Intracanal Cryotherapy Reduces Postoperative Pain in Teeth with Symptomatic Apical Periodontitis: A Randomized Multicenter Clinical Trial

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Abstract

Introduction: A prospective, multicentered, randomized clinical trial was designed to assess if controlled irrigation with cold saline could result in less incidence and intensity of postoperative pain in patients presenting with pulp necrosis and symptomatic apical periodontitis. **Methods:** A total of 210 patients (presenting with necrotic uniradicular teeth with a diagnosis of symptomatic apical periodontitis and a preoperative visual analog scale (VAS) score higher than 7) were randomly allocated in the control or experimental group after the completion of shaping and cleaning procedures. The experimental group received a final irrigation with 20 mL sterile cold (2.5°C) saline solution delivered to the working length with a sterile, cold (2.5°C) Endovac microcannula (Kerr Endo, Orange Country, CA) for 5 minutes. The same protocol was used in the control group with room temperature saline solution. Patients were instructed to record the presence, duration and level of postoperative pain, and analgesic medication intake. A logistic regression was used to compare the incidence of postoperative pain and the need for painkillers between groups. Differences in general pain intensity between groups were analyzed using the ordinal (linear) chi-square test. Postoperative pain after 6, 24, and 72 hours (recorded in a VAS scale) and the need for analgesic medication intake between the 2 groups were assessed using the Mann-Whitney *U* test. **Results:** Patients in the control group presented a significantly higher incidence of postoperative pain, intensity, and need for medication intake ($P < .05$). **Conclusions:** Cryotherapy reduced the incidence of postoperative pain and the need for medication intake in patients presenting with a diagnosis of necrotic pulp and symptomatic apical periodontitis. *(J Endod 2017;■:1–5)*

Key Words

Analgesics, cryotherapy, endodontic pain, postoperative pain, symptomatic apical periodontitis

Significance

Cryotherapy reduced the incidence of postoperative pain and the need for medication in patients presenting with a diagnosis of necrotic pulp and symptomatic apical periodontitis.

The management of postoperative pain is essential in endodontic practice. Hargreaves and Hutter (1) stated that this painful situation can be predicted, especially in teeth with preoperative pain, pulp necrosis, and symptomatic apical periodontitis. Pulp irritants initiate cellular, humoral, and neurovascular responses in pulp tissue (2). The biphasic response in the pulp (vasodilation, increased blood flow, intravascular fluid extravasation leading to increased pulpal pressure, and diminished pulpal blood flow) (3) leads to the development of irreversible pulpitis or pulp necrosis. If this situation extends to the periapical tissues, it may lead to the development of symptomatic apical periodontitis.

Symptoms associated with symptomatic irreversible pulpitis, pulp necrosis (4), and symptomatic apical periodontitis can be related to different factors including changes in periapical pressure, microbial factors, chemical mediators of pain, and psychological factors (5), which ultimately lead patients to seek emergency dental care (6).

One way to reverse the inflammatory process and control pain is with medication such as nonsteroidal anti-inflammatory drugs, paracetamol, or corticosteroids. However, despite being relatively safe drugs, side effects such as gastrointestinal intolerance (7–10) and renal, hepatic, and respiratory disorders such as asthma have been reported (11, 12). Even nonsteroidal analgesics with an enteric coating have been

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related to colon pathology, such as intestinal inflammatory disease, enteropathy with protein loss, iron deficiency anemia, and ulcers (7–9). To avoid these secondary effects, treatments such as manual lymphatic drainage, lasers, and cryotherapy (10) have been suggested.

Physiologic and clinical evidence suggests that applying cold through various methods may decrease the conduction velocity of nerve signals, hemorrhage, edema, and local inflammation and is therefore effective in the reduction of musculoskeletal pain, muscular spasm, and connective tissue distension (11).

A recently published *in vitro* study showed that constant intracanal delivery of cold saline solution at 2.5°C with negative pressure irrigation reduced the external root surface temperature more than 10°C, maintaining such a temperature for 5 minutes (13), which, according to the aforementioned studies, would be enough to produce a local anti-inflammatory effect in periradicular tissues.

