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Original Article

Evaluation of The Effect of Cryotherapy versus Post-Operative Ibuprofen Medication on Postoperative Pain in Mandibular Molar Teeth with Symptomatic Irreversible Pulpitis: A Randomized Controlled Trial

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Abstract

Aim: This research aimed to compare the effect of cryotherapy versus ibuprofen medication or normal saline regarding postoperative pain in mandibular molars with symptomatic irreversible pulpitis in a randomized clinical trial.

Subjects and methods: Thirty-six subjects were divided into three groups by random allocation. Access and chemomechanical preparation till size 30-35/.04 using M PRO gold rotary files were done. Group (A) received (20ml) normal saline irrigation at room temperature, group (B) received postoperative ibuprofen medication (400mg) immediately after root canal treatment, and group (C) received (20ml) intracanal cryotherapy irrigation at 2.5°C for 5 minutes. Obturation was performed using modified lateral condensation technique. Pain was recorded pre- and postoperatively at 6, 24, and 48 hours using modified visual analogue scale. Statistical analysis was performed. Significance level was set at ($p \leq 0.05$).

Results: Group C showed significantly lower postoperative pain (33.3%-median 0) compared to group B (83.4%-median 1.5) and group A (100%-median 3) at 6 hours, meanwhile, group B pain scores were significantly lower than group A ($p < 0.001$). There was no significant difference between groups B and C at 24 and 48 hours ($p>0.05$) while both being significantly lower than group A. There was no significant difference between groups regarding analgesic intake ($p>0.05$).

Conclusion: Using either of intracanal cryotherapy as a final irrigant or 400mg ibuprofen post-operative medication proved to be significantly effective in decreasing postoperative pain severity and the need for rescue medication.

Keywords: Cold saline; Intracanal cryotherapy; Post-operative ibuprofen; Postoperative pain.

I. INTRODUCTION

Pain is a frequent complication that reveals after few days or hours following endodontic therapy. According to reports, post-operative pain prevalence varied from 3% to 58% **(Sathorn et al, 2008)**. Causes of post-operative pain could be chemical, mechanical, and/or microbial insults that initiate an acute inflammation in the periapical tissues. The resulting pain may range from slight discomfort to severe pain that may sometimes exceed the pretreatment severity levels **(Siqueira et al, 2002)**. Incomplete canal debridement, debris and chemicals extrusion to the periapical area, and apical over instrumentation could be assumed as main causes of post-operative pain **(Walton 2002)**.

Various modalities have been investigated in literature that aim to reduce post-operative pain following root canal treatment. These include prescribing pre- and post-operative analgesics, application of intra-canal medicaments, administration of anesthetic agents, and using certain irrigation techniques as final irrigation with cold saline (intracanal cryotherapy) **(Walton 2002; AlRahabi 2017; Sadaf et al, 2020; Di Spirito et al, 2022).**

Post-operative medications have been considered the gold standard for relief of post-operative pain. They aim to reduce the amount of pain perception triggered by the irritated periapical area. Non-steroidal anti-inflammatory drugs (NSAIDs) have been known to be the most effective medications. Once distributed in blood, they reach injury area and inhibit releasing inflammatory mediators, hence blocking the formation of prostaglandins (PGs) which are responsible for pain perception. Ibuprofen is the most commonly used NSAIDs with many clinical studies that demonstrated high efficacy in controlling dental pain **(Parirokh et al, 2014; Di Spirito et al, 2022)**. Many investigations recommended taking ibuprofen regularly rather than on-demand to achieve maximum efficacy in reduction of post-operative pain **(Parirokh et al, 2014)**. On the other hand, all NSAIDs may predispose to some systemic harm such as gastrointestinal adverse effects, especially if used regularly **(Parirokh et al, 2014)**.

