was used for 5mins. Small ice packs were placed intraorally in the mouth on the vestibular surface for 30 minutes **Extraoral cryotherapy group** - 20 mL of room temperature saline solution was used	**Control group** - 20 mL room temperature saline solution was used for 5mins	When compared with the control group, all the cryotherapy groups exhibited lower postoperative pain levels on the first, third, fifth, and seventh days and lower levels of pain on percussion on the seventh day	1st, 3rd, 5th,7th day

Sr No	Author (Year)	Sample size	No. of visit	Type of tooth /Diagnosis	method of irrigation used	Final irrigation regimen in experimental group	Final irrigation regimen in Control group	Results	follow up (time interval)
						for 5mins. Ice packs were placed extraorally on the cheek surface for 30 minutes.			
6	Jain et al. (2018)[18]	60	multiple visits	mandibular 1st molar with symptomatic irreversible pulpitis with symptomatic apical periodontitis, irreversible pulpitis with asymptomatic apical periodontitis, irreversible pulpitis with normal periradicular tissues	28 gauge side vented needle	**Cryotherapy group** - final irrigation was carried out with saline at 2.5°C, using a 5 ml syringe with 28 gauge side vented needle for a minute.	**Control group** - final irrigation was carried out with saline at room temperature, using a 5 ml syringe with 28 gauge side vented needle for a minute.	At 6 hours post-operatively, there was a statistically significant reduction in pain in experimental group compared to control group. At 24 and 48 hours post-operatively, there was no statistically significant reduction in pain in experimental group compared to control group.	6, 24, and 48 h
7	Vieyra et al. (2019)[19]	240	single visit	maxillary/mandibular anterior or posteriorteeth with vital teeth with irreversible pulpitis	Endovac	**Group A** - 5 mL of cold (4°C) 17% EDTA followed by 10 mL of cold (4°C) sterile saline solution dispensed to the WL using a cold (4°C) metallic micro-cannula included in the Endo Vac System (Kerr Endo) and maintained intracanally for 1 minute. **Group B** - 5 mL of cold (2.5°C) 17% EDTA followed by 10 mL of cold (2.5°C) sterile saline solution dispensed to the WL using a cold (2.5°C) metallic micro-cannula included in the Endo Vac System for 1 minute.	**Control group** - 5 mL (room temperature) of 17% EDTA followed by10 mL (room temperature) of sterile saline solutiondelivered to the WL using a metallic micro-cannulainc luded in the Endo Vac System for 1 minute	No statistically significant difference (P > 0.05) among the groups was found regarding degree or duration of pain. There was no statistically significant difference (P > 0.05) among the 4oC and 2.5oC groups.	24, 48 and 72 hours
8	Bazaid et al. (2018)[20]	40	multiple visits	vital teeth, irreversible pulpitis with either normal apical tissues or apical periodontitis	side vented needles	**Group 2**: cryotherapy group (n=20) 2.5°C saline was used as the final irrigant for 2mins using a side vented needle Each group was subdivided into 2 subgroups (a & b (n=10) according to preoperative apical diagnosis. a= teeth with apical periodontitis b= teeth with normal apical tissues.	**Group 1**: control group (n=20) final irrigant used was saline at room temperature for 2 mins using side vented needle	A statistically significant difference was found when comparing the pain level in cryotherapy group (subgroup 2a) with control group (subgroup 1a) 24, 48 hours postoperatively. But there was no statistically significant difference when comparing the pain level in cryotherapy	24 hours, 48 hours

Sr No	Author (Year)	Sample size	No. of visit	Type of tooth /Diagnosis	method of irrigation used	Final irrigation regimen in experimental group	Final irrigation regimen in Control group	Results	follow up (time interval)
								(subgroup 1b) with control (subgroup 1b) after 24, 48 hours postoperatively	
9	Dr. Sudheer K. A et al. (2019)[21]	60	single visit	Single rooted vital tooth with vital teeth, symptomatic irreversible pulpitis	needle and syringe	**Cold saline group** - 10ml of saline at about 2.5°C was used for final irrigation for 3 minutes	**Control group** - 10 mL of 0.9% physiological saline solution at the room temperature was used for final irrigation for 3 mins	cold saline group showed a significant reduction in postoperative pain levels in comparison to control group at 6 to 24 h follow-ups	6, 24, 48 hours.
10	Vieyra et al. (2018)[22]	240	single visit	maxillary/mandibular anterior or posteriorteeth with vital pulp, irreversible pulpitis and no periapical lesion	endovac irrigation system	**Group A** - 5 mL cold (6 °C)17% EDTA followed with 10 mL cold (6 °C) sterile saline solution dispensed to the WL using a cold (6 °C) metallic micro-cannula included in the Endo Vac System (Kerr Endo) and maintained intracanally for one minute. **Group B** - 5 mL cold (2.5°C) 17% EDTA followed with 10 mL cold (2.5 °C) sterile saline solution dispensed to the WL using a cold (2.5 °C) metallic micro-cannula included in the Endo Vac System for one minute.	**Group C** - final irrigation with 5 mL (room temperature) 17% EDTA followed with 10 mL (room temperature) sterile saline solution delivered to the WLusing a metallic micro-cannula included in the Endo Vac System forone minute.	There was no statistically relevant difference (p> .05)among Group A and Group C compared with Group B. Group B showed less pain than the rest of the groups	24,48,72 hours
11	Chauhan et al. (2020)[23]	40	multiple visits	symptomatic apical periodontitis with pulpal necrosis	side vented needles	**Group 2:** cryotherapy group (n=20) where 20ml of 2.5°C saline was used as the final irrigant for 2 mins	**Group 1**: control group (n=20) where the final irrigant was 20ml of saline at room temperature for 2 mins	Patients in the control group presented a significantly higher incidence of postoperative pain intensity, and need for medication intake (P < .05). Cryotherapy reduced the incidence of postoperative pain and the need for medication intake.	6, 24, and 72 hours
12	Vieyra et al. (2019)[24]	120	single visit	maxillary/mandibular anterior or posteriorteeth with vital pulp	Endovac irrigation system	**Group 6 °C** -final irrigation with 5mL of cold (6 °C) 17% EDTA followed by 10mL of cold (6 °C) sterile saline solution **Group 4°C** - final irrigation with 5mL of cold (4 °C) 17% EDTA followed by 10mL of	**Group** RT - final irrigation with 5mL (room temperature) of 17% EDTA followed by 10 mL (room temperature) of sterile saline solution	No statistically major change between the groups was found regarding the degree or duration of pain.	24,48,72 hours