Therefore, the aim of this randomized clinical trial was to assess whether controlled irrigation with cold saline after cleaning and shaping procedures would result in a reduced incidence and intensity of postoperative pain in patients presenting with uniradicular teeth with pulpal necrosis and symptomatic apical periodontitis.

Materials and Methods

A prospective, multicentered, randomized clinical trial was designed and conducted in accordance with ethical principles (including the World Medical Association Declaration of Helsinki) after being independently reviewed and approved by the university institutional ethics board. Seven certified endodontists with an average private clinical practice of 15.33 years performed 30 root canal treatments each (a total of 210) in uniradicular teeth having a diagnosis of necrotic pulp and symptomatic apical periodontitis after power analysis calculations.

The aforementioned analysis was based on a sample size calculation with information derived from a previously conducted trial by the first author. These data estimated that a minimum sample size of 25 individuals per endodontist was required in order to detect differences between the experimental and control group for an effect size of 0.80 with an alpha error of 0.05. Further estimations, taking into consideration 15% dropouts, suggested a total adjusted sample size of 30 patients per endodontist.

All treatments were performed over 2 appointments. Root canal treatments were undertaken with the understanding and written consent of all subjects included in the study.

Patient Selection and Allocation

A total of 315 patients presenting with pain in uniradicular teeth were referred for emergency treatment. All patients were informed of the aims and design of the study, and written consent was obtained before their enrollment.

Pulpal sensibility was assessed before treatment using EndoIce (Hygenic Corp, Akron, OH), and proper palpation and percussion tests were performed. Only patients presenting with uniradicular teeth with a single canal and a diagnosis of necrotic pulp (negative thermal stimulation with EndoIce confirmed with an absence of bleeding during access cavity preparation) and symptomatic apical periodontitis were included in the study.

The patient was required to fill out a preoperative questionnaire that included a visual analog scale (VAS) score (0–10, with 0 being the total absence of pain and 10 the most unbearable pain) to register the level of pretreatment pain. Only those patients registering 8, 9, or 10 were included in the study.

Cases with the following criteria were also excluded: root canal retreatment, pregnancy, a history of medication for chronic pain or those compromising the immune response, failure to obtain authorization from patients, presence of difficult root canal anatomy (root canals with an extreme curvature [>30°], internal or external resorption, teeth with open apices, or a radiographically untraceable canal path), or any accident or complication occurring during treatment. Patients whose forms were incompletely or inadequately filled out were excluded also.

A total of 210 patients met the inclusion criteria and were included in the study. Each facility participating in the study had a list of 30 random numbers (www.random.org) assigned either to the control or experimental group. All patients entering the facility and fulfilling the previously mentioned criteria who agreed to participate in the study received a consecutive number; an assistant checked the list to verify the group to which that patient would be assigned. At the end of the shaping procedure, the assistant provided the information to the clinician.

Patient-related factors, such as age and sex, as well as preoperative tooth-related factors (tooth location, presence or absence of occlusal contacts, and presence or absence of radiolucent lesions) were registered.

Root Canal Procedure

All treatments were performed over 2 appointments. At the first appointment, all patients were anesthetized with 2 carpules of articaine 2% with epinephrine 1:200,000 (Septodont, Saint-Maur des-Fosses, France); in cases in which supplemental anesthesia was needed, intraligamental articaine 2% was injected. For the maxillary teeth, the 2 carpules were injected by slow local infiltration in the buccal vestibule. For the mandibular teeth, 1 of the carpules was used for an inferior alveolar nerve block and the other for a slow buccal infiltration around the tooth to be treated. After absolute rubber dam isolation and disinfection, the cavity access was performed with a new, sterile round bur, and the cervical third of the root canal was flared with a K3XF 25/10 rotary instrument (Kerr Endo, Orange County, CA) at 500 rpm. The root canal was irrigated with 3 mL 5.25% sodium hypochlorite (NaOCl). The working length (WL) was first determined with an Apex ID apex locator (Kerr Endo, Orange Country, CA) using no. 10 and 15 K-files and later confirmed radiographically. A glide path to the WL was then established, and a TF Adaptive ML1 (25/08) instrument (Kerr Endo) was used to the WL. A size 10 K-file was used to maintain apical patency 1 mm beyond the WL, and 3 mL NaOCl was again delivered up to 1–2 mm from the WL using a side-vented needle. The same irrigation protocol and patency sequence were repeated using an ML2 (35/06) TF Adaptive instrument (Kerr Endo). After gauging, larger root canals were flared to an ML3 (50/04) instrument (Kerr Endo) and the last instrument recorded.

