IJPSR (2024), Volume 15, Issue 11 (Research Article)

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 02 June 2024; received in revised form, 16 July 2024; accepted, 16 October 2024; published 01 November 2024

EVALUATION OF THE ANALGESIC EFFECT OF THE COMBINATION OF INTRA-CANAL ANALGESICS AND CRYOTHERAPY IN CONTROLLING PAIN DURING NON-SURGICAL ROOT CANAL TREATMENT - A RANDOMIZED CONTROL STUDY

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Keywords:

Cryotherapy, Endodontic pain, Intra-canal analgesics, Irrigant, Randomized Clinical Trial

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ABSTRACT: Aim: Patients often experience varying degrees of pain during or after root canal therapy. This study aimed to the analgesic effect of the combination of intra-canal analgesics and Cryotherapy in controlling pain during non-surgical root canal treatment. **Methodology:** This Double-blind, parallel, randomized clinical trial included 76 patients (42 men and 34 women) within the age range of 18-65 years with maxillary or mandibular premolars having symptomatic irreversible pulpitis or symptomatic apical periodontitis. Patients were divided into two groups: Group 1 received precooled analgesic solution for irrigation during root canal treatment, Group 2 used Ketorol DT tablets during and post root canal treatment. Pain levels were assessed using the visual analogue scale (VAS) before treatment, during treatment, and at 2, 6, 12, 24 hours inter and post-treatment. Statistical analysis included mean, standard deviation, Mann Whitney U test and Wilcoxon Signed Rank Post Hoc tests. **Results:** There is a significant decrease in the levels of pain in the patients at 6 hours post cleaning and shaping across both the groups. It is also observed that the decrease in the post operative pain at 6 hours interval post cleaning and shaping is significantly higher in the precooled analgesic group when compared to the oral medication group. **Conclusion:** Enhanced analgesic effect of pre cooled analgesic is effective in reduction of interappointment and post-operative endodontic pain.

INTRODUCTION: Patients frequently encounter flare-ups or postoperative pain during root canal treatments, leading to discomfort and anxiety that can strain the patient-doctor relationship. The incidence of post-endodontic pain (PEP) varies widely, from 3-58% [1, 2], with the highest prevalence at 40% within 24 hours, decreasing to 11% after a week [3].

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DOI: 10.13040/IJPSR.0975-8232.15(11).3371-78

This article can be accessed online on www.ijpsr.com

DOI link: https://doi.org/10.13040/IJPSR.0975-8232.15(11).3371-78

Pain is most intense in the first six hours and diminishes gradually. Factors influencing PEP include the condition of pulp and peri-radicular tissues, immune responses, psychological factors, pre-operative pain levels, and procedural issues like inadequate root canal instrumentation [4, 5].

To manage PEP, various strategies have been explored, such as prophylactic analgesics, long-acting anesthetics, occlusal reduction, corticosteroids, and cryotherapy [6]. Cryotherapy, effective in reducing pain, edema, inflammation, and recovery time, works by causing vasoconstriction and slowing cellular metabolism. This reduces tissue damage, oxygen demand, and

free radical production, making it beneficial in endodontic treatment [7, 8, 9]. Intracanal analgesics, such as aceclofenac and mefenamic acid, have shown efficacy in reducing postoperative pain [10]. Research indicates that intracanal use of ketorolac tromethamine provides significant pain relief at 12 and 24-hour intervals, although its immediate short-term effect is comparable to other methods [11, 12]. This study proposes combining intracanal analgesics with cryotherapy to alleviate pain during and after endodontic treatment in patients with symptomatic irreversible pulpitis. The goal is to achieve short-term pain relief through cryotherapy and extended pain alleviation with intracanal analgesics. This combined approach aims to enhance overall pain management during and after root canal procedures.