Sr No	Author (Year)	Sample size	No. of visit	Type of tooth /Diagnosis	method of irrigation used	Final irrigation regimen in experimental group	Final irrigation regimen in Control group	Results	follow up (time interval)
						cold (4° C) sterile salinesolution			
13	Alharthi et al. (2019)[25]	105	single visit	single rooted teeth, diagnosis not mentioned	two side–vented needle with gauge size 30	**Cryotherapy group** - 10 mL of cold (1.5–2.5°C) 0.9% normal saline solution was used for 5 mins **Room temperature saline group** -10 mL of room-temperature 0.9% normal saline solution was used for 5 mins	**Control group**- received no more irrigation.	There was no significance difference between Cryotherapy group and Room temperature saline group. The highest post-endodontic pain was in control group. In general, the post-endodontic pain (6 h, 24 h, and 48 h)decreased with time in all groups.	6, 24, and 48 h

Risk of bias in individual studies

Risk of bias was assessed by the two independent reviewers for RCTs included in the review and discrepancies were resolved by discussion and appropriate consultation with a third reviewer. The domains for risk assessment were graded as low, uncertain or high risk, based on selection bias (random sequence generation and allocation concealment), performance bias (blinding), attrition bias (incomplete outcome data), detection bias (assessor blinding) and reporting bias (selective reporting). Thus, the overall risk for individual studies were assessed as low, moderate or high risk based on the domains and criteria.

RESULTS

Data analysis

The PRISMA guidelines were followed for the methodology. The study selection process is summarized in Figure. 1 (PRISMA flow chart). All the titles and abstracts were screened based on the stringent selection criteria. Subsequently the full texts were assessed independently by the two reviewers. A total of thirteen studies over the past five years met the inclusion criteria for full text reading and all thirteen were included for further analysis.