Ultrasonic activation of 3 mL fresh NaOCl was performed using an Irrisafe ultrasonic 20.00 tip (Satelec, Mérignac, France) at 50% power of the MiniEndo ultrasonic unit (Kerr Endo) to place the tip 3 mm from the WL; this was repeated 3 times for 20 seconds for each activation. Then, 17% EDTA was gently delivered to 1 mm from the WL as a final irrigant and maintained intracanally for 1 minute. The root canals were then dried with sterile paper points. At this time, the assistant informed the practitioner as to which group the patient should be allocated. The patient was blind to the intervention assigned.

Experimental Group (*n* = 105)

Patients assigned to the experimental group received a final irrigation with 20 mL cold (2.5°C) sterile saline solution delivered to the WL using a cold (2.5°C) sterile microcannula attached to the Endovac negative pressure irrigation system (Kerr Endo) for 5 minutes (13). Care was taken to ensure that the microcannula would suction properly

by observing the system's transparent evacuation tube. In case there was any blockage, the microcannula was immediately replaced.

Control Group (n = 105)

Patients assigned to the control group were treated identically to the experimental group, except that the saline solution used for 5 minutes at the end of the first appointment was delivered at room temperature. After these irrigation regimens, the patients were asked to fill out the VAS questionnaire to register their intraoperative pain, and root canal treatment continued as follows in both groups. The canal was suctioned and dried with sterile paper points, and calcium hydroxide (at a previously measured pH of 12) was placed intracanally with a Lentulo spiral 2 mm from the WL. A temporary filling was then placed, and the occlusion was checked.

The patients were then informed that they could experience pain in the days immediately after treatment and were given a second questionnaire to record the presence, duration in days, level of postoperative pain, and analgesic intake. The level of pain was defined as follows: mild pain, any discomfort of any duration that does not require analgesics; moderate pain, pain that requires and is relieved with analgesics; and intense pain, any pain that is not relieved with analgesics. Three VASs were also included in the questionnaire to register the level of pain 6 hours, 24 hours, and 3 days after treatment. The recommended medication for pain was ibuprofen (600 mg/8–12 h). Patients were instructed to return the questionnaire at the second appointment.

The second session occurred approximately 7 days later. Patients were then anesthetized, the tooth was isolated, the temporary filling was removed, and calcium hydroxide was removed by using the last instrument used to flare at the WL during the first appointment using copious irrigation with 10 mL NaOCl followed by ultrasonic activation of NaOCl and another 5 mL 17% EDTA. The root canals were dried and filled.

The information from all patients was then transferred to an Excel (Microsoft, Redmond, WA) spreadsheet that also included a code number for the clinician, the name of the patient, sex, age, treatment group (experimental or control), tooth number, presence or absence of a radiographically visible periradicular lesion, the periapical index score (1–5), and whether the tooth was in occlusion.

Statistical Analysis

As a first set of analysis, a logistic regression was used to compare the incidence of postoperative pain and the need for painkillers between groups while controlling any other possible confounding factor. Apart from the intervention (control or using cryotherapy), the multiple patient- and tooth-related factors preoperatively registered were introduced into the analysis as follows: patient-related factors (age and sex) and tooth-related factors (presence of occlusal contacts [yes or no], arch [maxillary or mandibular], and presence of radiolucent lesions [yes or no]). Because it was a multicenter study, the endodontists performing the treatment were also included as a variable in the analysis.

A stepwise protocol was used to statistically enter and exclude factors from the logistic regression model for a better global fitting. Odds ratios and their 95% confidence intervals (CIs) were also estimated to measure the magnitude of the effect and quantify the strength of the association of the factor with the occurrence of the event.