MATERIAL AND METHODOLOGY: This study, approved by the Kempegowda Institute of Medical Sciences Ethical Committee (CTRI/2023/09/057346), was conducted at Vokkaligara Sangha Dental College. It followed a double-blinded, parallel, randomized controlled design with a 1:1 allocation ratio. While the patient and assessors were blinded, the operator was not due to the nature of the treatment protocols. The study, adhering to Consort guidelines, involved 76 patients diagnosed with symptomatic irreversible pulpit is requiring non-surgical root canal treatment with the inclusion and exclusion criteria detailed in **Table 1**. Sample size was determined based on pilot study results, with 38 patients per group, ensuring 80% study power and a 0.05 error margin [13]. Patients, 42 men and 34 women aged 18-65, were randomly assigned to two groups using digital randomization software and block randomization with sequentially numbered, opaque, sealed envelopes (SNOSE) [14].

TABLE 1: INCLUSION AND EXCLUSION CRITERIA FOR THE STUDY

Inclusion Criteria	Exclusion Criteria
Patients diagnosed with maxillary or mandibular premolars having symptomatic irreversible pulpitis or symptomatic apical periodontitis	Patients with systemic disorders that could alter pain perception like diabetes, schizophrenia etc.
ASA type 1 and 2 patients who have not been on NSAIDS or steroid medications in the past 1 day. (18-65 years)	Patients with a history of allergies to local anesthesia or analgesic drugs.
Patients with a pre-operative pain score of $\geq$ 5 on numerical scale	Fractured teeth, Endodontically treated teeth, immature apices and external root resorption
	Presence of other symptomatic teeth that cause pain and discomfort in patients other than tooth of interest.

Group 1: Use of precooled analgesic solution for irrigation during root canal treatment.

Group 2: Use of Ketorol DT tablets during and post root canal treatment.

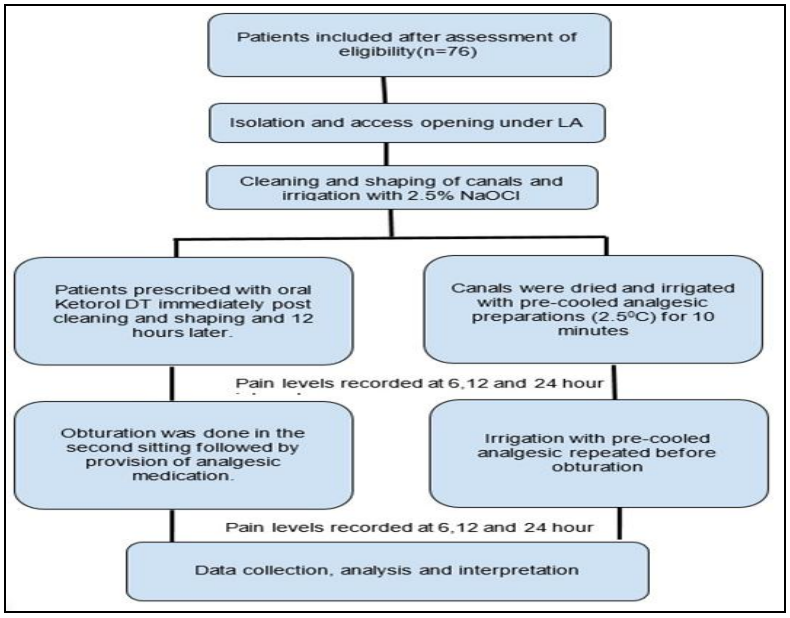

FIG. 1: DETAILED FLOWCHART OF CLINICAL PROTOCOL FOR THE STUDY.

Procedures included anesthetizing and isolating the tooth, access cavity preparation, pulp chamber debridement, canal shaping with Hyflex CM files, and irrigation with 3% NaOCl and 17% EDTA. For Group 1, precooled analgesic solution (Ketorolac tromethamine) was prepared and stored at 1-3°C for final irrigation. Group 2 received oral Ketorol DT tablets. Pain levels were assessed preoperatively and at multiple intervals post-treatment (immediately, 6 hours, 12 hours, and 24 hours) using a visual analog scale by a different operator. After 48 hours, patients returned for continuation and completion of treatment, with pain reassessed before and after obturation. Group 1 received additional precooled solution irrigation, while Group 2 continued with Ketorol DT tablets. Emergency pain medication was prescribed if necessary. The study aimed to evaluate the effectiveness of combining intracanal analgesics and cryotherapy for managing pain during and after endodontic treatment. The detailed methodology is depicted in a flowchart **Fig. 1.**