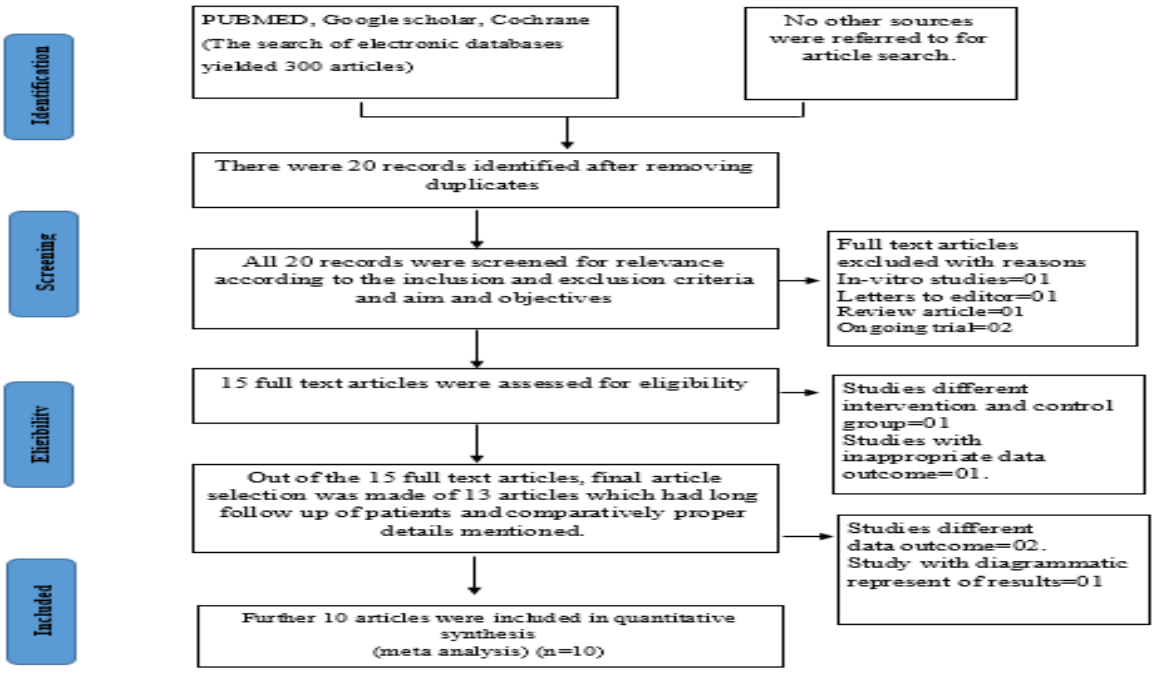


Figure 1: PICOS Search Strategy Flowchart

Study characteristics

Thirteen articles were selected for qualitative synthesis and ten articles [14,15,16,17,18,19,22,23,24,25] for quantitative synthesis. The characteristics of all the included studies are listed in Table 1. All the studies were in-vivo clinical trials performed on adult patients with age ranging from 18-65 years. Two studies[15,16] did not mention the age of the participants. Pre-operative pulpal status assessment of these studies showed that eleven studies included teeth with irreversible pulpitis[13–23], of which four studies[19,21,22,24] included teeth indicated for intentional root canal treatment for prosthetic reason. Preoperative periapical status assessment revealed seven studies[14–18,20,23] included teeth with both apical periodontitis or normal periapical status, while one study did not mention the pulpal or periapical diagnosis[25]. Root canal treatments were performed in a single visit in eight studies[13,14,17,19,21,22,24,25] and in two visits in the other five studies[15,16,18,20,23]. In two visit endodontic treatment postoperative endodontic pain evaluation was done at the end of the first appointment. Assessment of the tooth type revealed four studies[14,19,22,24] included both multirooted and single rooted teeth, while one study[17] included only molars and one study included only mandibular fist molars[18]. Three studies[16,20,23] did not mention the type of tooth while four studies included only single rooted teeth[13,15,21,25]. Final irrigation was performed using cold saline at a temperature range of 1.5°C – 6°C with 2.5°C being the most commonly used temperature. Three studies used cold EDTA in the final irrigation regimen followed by the use of cold saline[19,22,24]. The method of irrigation assessment revealed that conventional needle and syringe was used for irrigation in eight studies[14,16–18,20,21,23,25] while five studies used sterile microcannula attached to negative pressure irrigation system (Endovac)[13,15,19,22,24] The final rinse volume ranged from 5 mL[14,18], 10 mL[19,22,24,25] to 20 mL[13,15–17,23] and duration of use ranged between 1 min[18,19,22,24] and 5 min[13–17,25]. Follow up of postoperative pain ranged from 6hrs to 7days and was recorded using a visual analogue scale (VAS)[13–23,25] . Seven studies evaluated preoperative pain levels[14–17,20,21,23], one study excluded patients with preoperative pain[25] and five studies did not evaluate preoperative pain[13,18,19,22,24].

The meta-analysis was conducted on ten studies[14,15,16,17,18,19,22,23,24,25] which have qualified with required data outcome that could be analysed quantitatively. The other studies were excluded as the data reported could not be analysed (which was not in mean+/-sd format). The results are depicted as forest plot in Figure.2. We considered heterogeneity significant if the I^2 values were above 50 %.(Cochrane collaboration). With the meta-analysis conducted for the selected studies, the heterogeneity was insignificant I^2 = 89%, hence we applied the random effect model. The mean difference was -0.26(-0.49, -0.03) thus indicating that the mean VAS score experience was more in control group than the cryotherapy intervention.

Further a subgroup analysis for the different time intervals at which pain was assessed was conducted. With the meta-analysis conducted for the selected studies at 6 hours (I^2 = 85%, MD = -1.15(-2.15, -0.15), p = 0.02) [Figure 3A] and 24hrs (I^2 = 91%, MD = -0.39(-0.79, 0.01), p = 0.05) [Figure. 3B] the mean VAS score experience was more in control group than the cryotherapy intervention. While at 48hrs (I^2 = 09%, MD =-0.02(-0.08, 0.03), p = 0.41) [Figure. 3C] and 72hrs (I^2 = 88%, MD = -0.14(-0.49, 0.21), p= 0.43) [Figure. 3D] there was no significant reduction in postoperative pain.

Risk of bias

The methodological quality of all the studies was done using the risk-of-bias assessment tool as elaborated in Cochrane Handbook for Systematic Review of Interventions (version 5.1.0). The results are presented in [Figure. 4 A and B] as the risk of bias graph and summary respectively which was generated using the RevMan software (v5.3). There are six domains under which the methodology of individual studies is assessed and granted a level of risk. The quality assessment of included twelve studies was done with representation [Figure. 4 A and B]. One study[16] (Jaiswal et al) was excluded for assessment due to the contradiction in the study design. All the studies showed either unclear allocation concealment or no mention of blinding of participants or the outcome assessed which was not possible due to the study design. All the studies had moderate level of methodology overall that could be followed and none had a high risk of level of quality.