A recent technique of intracanal cryotherapy was suggested to employ the impact of cold saline irrigation on decreasing the tissue inflammation. Studies have demonstrated that application of cold saline with average temperature ranging from 0-6ºC on the injured periapical area, results in adequate vasoconstriction and reduce metabolic activity of cells **(Keskin et al, 2017; Gundogdu & Arslan 2018)**. Consequently, release of inflammatory mediators slows down to a level that is insufficient to trigger severe post-operative pain response. Several clinical trials that used different temperatures of cold saline with various exposure time, have provided a growing evidence that supports the use of intracanal cryotherapy in reduction of post-operative pain **(Gundogdu & Arslan 2018; Alharthi et al, 2019; Gupta et al, 2021)**. Furthermore, it was proposed as an adjunctive therapy besides analgesics to control post-operative pain. However, additional clinical studies are required to justify using intracanal cryotherapy as a possible alternative to medication in the relief of post-operative pain to overcome medications' side effects and their inappropriate intake by patients **(Akpinar & Kaya 2021)**.

Therefore, this study was conducted to evaluate the effectiveness of intracanal cryotherapy versus ibuprofen medication or normal saline in regarding post-operative pain in cases with symptomatic irreversible pulpitis in lower molars. The null hypothesis was that there was no difference in effect regarding post-operative pain between intracanal cryotherapy and ibuprofen medication or normal saline in cases with symptomatic irreversible pulpitis in mandibular molar teeth.

II. SUBJECTS AND METHODS

The Ethics Committee of Cairo University's Faculty of Dentistry in Egypt gave its approval to this prospective, double-blind, parallel,

randomized clinical investigation with 1:1:1 allocation ratio (Approval No. 19/5/22). The study protocol was registered with the NCT number (NCT05341999) on www.clinicaltrial.gov, and the PRIRATE criteria (2020) for randomized trials were followed **(Nagendrababu et al, 2020)**.

Patients who were referred by Cairo University's Faculty of Dentistry's Department of Endodontics and had non-contributary medical history, between May 2022 and September 2022 were screened.

In order to apply a statistical test of the null hypothesis—which states that there is no difference in post-operative pain between the various tested groups—a power analysis was created with sufficient power. Using power of 80%, alpha level of 0.05, beta of 0.2, and an estimated mean for group 2 derived from the findings of a prior investigation by **Alharthi et al, 2019**. It was anticipated that there would be thirty cases in total (10 cases per group). To account for potential dropouts, the sample size was increased by 20% to 36 cases (12 cases per group).

The study had three treatment groups (cryotherapy, postoperative medication, and control group). A random sequence generator software (http://www.random.org/) was used to randomly place patients in each group. A single master degree student completed all root canal treatments in one session.

The study was double-blinded where the participants (i.e. outcome assessors) and the statistician were not informed of the intervention used. Numbers of patients were written on 8 folded papers and placed in an opaque sealed envelope. When an outpatient met the eligibility criteria, the patient was asked to draw from the concealed envelope containing a number which determined his assignment to one of the 3 groups according to the randomized sequence. The assistant supervisor created the random sequence and allocated study participants to one of the 3 groups. Informed consent papers were collected and every person involved in the trial were told about the research.

Inclusion and exclusion criteria:

The inclusion criteria were patients who ranged in age from 18 to 60, did not have any systemic conditions or allergies to local anaesthesia, mandibular molar teeth with preoperative sharp (moderate or severe) pain, positive reaction to cold sensibility test by ethyl chloride (Egyptian Pharmaceutical Trading Company, Egypt) and normal periapical radiographic appearance or a little widening in lamina dura

The exclusion criteria were teeth having necrotic pulp, history or presence of fistulous tract or swelling, chronic / acute apical abscess, evidence of periodontal bone loss, non-steroidal anti-inflammatory drug allergy, and patients who took analgesics, antibiotics, or anti-inflammatories within a week.