RESULTS: The pain scores of the patients were tabulated on excel sheets to formulate the master chart of the study. Statistical analysis of the data by subjecting them to Mann Whitney U test and Wilcoxon Signed Rank Post Hoc tests revealed that there is a significant decrease in the levels of pain in the patients at 6 hours post cleaning and shaping across both experimental groups as illustrated in **Fig. 2.**

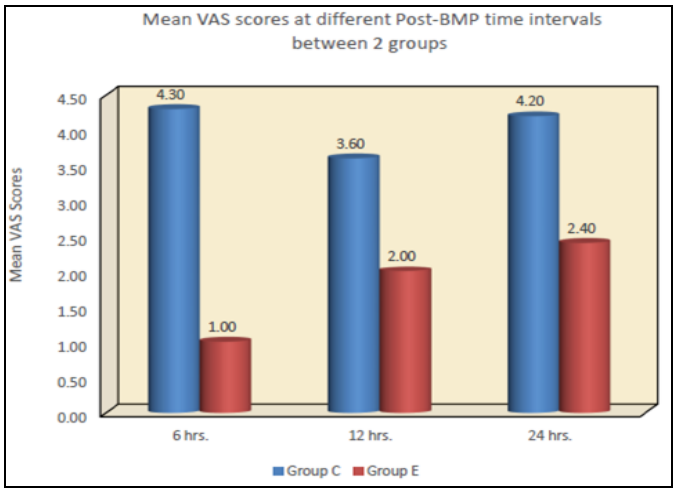

FIG. 2: MEAN VAS SCORES AT DIFFERENT TIME INTERVALS AFTER THE 1ST SITTING ACROSS BOTH GROUPS

The correlation of the pain score levels at interappointment and post obturation time intervals for both groups have been tabulated in **Table 2, 3** and **4**. It is also observed that the decrease in the post operative pain at 6 hours interval post cleaning and shaping is significantly higher in the precooled analgesic group when compared to the oral medication group.

TABLE 2: COMPARISON OF MEAN VAS SCORES AT DIFFERENT POST-BMP TIME INTERVALS BETWEEN 2 GROUPS USING MANN WHITNEY TEST

Time	Groups	N	Mean	SD	Mean Diff	p-value
6 hrs	Group C	10	4.30	1.77	3.30	0.002
	Group E	10	1.00	1.33		
12 hrs	Group C	10	3.60	1.78	1.60	0.04
	Group E	10	2.00	1.63		
24 hrs	Group C	10	4.20	1.99	1.80	0.04
	Group E	10	2.40	1.84		

$p < 0.05$, indicating statistical significance.

TABLE 3: COMPARISON OF MEAN VAS SCORES AT DIFFERENT POST-OBTURATION PERIODS BETWEEN 2 GROUPS USING MANN WHITNEY TEST

Time	Group	N	Mean	SD	Mean Diff	p-value
6 hrs	Group C	10	2.10	1.52	1.60	0.01*
	Group E	10	0.50	0.85		

12 hrs	Group C	10	1.00	0.94	1.00	0.005*
	Group E	10	0.00	0.00		
24 hrs	Group C	10	0.20	0.42	0.20	0.15
	Group E	10	0.00	0.00		

$p < 0.05$, indicating statistical significance.