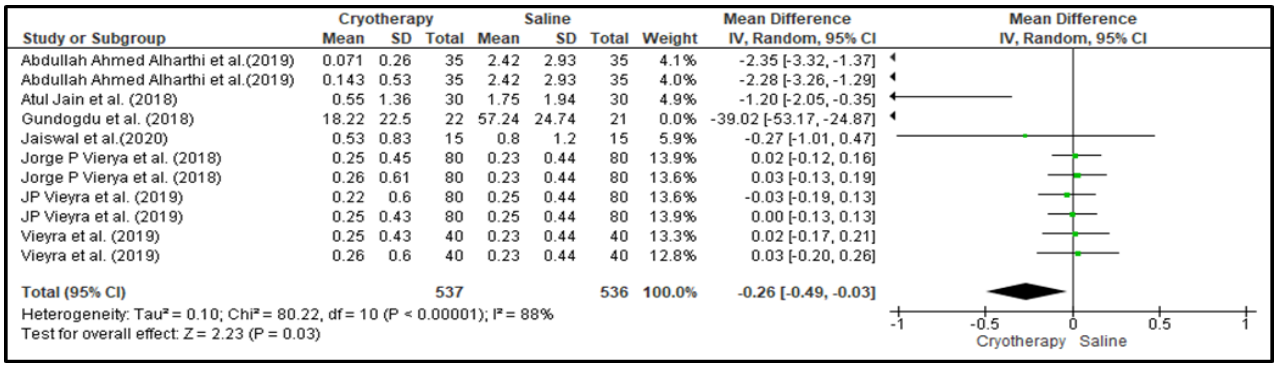
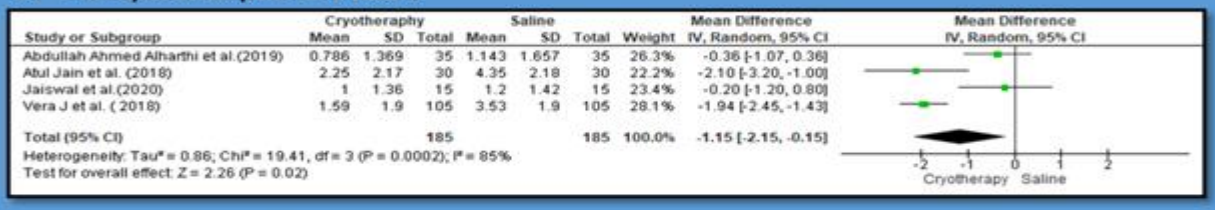


Figure 2: Forest plot

A. Postoperative pain at 6 hours

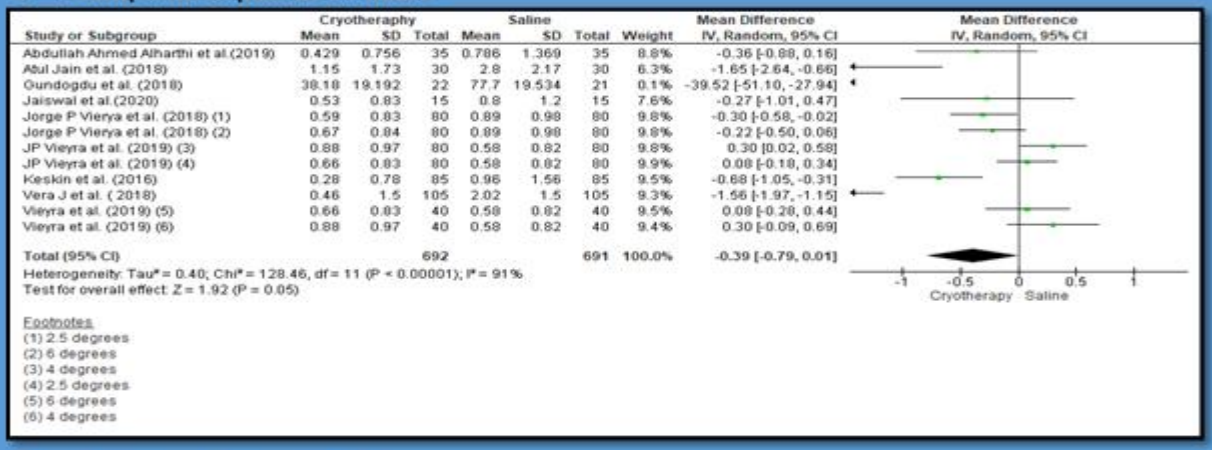


Study or Subgroup	Cryotheraphy Mean	SD	Total	Saline Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Abdullah Ahmed Alharthi et al.(2019)	0.786	1.369	35	1.143	1.657	35	26.3%	-0.36 [-1.07, 0.36]
Atul Jain et al. (2018)	2.25	2.17	30	4.35	2.18	30	22.2%	-2.10 [-3.20, -1.00]
Jaiswal et al.(2020)	1	1.36	15	1.2	1.42	15	23.4%	-0.20 [-1.20, 0.80]
Vera J et al. (2018)	1.59	1.9	105	3.53	1.9	105	28.1%	-1.94 [-2.45, -1.43]
Total (95% CI)			185			185	100.0%	-1.15 [-2.15, -0.15]

Heterogeneity: Tau² = 0.86; Chi² = 19.41, df = 3 (P = 0.0002); I² = 85%
Test for overall effect: Z = 2.26 (P = 0.02)