Treatment procedure:

After confirming with cold sensibility testing using ethyl chloride spray that teeth were vital, modified Visual Analogue Scale (VAS) was given to the participants and the patients were taught how to record the pain level. It is a line numbered from 0-10 (0, “no pain” / 1–3, “mild pain” / 4–6, “moderate pain” / 7-10, “severe pain”). The participants were instructed to record the pain level before treatment. An initial radiograph was taken (FONA Digital ScaNeo imaging plate size 2). The tooth was anaesthetized by inferior alveolar nerve block technique by 2% lidocaine HCL with 1:100000 adrenaline (1.8 ml, Novocol Pharmaceutical of Canada, Ontario, Canada), and intrapulpal injection was the supplemental anesthesia of choice when needed. Access cavity opened using a round bur and an endo-z bur (Dentsply, Ballaigues, Switzerland). Further confirmation of the diagnosis was achieved upon visualization of bleeding from access.

The rubber dam (Dental Dam, Sanctuary Dental, UK), was used to isolate the tooth, and the canal was explored for patency using #10 K-files (MANI, Industrial park, Japan) in a watch-winding motion. Working length was measured by Root ZX mini electronic apex locator (J. Morita, USA) and confirmed using periapical radiograph to be (0.5 -1) mm from radiographic apex. Mechanical preparation was done by M PRO gold rotary instruments (IMD, Shanghai, China) in continuous rotary brushing motion ending the preparation at size #35/.04 in roots with one canal and #30/.04 in roots with two canals.

Each canal was irrigated by 3 ml 2.5% sodium hypochlorite irrigant (Medical company, Egypt) between each subsequent instrument, and introduced to the canal using a 30_gauge side vented needle placed short 1mm from the WL without binding. Canals were dried using sterile paper points.

According to the randomization sequence, patients were distributed to one of 3 groups: Group A (Control group, n=12): final irrigation was carried out using (20ml) normal saline at room temperature, Group B (Intervention group I, n=12): final irrigation was carried out by normal saline at room temperature and the patients were given 400 mg Ibuprofen medication (Abbott Pharma, Egypt) as a single dose as soon as the root canal procedure is completed, Group C (Intervention group II, n=12): intracanal cryotherapy final irrigation was done using (20ml) of 2.5°C cold saline for 5 min. An icebox with a thermometer adjusted at 2.5°C was used to store cold saline **(Gundogdu & Arslan 2018; Alharthi et al, 2019)**.

The sterile paper points (Meta Biomed Co., Korea) were used to dry the canals, and a radiograph with master cone was taken, then obturated with the matching gutta-percha cones (Meta Biomed Co., Korea) using modified lateral condensation technique, and sealed with a resin_based sealer ADSEAL (Meta Biomed Co., Korea). A temporary filling was used to seal the access cavity and patients were instructed to return for final restoration placement.

The participants recorded their level of pain at 6, 24, and 48 hours postoperatively. Those with strong or persistent pain, participants were instructed to take 400 mg of ibuprofen (Abbott Pharma, Egypt) not more than 6 hours apart, and to record their tablet intake within 48 hours post-operatively.

Statistical analysis:

Data were gathered and tabulated. Categorical data were analyzed using chi-square test for intergroup comparisons and McNemar's test. Numerical data were explored for normality using Shapiro-Wilk test. The mean and standard deviation of normally distributed data were displayed, and the one-way ANOVA test was used for analysis. Non-parametric data were presented as median and interquartile range (IQR). Ordinal and non-parametric numerical data were analyzed using Kruskal-Wallis followed by Dunn's post-hoc test with Bonferroni correction for intergroup comparisons and Friedman's followed by Nemenyi post-hoc test for intragroup comparisons. The significance level was set at $p \leq 0.05$.

III. RESULTS

The statistical analysis covered all 36 patients. Figure 1 shows the patient enrollment procedure as well as each study phase.

Regarding baseline data: Gender and age distribution within the groups were compatible, and there were no statistically significant differences found ($P > .05$) as seen in Table 1

The three groups' preoperative pain scores were almost identical and did not significantly difference ($P>.05$).