Differences in the general intensity of pain between groups were analyzed using the ordinal (linear) chi-square test. Differences in VAS-recorded values after 6, 24, and 72 hours and in the amount of analgesic intake between the 2 groups were assessed with the Mann-Whitney U test after confirmation of the violation in the assumption of the normal distribution of data.

Results

Table 1 shows the distribution of pretreatment data in both pools of patients. A total of 186 patients returned the questionnaires fully completed, which were used for the analysis (93 in the experimental group and 93 in the control group).

Patients in the control group (those not submitted to cryotherapy) had a significantly higher incidence of postoperative pain ($P = 1.1 \times 10^{-5}$) with an OR of 12.1 (95% CI, 3.7–33.1). The need for medication intake was also significantly higher in the control group ($P = 4.7 \times 10^{-9}$) with an OR of 7.7 (95% CI, 3.9–15.3).

None of the patient- or tooth-related factors included in the study were found to significantly influence the incidence of postoperative pain. Results for the incidence and intensity of postoperative pain in each group are shown in Tables 2 and 3 as well as the mean values and standard deviations for VASs after 6, 24, and 72 hours after treatment and the mean duration of pain.

Patients in the cryotherapy group suffered significantly less pain after 6, 24, and 72 hours and needed fewer analgesics postoperatively ($P < .05$). There were no significant differences in the incidence of intraoperative pain whether cryotherapy was performed or not. Patients in the control group also showed significantly higher intensity of pain in general and longer duration ($P < .05$).

Discussion

This prospective, randomized clinical trial was conducted to determine whether an innovative approach can reduce the postoperative pain experienced by patients seeking emergency treatment because of preoperative pain, pulp necrosis, and symptomatic apical periodontitis. The benefits of cryotherapy have been reported in the medical literature (10). Cold causes vasoconstriction with an antiedema effect and, hence, a consequent reduction of inflammation (14). At the same time, leukocytes play a central role in a soft tissue lesion's inflammatory response (15). Cryotherapy has been shown to be useful in diminishing the number of leukocytes adhering to the endothelial wall of capillaries, leading to fewer of these cells migrating to the affected tissues, reducing endothelial dysfunction and the inflammatory response (15).

TABLE 1. Distribution of Pretreatment Data in Both Pools of Patients (n) and P Values from the Multivariate Analysis for Each Independent Factor

Variable/categories	Intervention		P value
	Control	Cryotherapy	
Sex			
Male	36	33	.77
Female	57	60	
Location			
Maxillary	67	62	.15
Mandibular	26	31	
Periapical radiolucency			
No	28	39	.33
Yes	65	54	
Occlusal contact			
No	15	24	.58
Yes	78	69	
Age group			
<30	25	15	.46
30–50	48	53	
>50	20	25	

TABLE 2. Results (n) for General Incidence and Intensity of Pain

Incidence	Intensity	Intervention	
		Control	Cryotherapy
No		5	31
Yes	Mild	30	49
	Moderate	43	11
	Intense	15	2

The first physiologic tissue response to cryotherapy is a drop in local temperature, leading to reduced cellular metabolism. This causes cells to use less oxygen and reduces blood flow as induced by vasoconstriction, leading to limitation of the damage (14). In addition, it affects peripheral nerve endings by diminishing the threshold needed to activate the tissue nociceptors and the speed of painful nerve impulses.

Key receptors to environmental cold include the transient receptor potential subfamily ionic channel M, member 8, and the transient receptor potential cationic channel subfamily A, member 1, which play a role in hyperalgesia (16). Cryotherapy induces a local anesthetic effect by lowering the activation threshold of these tissue nociceptors and the conduction velocity of pain signals.