Mean Difference IV, Random, 95% CI
-2 -1 0 1 2
Cryotherapy Saline

B. Postoperative pain at 24 hours



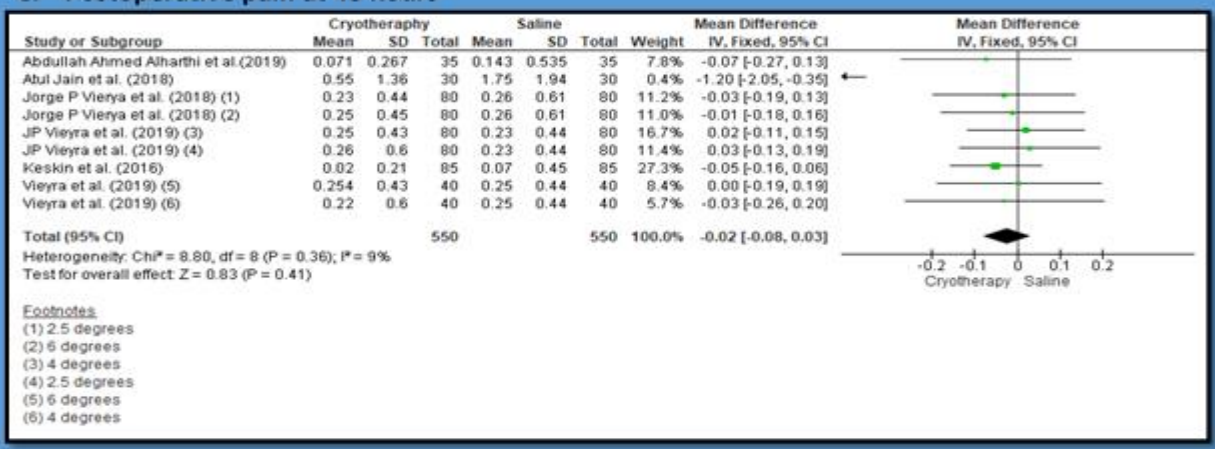
Study or Subgroup	Cryotheraphy Mean	SD	Total	Saline Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Abdullah Ahmed Alharthi et al.(2019)	0.429	0.756	35	0.786	1.369	35	8.8%	-0.36 [-0.88, 0.16]
Atul Jain et al. (2018)	1.15	1.73	30	2.8	2.17	30	6.3%	-1.65 [-2.64, -0.66]
Gundogdu et al. (2018)	38.18	19.192	22	77.7	19.534	21	0.1%	-39.52 [-51.10, -27.94]
Jaiswal et al.(2020)	0.53	0.83	15	0.8	1.2	15	7.6%	-0.27 [-1.01, 0.47]
Jorge P Vieyra et al. (2018) (1)	0.59	0.83	80	0.89	0.98	80	9.8%	-0.30 [-0.58, -0.02]
Jorge P Vieyra et al. (2018) (2)	0.67	0.84	80	0.89	0.98	80	9.8%	-0.22 [-0.50, 0.06]
JP Vieyra et al. (2019) (3)	0.88	0.97	80	0.58	0.82	80	9.8%	0.30 [0.02, 0.58]
JP Vieyra et al. (2019) (4)	0.66	0.83	80	0.58	0.82	80	9.9%	0.08 [-0.18, 0.34]
Keskin et al. (2016)	0.28	0.78	85	0.96	1.56	85	9.5%	-0.68 [-1.05, -0.31]
Vera J et al. (2018)	0.46	1.5	105	2.02	1.5	105	9.3%	-1.56 [-1.97, -1.15]
Vieyra et al. (2019) (5)	0.66	0.83	40	0.58	0.82	40	9.5%	0.08 [-0.28, 0.44]
Vieyra et al. (2019) (6)	0.88	0.97	40	0.58	0.82	40	9.4%	0.30 [-0.09, 0.69]
Total (95% CI)			692			691	100.0%	-0.39 [-0.79, 0.01]

Heterogeneity: Tau² = 0.40; Chi² = 128.46, df = 11 (P < 0.00001); I² = 91%
Test for overall effect: Z = 1.92 (P = 0.05)

Mean Difference IV, Random, 95% CI
-1 -0.5 0 0.5 1
Cryotherapy Saline

Footnotes
(1) 2.5 degrees
(2) 6 degrees
(3) 4 degrees
(4) 2.5 degrees
(5) 6 degrees
(6) 4 degrees

C. Postoperative pain at 48 hours



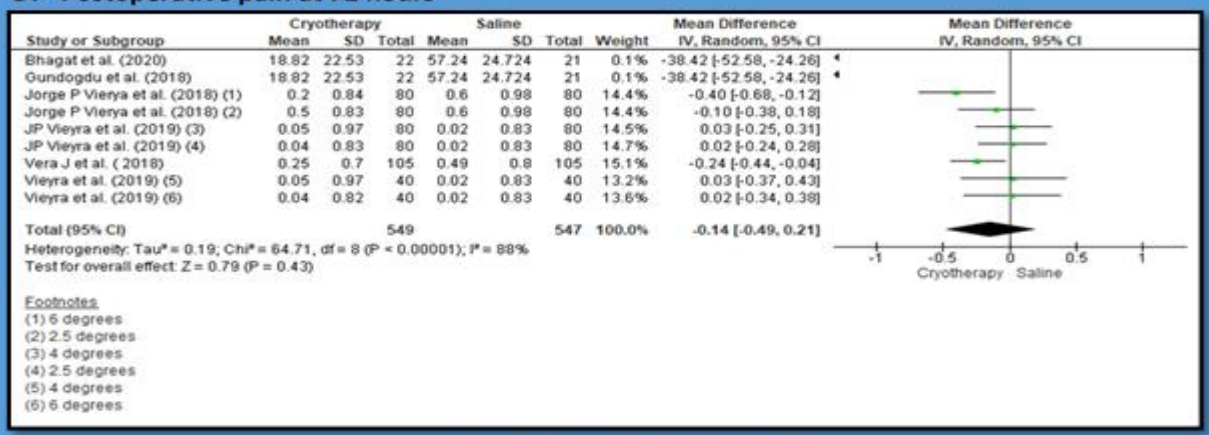
Study or Subgroup	Cryotheraphy Mean	SD	Total	Saline Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Abdullah Ahmed Alharthi et al.(2019)	0.071	0.267	35	0.143	0.535	35	7.8%	-0.07 [-0.27, 0.13]
Atul Jain et al. (2018)	0.55	1.36	30	1.75	1.94	30	0.4%	-1.20 [-2.05, -0.35]
Jorge P Vieyra et al. (2018) (1)	0.23	0.44	80	0.26	0.61	80	11.2%	-0.03 [-0.19, 0.13]
Jorge P Vieyra et al. (2018) (2)	0.25	0.45	80	0.26	0.61	80	11.0%	-0.01 [-0.18, 0.16]
JP Vieyra et al. (2019) (3)	0.25	0.43	80	0.23	0.44	80	16.7%	0.02 [-0.11, 0.15]
JP Vieyra et al. (2019) (4)	0.26	0.6	80	0.23	0.44	80	11.4%	0.03 [-0.13, 0.19]
Keskin et al. (2016)	0.02	0.21	85	0.07	0.45	85	27.3%	-0.05 [-0.16, 0.06]
Vieyra et al. (2019) (5)	0.254	0.43	40	0.25	0.44	40	8.4%	0.00 [-0.19, 0.19]
Vieyra et al. (2019) (6)	0.22	0.6	40	0.25	0.44	40	5.7%	-0.03 [-0.26, 0.20]
Total (95% CI)			550			550	100.0%	-0.02 [-0.08, 0.03]