Regarding the percentages of post-operative pain are presented in Figure 2; post-operative pain medians and interquartile ranges (IQR) are presented in Figure 3 and Table 2. Both percentages and medians were significantly lower in group C compared with other groups at

6 hours, meanwhile, group B had significantly lower pain scores than group A ($p<0.001$). At 24 and 48 hours, group A had significantly higher pain severity compared to other groups ($p<0.001$) and there was no significant difference between groups B and C.

Regarding post-operative pain severity when assessed at different intervals for each group, severity measured pre-operatively was significantly higher than that measured at other intervals in all groups, Table 2 and Figure 4 ($p<0.001$).

In terms of incidence of analgesic intake (first day: group A (25%), B (8.3%), C (0%) and second day: group A (8.3%), B & C (0%)), there was no statistically significant difference between different groups with majority of patients not taking analgesics in all groups ($P>0.05$), In the first day no patients took tablets in group C, while in the second day no patients took tablets in groups B and C.

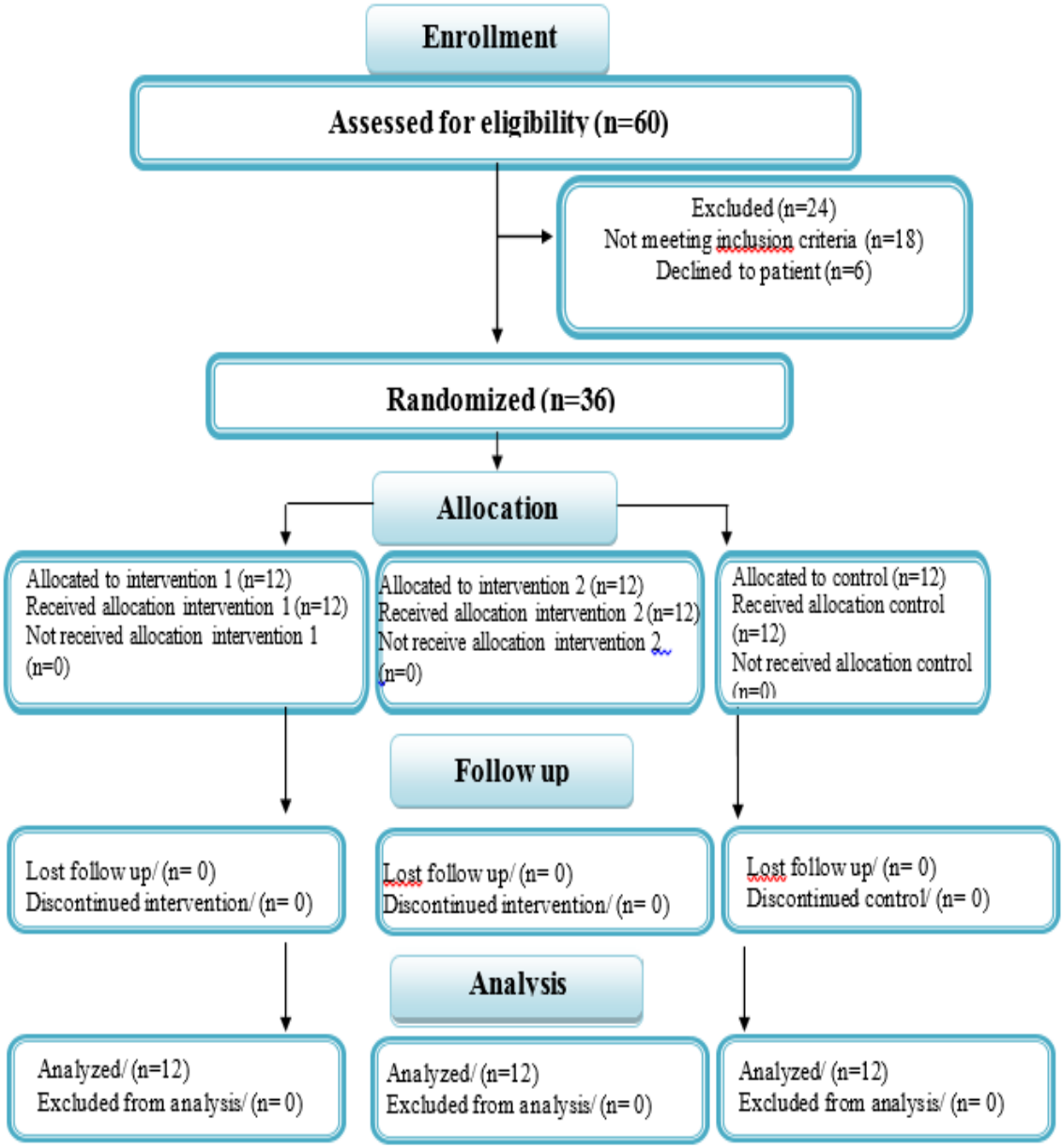

Figure (1): CONSORT 2010 Flow diagram of the trial design

Table (1): Summary statistics and Intergroup comparisons for demographic data calculated with Chi square and One-way ANOVA.

Parameter			Group (A)	Group (B)	Group (C)	p-value
Sex	**Male**	**n**	4	4	4	**1ns**
		%	33.3%	33.3%	33.3%	
	Female	**n**	8	8	8	
		%	66.7%	66.7%	66.7%	
Age (years)	**Mean±SD**		31.58±11.67	36.75±9.33	29.67±8.03	**0.202ns**

*; significant ($p \leq 0.05$) ns; non-significant ($p>0.05$)

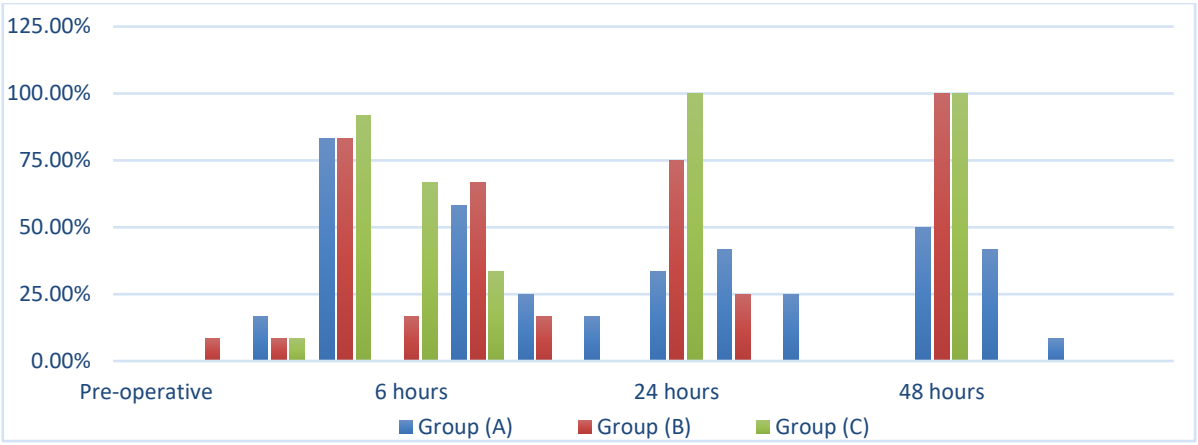

Figure (2): Bar chart showing percentage of pain severity in different groups.