An optimal dosage for cryotherapy has not been determined; it varies depending on the nature of the tissue. When minimal fat and muscle are present (eg, when applied to a finger), 3 to 5 minutes of cryotherapy has been recommended. This time is minimal compared with the approximate 20 minutes recommended for areas with more deeply affected tissue like the hip (17, 18). Cold transmission to the periodontal ligament may also be different in apical and coronal portions of the root because of differences in dentin properties (width and mineralization) at both levels. Cervical dentin has more dentinal tubules, which are also larger, both making it more difficult to transmit therapeutic effectors to the adjacent tissues. On the other hand, apical dentin being more mineralized and denser with fewer tubules would facilitate more efficient cold transmission (19). Also, in the apical third of uniradicular teeth, 1 to 7 pulp ramifications in diameters up to 75 μm can be found (20). At the same time, there are some risks and contraindications for cryotherapy such as Raynaud disease, which affects small blood vessels in extremities, and cold hypersensitivity, which can present with urticaria because of histamine release after reheating the zone. This causes red dots in the skin and cold-induced erythema, resulting in post-therapy redness, itching, severe pain, and muscular spasm (21). Hemoglobinuria is another contraindication because red blood cells decompose so quickly that hemoglobin cannot combine with blood proteins. Above all, cold therapy is not recommended in cases of altered nerve sensitivity or on areas where larger nerves are close to the surface (22). Its use is also controversial in patients having certain systemic diseases or cardiac conditions like arrhythmia, angina pectoris, and hypertension because vasoconstriction raises blood pressure (23).

Using cold saline solutions as a final intracanal has been shown to reduce the external root surface temperature more than 10°C irrigation and maintain it for 4 minutes. It has been theorized that this reduction may be enough to produce a local anti-inflammatory effect in the periradicular tissues (13). Two studies so far have used intracanal therapy to evaluate its effect on postoperative pain in patients with both symptomatic and asymptomatic, irreversible pulpitis with either normal apical tissues or symptomatic apical periodontitis. Both studies showed significant lower postoperative pain levels when cryotherapy was applied compared with control groups (24, 25). In the present study, only patients presenting uniradicular teeth with a single canal and a diagnosis of necrotic pulp and symptomatic apical periodontitis were included. Furthermore, the patients were required to fill out a preoperative questionnaire to register the level of pretreatment pain, and only those patients registering from 8 to 10 on the preoperative VAS were included.

TABLE 3. Mean (Standard Deviation) Results for Postoperative Pain (PP) after 6, 24, and 72 Hours (Visual Analog Scale) and Duration (Days)

Variable	Intervention	
	Control	Cryotherapy
PP 6 h	3.53 (1.9)	1.59 (1.9)
PP 24 h	2.02 (1.5)	0.46 (1.5)
PP 72 h	0.49 (0.8)	0.25 (0.7)
Duration (d)	1.78 (1.1)	1.12 (1.7)

The presence of preoperative pain has been cited as a predictive factor in the incidence of postoperative endodontic pain in previous studies (26–28). This is 1 of the reasons for including only patients rating preoperative pain higher than 7. From the authors' point of view, it also seemed more relevant to clinically examine how cryotherapy could help reduce and control intense preoperative pain. However, at the same time, the high preoperative pain rating might be the explanation for the higher overall incidence of postoperative pain when compared with previous studies in which both symptomatic and asymptomatic patients are included (28).

At the same time, postoperative pain is the result of a complex multifactorial process that is influenced by factors inherent in patients, in the tooth to be treated, and in the intervening operator. Prior studies have identified patient- and tooth-related factors that influence the incidence and duration of postoperative pain (28). Our restrictive inclusion criteria helped control confounding factors that could have influenced the results attributed to the effects of cryotherapy. Moreover, this is also the reason, despite being a randomized clinical trial (in which all preoperative factors are supposed to be uniformly distributed), a multivariable model was used in the first set of analyses in this study. The analysis showed that the large sample size used in the study and the randomization procedure have allowed the similar distribution of possible confounding factors between the control and experimental groups. Such a strict approach in both selecting the patients participating in the study and analyzing the data in this randomized multicenter clinical trial allow us to conclude that cryotherapy reduced the incidence of postoperative pain and the need for medication in patients presenting with a diagnosis of necrotic pulp and symptomatic apical periodontitis.

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The authors deny any conflicts of interest related to this study.

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