Heterogeneity: Chi² = 8.80, df = 8 (P = 0.36); I² = 9%
Test for overall effect: Z = 0.83 (P = 0.41)

Mean Difference IV, Fixed, 95% CI
-0.2 -0.1 0 0.1 0.2
Cryotherapy Saline

Footnotes
(1) 2.5 degrees
(2) 6 degrees
(3) 4 degrees
(4) 2.5 degrees
(5) 6 degrees
(6) 4 degrees

D. Postoperative pain at 72 hours



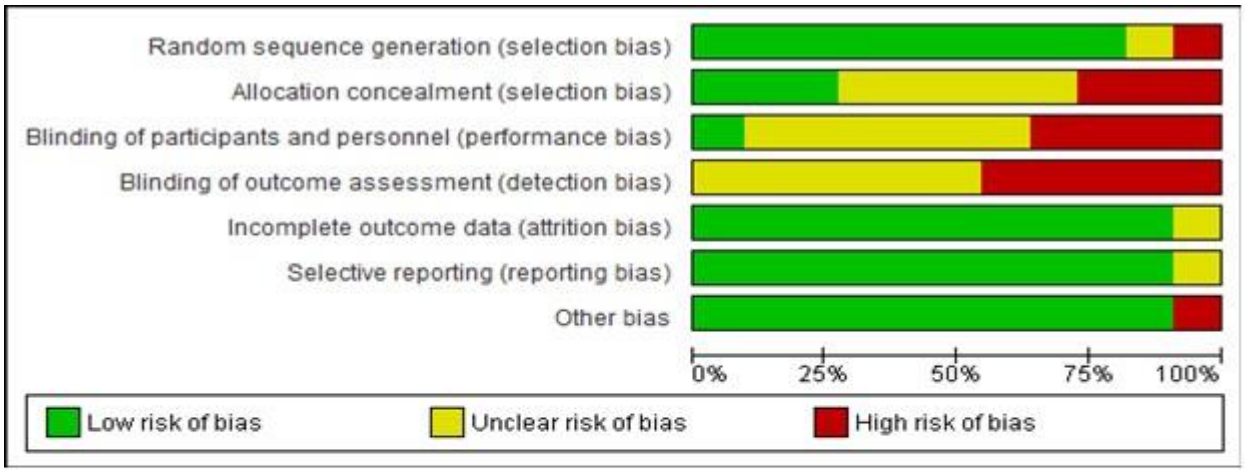
Study or Subgroup	Cryotheraphy Mean	SD	Total	Saline Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Bhagat et al. (2020)	18.82	22.53	22	57.24	24.724	21	0.1%	-38.42 [-52.58, -24.26]
Gundogdu et al. (2018)	18.82	22.53	22	57.24	24.724	21	0.1%	-38.42 [-52.58, -24.26]
Jorge P Vieyra et al. (2018) (1)	0.2	0.84	80	0.6	0.98	80	14.4%	-0.40 [-0.68, -0.12]
Jorge P Vieyra et al. (2018) (2)	0.5	0.83	80	0.6	0.98	80	14.4%	-0.10 [-0.38, 0.18]
JP Vieyra et al. (2019) (3)	0.05	0.97	80	0.02	0.83	80	14.5%	0.03 [-0.25, 0.31]
JP Vieyra et al. (2019) (4)	0.04	0.83	80	0.02	0.83	80	14.7%	0.02 [-0.24, 0.28]
Vera J et al. (2018)	0.25	0.7	105	0.49	0.8	105	15.1%	-0.24 [-0.44, -0.04]
Vieyra et al. (2019) (5)	0.05	0.97	40	0.02	0.83	40	13.2%	0.03 [-0.37, 0.43]
Vieyra et al. (2019) (6)	0.04	0.82	40	0.02	0.83	40	13.6%	0.02 [-0.34, 0.38]
Total (95% CI)			549			547	100.0%	-0.14 [-0.49, 0.21]

Heterogeneity: Tau² = 0.19; Chi² = 64.71, df = 8 (P < 0.00001); I² = 88%
Test for overall effect: Z = 0.79 (P = 0.43)