(Group A: control, group B: ibuprofen medication, group C: intracanal cryotherapy)

Table (2): Inter, intragroup comparisons and summary statistics for pain intensity calculated with Kruskal-Wallis and Friedman's test

Time	Median (IQR)			p-value
	Group (A)	**Group (B)**	**Group (C)**	
Pre-operative	8 (7.75-9)^{Aa}	8 (7-9)^{Aa}	8 (7-10)^{Aa}	**0.659ns**
6 hours	3 (3-4.5)^{Aab}	1.5 (1-3)^{Bab}	0 (0-1.25)^{Cb}	**<0.001***
24 hours	2 (0-3.25)^{Abc}	0 (0-0.25)^{Bbc}	0 (0-0)^{Bb}	**0.001***
48 hours	0.5 (0-1)^{Ac}	0 (0-0)^{Bc}	0 (0-0)^{Bb}	**<0.001***
p-value	**<0.001***	**<0.001***	**<0.001***	

Values with different upper and lowercase superscript letters with the same horizontal row and vertical column respectively are significantly different *; significant ($p \leq 0.05$) ns; non-significant ($p>0.05$).

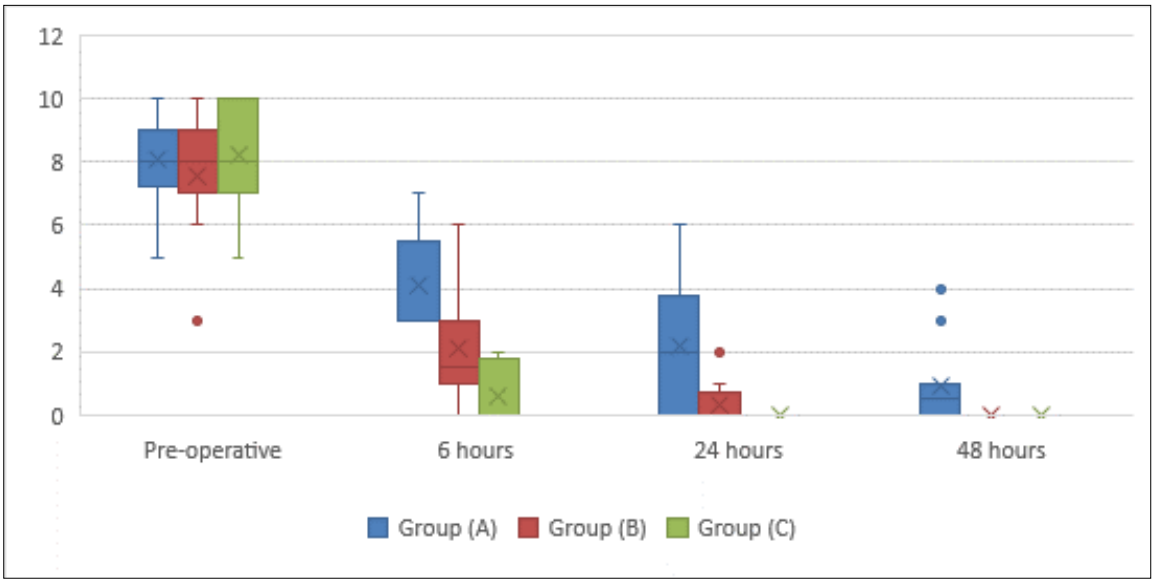

Figure (3): Box plot showing pain intensity values for different groups.
(Group A: control, group B: ibuprofen medication, group C: intracanal cryotherapy)