TABLE 4: COMPARISON OF MEAN VAS SCORES BETWEEN DIFFERENT POST OBTURATION TIME INTERVALS IN EACH GROUP USING FRIEDMAN'S TEST FOLLOWED BY WILCOXON SIGNED RANK POST HOC TEST

Group	Time	N	Mean	SD	p-value [a]	Sig. Diff	p-value [a]
Group C	6 hrs	10	2.10	1.52	0.001*	6h vs 12h	0.03*
	12 hrs	10	1.00	0.94		6h vs 24h	0.01*
	24 hrs	10	0.20	0.42		12h vs 24h	0.04*
Group E	6 hrs	10	0.50	0.85	0.06	6h vs 12h	..
	12 hrs	10	0.00	0.00		6h vs 24h	..
	24 hrs	10	0.00	0.00		12h vs 24h	..

$p < 0.05$, indicating statistical significance.

Comparison of the mean pain score for both the groups at 6 hours, 12 hours and 24 hours post cleaning and shaping reveal that the pain levels are found to be significantly less in the precooled analgesic group when compared to oral medication group across all time intervals. Observation of the pain levels across both groups post obturation reveal that there is a significant difference between the preoperative pain and post operative pain levels across both the groups as displayed in **Fig. 3**. Post operative pain score evaluation of both groups revealed that the postoperative scores of precooled analgesics at 6 hours, 12 hours and 24 hours was less than the oral medication group. The variation in pain levels of patients of both experimental and control groups across different time intervals post the first and second sittings have been illustrated in **Fig. 4** and **5**. None of the patients required the emergency pain medication across both the groups.