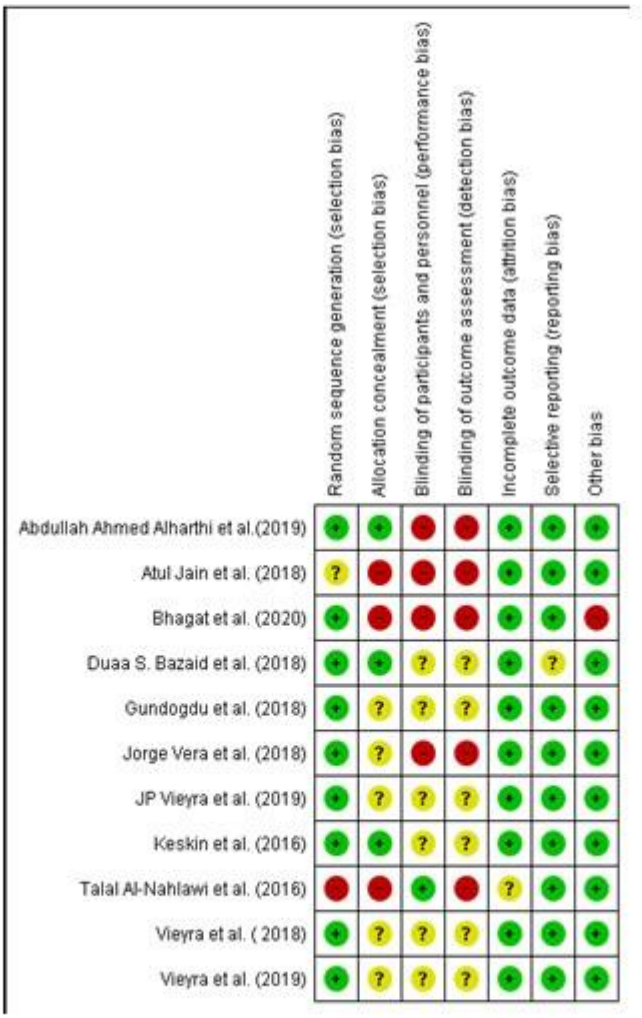
Mean Difference IV, Random, 95% CI
-1 -0.5 0 0.5 1
Cryotherapy Saline

Footnotes
(1) 6 degrees
(2) 2.5 degrees
(3) 4 degrees
(4) 2.5 degrees
(5) 4 degrees
(6) 6 degrees

FIGURE 3: Subgroup analysis



A. Risk of Bias Assessment



B. Risk Assessment Table

Figure 4: Risk of Bias Assessment

DISCUSSION

Necrotic pulps usually provide an environmental condition that is conducive to the establishment of several different oral bacterial species, particularly strictly anaerobic bacteria[3]. Among the studies included in this systematic review only three studies[15,16,23] included teeth with necrotic pulp while teeth with vital pulp were included in other studies[13,17,19–22,24]. Positive relationship between necrotic teeth with painful apical pathosis and flare-up rate was found in most of the studies[26,27].

Also, cases with pre-existing periapical pathology have a higher possibility of exacerbation of pre-existing periapical inflammation which could be attributed to the passage of minor quantity of irritants and microorganisms into the

periapical region[28]. Out of the thirteen articles reviewed, seven articles[14–18,20,23] have included teeth with periapical pathology while five articles[13,19,21,24] have included teeth with no periapical pathology. Six[14,15,17,18,20,23] out of seven studies which included cases with pre-existing periapical inflammation (apical periodontitis) reported reduction in postoperative pain due to the effect of intracanal cryotherapy while one study by Jaiswal et al.[16] reported no significant difference in the postoperative pain with the use of intracanal cryotherapy.

In a randomized multicentre clinical trial by Vera et al.[15], cryotherapy was shown to reduce both the incidence of postoperative pain and the need for medication in patients presenting with a diagnosis of necrotic pulp and symptomatic apical periodontitis[15] Results of the studies which evaluated the effect of cryotherapy in reducing postoperative pain in cases of irreversible pulpitis with and without apical periodontitis[18,20] showed that cryotherapy was effective only in patients diagnosed with apical periodontitis, whereas in patients with only irreversible pulpitis, there was no significant difference in the incidence of postoperative pain between the groups[20]. This could be attributed to the anti –inflammatory effect of cryotherapy which is produced due to the reduction in the temperature, caused by the use of cold saline resulting in decrease in the periapical tissue edema and inflammation[20].

With the increase in preference of single visit endodontics by both the dentist and patient owing to its efficiency and convenience, effectiveness of intracanal cryotherapy in reducing postoperative pain in single visit endodontic treatment should be evaluated. However, the importance of multivisit endodontic treatment in case of necrotic, non-vital teeth with periapical pathology or retreatment cannot be completely overviewed. Hence, it is important to evaluate the effectiveness of intracanal cryotherapy in reducing postoperative pain in both single visit and multivisit endodontics. Recent studies[13,14,17,21,23] that evaluated the effect of cryotherapy on single-visit root canal treatment (RCT), showed a reduction in the pain levels as compared to the control group, while four other studies[19,22,24,25] showed no significant difference between the groups. Multivisit endodontics were performed in four studies[15,16,18,20] in which three studies[15,18,20] showed reduction in postoperative pain after the use of intracanal cryotherapy.

Inclusion of both single and multirooted teeth in studies[14,19,22,24] may also affect the results of the study due to noncategorization of the variables resulting in comparison between teeth with different anatomical configurations. Hence, considering all the above mentioned factors, single rooted anterior teeth and multirooted posterior teeth need to be evaluated separately and cannot be considered at par with each other.