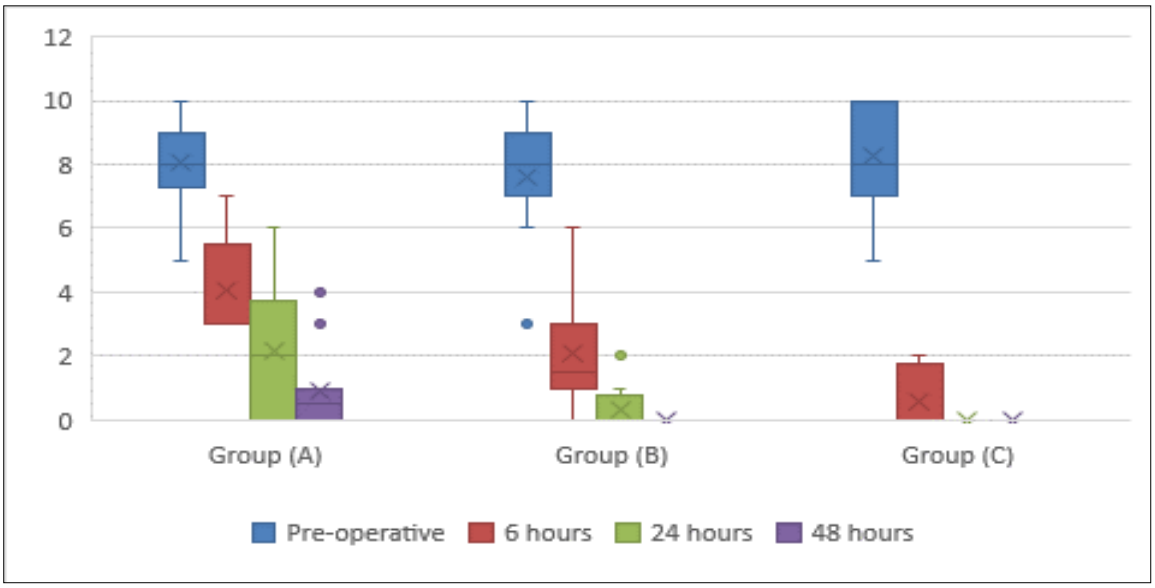

Figure (4): Box plot showing pain intensity values for different intervals.
(Group A: control, group B: ibuprofen medication, group C: intracanal cryotherapy)

IV. DISCUSSION

In literature, number of techniques attempting to reduce post-operative pain for patients receiving root canal therapy have been researched. Recently, the use of cold saline during the final irrigation (intracanal cryotherapy) have been proven to lower post-operative pain levels **(Gundogdu & Arslan 2018; Alharthi et al, 2019; Gupta et al, 2021)**. However, only one study was found comparing cryotherapy to the gold standard post-operative NSAIDs **(Akpinar & Kaya 2021)**, which are used extensively to reduce post-operative pain following root canal treatment and could lead to unwanted side effects **(Parirokh et al, 2014; Di Spirito et al, 2022)**. The aim of this study was to evaluated the effectiveness of cryotherapy

versus ibuprofen medication or normal saline in regarding post-operative pain in cases with symptomatic irreversible pulpitis in mandibular molars.

Mandibular molars with SIP were selected for the research as endodontic treatment of teeth with SIP are considered to be more painful than treating teeth with pulpal necrosis or asymptomatic apical periodontitis **(Ali et al, 2012)**. Patients were treated in single visit where a systematic review has shown that single visit regimen are more effective in treating apical periodontitis and causing less postoperative problems **(Moreira et al, 2017)**.

It was determined that #30-35 taper 4% would be effective for chemo-mechanical preparation. According to previous research, size #30 ISO is the smallest size that can be used to adequately transfer the irrigant to the apical region. However, apical preparations with tapers 6%, result in decreased fracture resistance of teeth. while preventing over-removal of radicular dentin **(Akhlaghi et al, 2014; Shazra et al, 2021; De Deus et al, 2022)**. According to literature review, it can be concluded that using 2.5% NaOCl irrigation concentration is appropriate for endodontic treatment with lower cytotoxic properties **(Marion et al, 2012)**. In this investigation, root canals were sealed off utilizing AdSeal resin-based sealer and lateral condensation method which demonstrated a decreased incidence of post endodontic pain **(Wong et al, 2015)**. AdSeal resin-based sealer offers excellent root canal adaptability, biocompatibility, apical sealing, insoluble nature, radioopacity, and film thickness **(Marciano et al, 2011)**.

Patient's pain levels were assessed at 6, 24, and 48 hours. After endodontic treatment, periapical inflammation activates proprioceptive nerve fibers in the periodontal ligament causing pain after treatment that resolves within 24 to 48 hours **(Seltzer & Naidorf 1985)**. It has been shown that severity pain after treatment are highest in the first 24 hours and subsequently significantly declined to negligible levels **(Pak & White 2011)**.