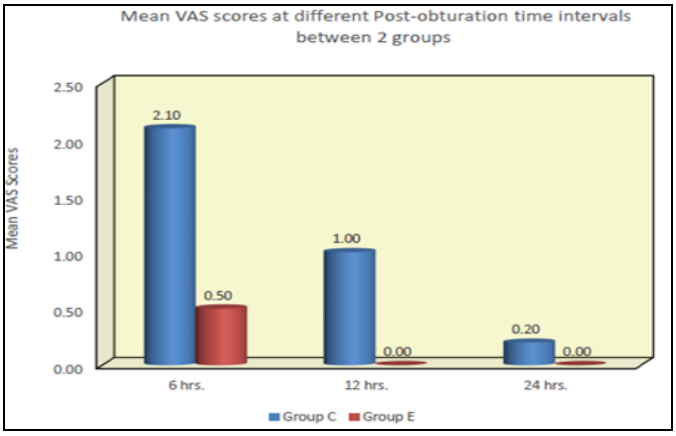

FIG. 3: MEAN VAS SCORES AT DIFFERENT TIME INTERVALS AFTER THE 2ND SITTING ACROSS BOTH GROUPS

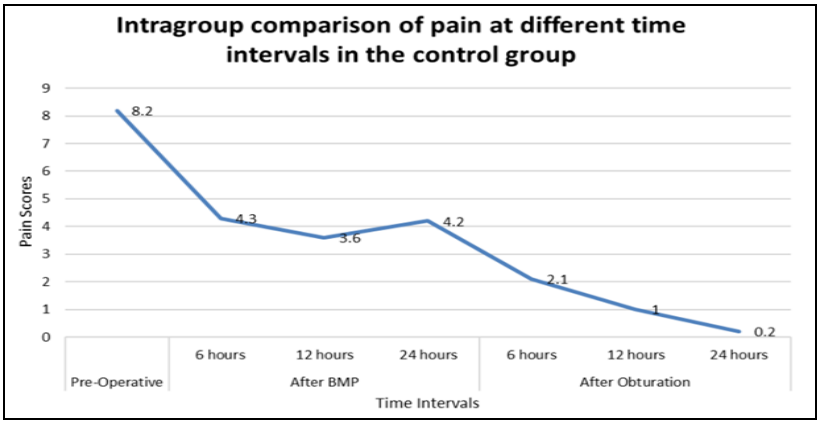

FIG. 4: VARIATION IN THE PAIN LEVELS AT DIFFERENT TIME PERIOD OF EVALUATION IN CONTROL GROUP PATIENTS

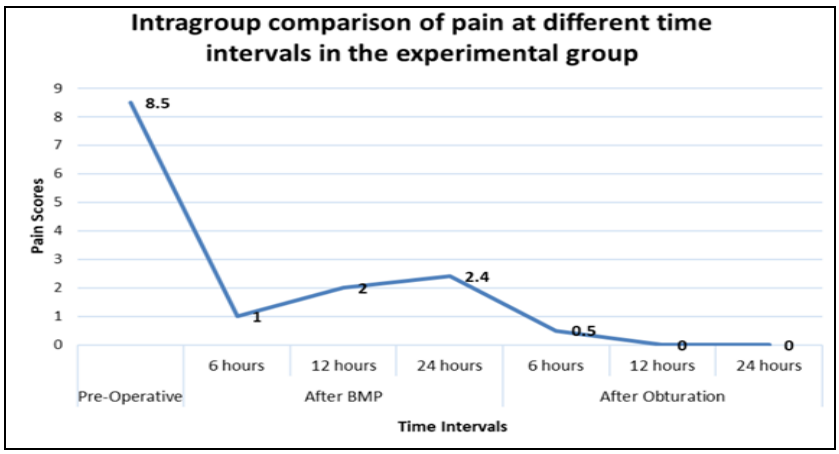

FIG. 5: VARIATION IN PAIN LEVELS AT DIFFERENT TIME PERIODS OF EVALUATION IN THE COMBINATION ANALGESIC STRATEGY GROUP

DISCUSSION: Management of pain during root canal treatment is essential to ensure a comfortable experience for the patients. The classic presentation of post-endodontic pain is similar to the typical acute inflammatory reaction in any other connective tissue in the body. It consists of vasodilation, increased vascular permeability and transmigration of leukocytes from the blood vessels to the site of injury [12]. These biological activities are induced by the inflammatory mediators which cause tissue damage and result in pain and swelling.

Every pain management strategy is based on the management of these inflammatory mediators and controls the inflammatory response produced by their action on the local tissues. This study mainly focuses on controlling the inflammatory response localized to the region of interest without a systemic influence on the patients. Both the strategies adopted for pain management in this study, cryotherapy and intracanal analgesics act on the periapical region and produce a localized response to that region to alleviate pain. This helps manage pain in patients who have side effects such as gastrointestinal intolerance, renal, hepatic and respiratory disorders when they consume analgesic medications.

Cryotherapy is a highly effective analgesic technique that is influenced by various factors such as the heat difference between the tissues and the object applied, the thermal conductivity of the tissues and exposure time [7]. The clinical manifestations of cryotherapy are based on the physiological responses that follow the application of cold such as Decrease in local blood flow, Inhibition of neural receptors in the skin and subcutaneous tissues, Increase or decrease in cellular metabolic activity.

The use of analgesics has produced a significant decrease in the concentration of inflammatory mediators at the periapical region as reported by Tuncer *et al* in 2014 [15]. Martin Rogers *et al* and Penniston *et al* have evaluated the use of Ketorolac Tromethamine to handle post-operative pain by using it as an intracanal irrigant [12, 16]. They reported that Ketorolac tromethamine produced a significant difference in postoperative pain when compared to control groups without causing any cytotoxic effects in the periapical region.

This study aims to combine the mechanisms of both pain-alleviating strategies to produce sustained pain relief in patients during intraoperative and post-operative intervals. Application of cold irrigant solutions as intracanal irrigants for a prescribed duration of time produces a substantial decrease in the temperature at the periapical region which results in vasoconstriction and the resultant decrease in the influx of pain causing inflammatory mediators. The intensity of the vasoconstriction effect reaches the highest value at a temperature of 15 degrees Celsius and it has been reported that lowering the body temperature decreases peripheral nerve conduction in particular when it reaches below 7 degrees celsius there is complete deactivation of myelinated A-delta fibers whereas deactivation of unmyelinated C fibers occurs at 3-degree celsius as reported by Franz and Iggo [17]. Cryotherapy

activates temperature-sensitive thermoreceptors thereby blocking nociception which causes pain in patients inter and post-endodontic treatment. Thus the resultant analgesic effect is mediated by the decrease in the release of inflammatory mediators and slower conduction of neural pain signals [18].