Use of negative apical pressure irrigation by Al Nahlawi et al.[13] in conjunction to intracanal cryotherapy showed a reduction in post-obturation pain at 6 hours, when compared with control group where Endovac system was not used. This could be attributed to the less irritation and more efficient cleaning of the EndoVac system [29]. Thus, four studies[13,15,19,22] included in this review did not include the conventional technique of irrigation and instead have used EndoVac system across all the groups. On the contrary other studies[14,17,18,20,23] using conventional needle and syringe for irrigation, showed a decrease in postoperative pain in cryotherapy group compared to the control group.

A strong positive correlation is seen between preoperative pain and postoperative pain values, where preoperative pain scores significantly influences the immediate postoperative pain score[5,7]. This could be explained by the preoperative presence of an infected root canal system and/or periapical region, which, may become secondarily irritated during treatment resulting in postoperative pain[26]. Seven studies[14–17,20,21,23] included in this review evaluated preoperative pain and found intervention to be effective.

Cryotherapy is derived from Greek words “cryos” denoting “cold” and “therapeia” denoting “cure”[30]. It is a form of treatment in which the body is briefly exposed to very cold temperatures in order to bring about healing and other therapeutic results. Cryotherapy can be applied to the inflamed periradicular tissues by irrigating agents like EDTA or saline at lower temperature, as final irrigating agents[21]. Cold EDTA was used in three studies[19,22,24] followed by application of cold saline while ten other studies[13–18,20,21,23,25] used only cold saline as the final irrigating agent. Irrigating agents were used at a lower temperature range of 1.5°C – 6°C, with 2.5°C being the most commonly used temperature. This can be attributed to the findings of Franz and Iggo[31] which stated that lowering the body temperature decreases peripheral nerve conduction, and in particular, when it reaches about 7°C, there is complete deactivation of myelinated A-δ fibres, whereas deactivation of nonmyelinated C-fibre occurs at about 3°C. Lower temperatures used in cryotherapy also triggers thermal receptors, which on stimulation blocks nociception within the spinal cord and as a result reduces the transmission of painful stimuli. Vera et al.[15] in his in vitro study demonstrated a reduction in the external root surface temperature by more than 10°C for 4 minutes with the use of 2.5°C saline solution as the final irrigating agent. This decrease in temperature is said to produce local anti-inflammatory effect which is beneficial to inflamed periradicular tissues. An optimal dosage for cryotherapy has not been determined; the two studies[14,18] included in this review used a volume of 5ml, while five studies[19,21,22,24,25] used 10 ml and five studies[13,15–17,23] used 20ml of cold irrigating solution over a duration of 2-5 mins.

Postoperative pain most often occurs during the first 24–48 hours after obturation, and generally recedes in a few hours, although it occasionally persists for several days[5]. Thus any strategy used for reduction of postoperative pain

should be most effective during the first 24-48 hours. Cryotherapy has been found to be effective in reducing postoperative pain at 6hrs[13,15,18,21,23], 24hrs [13–15,17,18,20,21,23], 48hrs[13,14,20,21] and 72hrs [15,17,23]. This can be attributed to the three basic physiologic tissue responses -decrease in metabolic activity, blood flow and inhibition in neural receptors. Drop in local temperature is the first physiologic tissue response to cryotherapy, resulting in reduced cellular metabolism. This causes cells to use less oxygen and reduces blood flow as induced by vasoconstriction, which produces an antiedema effect and, hence, a consequent reduction of inflammation[32].

Meta-analysis was conducted for the eligible studies which accounted for ten[14,15,16,17,18,19,22,23,24,25] studies in which the data outcome was analyzed quantatively. Outcomes were extracted based on VAS score as the pain parameter. The heterogeneity was higher hence random effect model was applied and the cumulative mean difference was derived. The mean difference showed that the VAS score was higher in the control group than the cryotherapy group. This indicated the effectiveness of intervention of intracanal cryotherapy in reducing pain during endodontic therapy rather than just using saline at room temperature. The temperature of solution used during irrigation showed variation at 2°C, 4°C and 6°C. The use and effect of cryotherapy was thus proved statistically effective in our systematic review and meta-analysis.

Limitations

The variability among the studies with respect to the method of application of intracanal cryotherapy, such as the use of different irrigation techniques, the different temperatures and volumes used could be seen as a limitation. Direct extrapolation of the dependent and independent variables in assessment of post-endodontic pain which is multifactorial in nature may not be possible in randomized clinical trials. Technical difficulties in maintaining the temperature of the irrigant have neither been specified nor addressed.

Future studies

Effect of intracanal cryotherapy on the physiological healing process of periapical tissues and the duration required for complete healing to occur needs to be further evaluated. Standardizing should be taken into consideration in order to eliminate potential confounding factors and allow the analysis of these factors individually. Also, further studies need to be undertaken to identify an optimal dosage, duration and volume of intracanal cryotherapy.

CONCLUSION

Within the limitations of the study, it can be concluded that intracanal cryotherapy using cold saline or 17% EDTA at a temperature range of 2.5°C to 6°C as final irrigating agent helps in reducing postoperative pain at 6 hrs and 24 hrs following single-visit or multi visit root canal treatment in teeth diagnosed with irreversible pulpitis with apical periodontitis. Thus, intracanal cryotherapy can be suggested as a simple, cost-effective, and non-toxic method for management of postoperative pain following endodontic treatment.

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Source of Support: The author(s) received no financial support for the research, authorship, and/or publication of this article.

Conflict of Interest: The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.