Following root canal therapy, NSAIDs are indicated as first line of analgesic treatment. Ibuprofen has acknowledged as the prototype medicine for post endodontic pain reduction following endodontic therapy **(Di Spirito et al, 2022)**. Furthermore, most studies on the effectiveness of several procedures and drugs have employed ibuprofen **(Di Spirito et al, 2022; Parirokh et al, 2014)**. Ibuprofen has a reported ceiling impact of 400 mg, and raising amount of the painkiller did not significantly boost its analgesic effect (**Parirokh et al, 2014)**. As a result, in the current study, 400 mg ibuprofen was administered as postoperative medication.

According to the findings of our study, single dose 400mg ibuprofen resulted in a statistically significant decrease in post-operative pain in comparison to control group at 6, 24, and 48 hours intervals. These results align with previous studies **(Di Spirito et al, 2022; Parirokh et al, 2014)**, which found that ibuprofen significantly reduced pain scores and rescue analgesic intake after endodontic treatment.

Results of this study have shown that effectiveness of intracanal cryotherapy on post-operative pain was reflected at 6, 24, and 48 hours intervals, with statistically significant decrease in post-operative pain severity in the cryotherapy group compared to the control group. Furthermore, it significantly reduce post-operative pain compared to the ibuprofen group at 6 hours. This is in agreement with previous studies **(Gundogdu & Arslan 2018; Alharthi et al, 2019; Gupta et al, 2021; Akpinar & Kaya 2021)**, showing that intracanal cryotherapy is a simple cost-effectives supplementary step that may be added to endodontic treatment to reduce post-operative pain scores.

Cryotherapy causes three main physiologic tissue responses: reduced blood flow, metabolic activity, and suppression of neural receptors in the subcutaneous tissues. This makes it effective in the short term for lowering inflammation, discomfort, edema, and recovery time as it worked as a local anti-inflammatory in the

periapical area. This analgesic effect is caused by a combination of slower neural pain signal propagation and reduced release of chemical pain mediators **(Monteiro et al, 2021; Emad et al, 2021; Hespanhol et al, 2022; Keskin et al, 2023)**.[24,25,26,27] Furthermore, intracanal usage of cold saline irrigant at 2.5°C was found to produce more than 10°C drop in temperature of external root surface **(Monteiro et al, 2021; Hespanhol et al, 2022)**.

Interleukins (ILs) are the primary inflammatory response mediators, with local effects including raised synthesis of prostaglandins and proteolytic enzymes. Acute inflammation is induced and controlled by pro-inflammatory mediator IL6. Intracanal cryotherapy decreased the number of leukocytes attached to capillary endothelial walls and reduced cell metabolism resulting in a reduction in periapical IL6 expression **(Emad et al, 2021; Keskin et al, 2023).**

Ascorbic acid Results showed that patients in intracanal cryotherapy group used less rescue medication than those in control group, albeit this difference was not statistically significant. This outcome is consistent with a prior study **(Ezzat et al, 2023)**.

The limitation of this study was that there was no placebo group to be compared with the ibuprofen group.

V. CONCLUSION:

The use of either intracanal cryotherapy as a final irrigant or ibuprofen as a single post-operative dose proved to be significantly effective in decreasing post-operative pain severity at 6, 24, and 48 hours compared to control group. Intracanal cryotherapy was significantly more effective compared to post-operative medication at 6 hours.

Conflict of Interest:

The authors declare no conflict of interest related to this study.

Funding:

This study was self-funded.

Ethics:

This study protocol was approved by the ethical committee of the faculty of dentistry- Cairo university on: 31/5/2022, approval number: 19/5/2022.

Data availability:

Data are available to be sent upon request.

Author contribution:

All authors contributed to the study's conception and design, material preparation, data collection, and analysis. All authors read, reviewed, and approved the final manuscript.

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