Intracanal analgesics have been reported to produce a substantial reduction in the concentration of Substance P as reported by Lavanya *et al* in their study in which they evaluated the efficiency of using Ketorol DT injectable solution as a stand-alone irrigant for single sitting root canal treatment [19]. It was found that Ketorolac DT, used as an intracanal irrigant produced the most reduction in Substance P and as a result reduced postoperative pain when compared to sodium hypochlorite and saline.

The use of pre-cooled analgesics has produced a substantial reduction in pain levels in our study which has been conducted following a methodology similar to cryotherapy and intracanal analgesics studies. The results of the study when compared to the effect produced in the other comparative studies reveal that the combination protocol produces an enhanced reduction in pain when compared to the individual pain control strategies.

This can be attributed to slower absorption of the small concentrations of ketorolac DT that has permeated to the periapical region because of the vasoconstrictive effect produced by the cryotherapy. This prolongs the duration of the analgesic effect in the periapical region and thus sustains pain relief for up to 10 - 14 hours post-endodontic treatment. The reduced accumulation of inflammatory markers due to vasoconstriction produces phase 1 analgesia at the periapical region while phase 2 analgesia is initiated when ketorolac DT in the periapical region gets absorbed in the local circulation to produce further analgesic effects. This two stage onset of analgesia maintains anti-inflammatory effect in the region for a sustained duration of time than the individual strategies. The effects of phase 1 and phase 2 analgesia can be observed in figure 4 across the time durations of 6 hours, 12 hours and 24 hours in between the appointments as well post completion of endodontic treatment. The analgesic effect of the combination analgesic strategy is highlighted in the inter appointment duration where a significant decrease in the pain levels when compared to the pre-operative pain is observed. Maximum analgesic effect is observed at 6 hours of duration in the interappointment period post cryotherapeutic irrigation of the dissolved irrigant. The effect of cryotherapy is sustained up to a duration of 6 - 8 hours after which the vasoconstrictive effects of cryotherapy are reduced and analgesic metabolism is accelerated to produce sustained analgesia up to 12-15 hours after irrigation.

Continuous irrigation of a localized region with precooled irrigants cooled to a temperature of 2-4^{0}C results in the onset of Lewis-Hunting reaction, which produces alternating bouts of vasoconstriction and vasodilation for every 15 minutes up to 90 minutes [20, 21]. The analgesic effect of the intracanal irrigant is initiated in the vasodilatory duration during which the drug is absorbed into the periapical tissues in the local environment. The combined effect of the analgesic strategy reduces the accumulation of inflammatory mediators such as IL-6, PGE2, substance P etc. which reduces the overall onset of pain for the patients across inter appointment and post appointment durations. The pain levels are found to be significantly less in patients post endodontic treatment when compared to the pre endodontic pain levels with both groups reporting decreased pain levels. This reduction could be attributed to the decrease in the microbial load during cleaning and shaping and obturation of root canals.

The results of this study reveal the enhanced analgesic effect of the combination strategy and further evidence and understanding regarding the same can be obtained by performing this study on a larger sample population. Better delivery of the analgesic medication under cryotherapy could be achieved by using modified preparations such as microspheres, nanoparticles or hydrogels that could achieve enhanced analgesia. These modified preparations can help in standardizing the protocol and optimizing the analgesic effect achieved by the protocol. Future studies can be conducted with modified preparations of the analgesic medication as well as other drugs that can help reduce pain and inflammation such as ibuprofen and celecoxib.

ACKNOWLEDGEMENT: Nil.

Source of Funding: Nil.

CONFLICTS OF INTEREST: None.

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How to cite this article:
Sundaravaradhan R, Rao A and Anithakumari R: Evaluation of the analgesic effect of the combination of intra-canal analgesics and cryotherapy in controlling pain during non-surgical root canal treatment - a randomized control study. Int J Pharm Sci & Res 2024; 15(11): 3371-78. doi: 10.13040/IJPSR.0975-8232.15(11).3371-78.

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