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The effect of pulpotomy using a Calcium-Enriched Mixture cement versus one-visit root canal therapy on postoperative pain relief in irreversible pulpitis: a randomized clinical trial

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Abstract The purpose of this noninferiority trial was to compare postoperative pain relief after one-visit root canal therapy (ORCT) with a pulpotomy performed with a new endodontic calcium-enriched mixture cement (PCEM) in human permanent molars with irreversible pulpitis. A total of 407 selected patients were randomly allocated into the ORCT group ($n = 202$) or the PCEM group ($n = 205$). Numerical Rating Scale questionnaires were used to record pain intensity (PI) by the patients during the first 7 days after treatment. While there was no statistically significant difference in the mean PI at baseline between the two study groups ($P = 0.45$), changes in mean PI were significantly different between them ($P < 0.001$). In the ORCT group, pain relief was achieved after 36 h [95% confidence interval (CI), 27.00–45.00], compared to 18 h in the PCEM group (95% CI, 15.00–21.00), a significant difference ($P < 0.01$). Comparison of the mean PI sum recorded over 7 days showed that patients in the ORCT group experienced significantly more pain than those in the PCEM group ($P < 0.001$); a similar difference was observed for pain in response to percussion tests ($P < 0.001$). Treatment with PCEM thus had the better pain-reducing effects than ORCT in irreversible pulpitis cases.

Key words CEM cement · NEC · Pain · Pulpitis · Pulpotomy

Introduction

The most common reason for performing endodontic treatment is irreversible pulpitis, which is characterized by prolonged sensitivity to cold or heat. Posterior teeth more often need a root canal treatment (RCT) than their anterior

counterparts.^{1,2} The usual emergency treatment to relieve pain in irreversible pulpitis is removal of caries and inflamed pulp, cleaning of the root canal, and prescription of analgesics, corticosteroids, or antibiotics.^{3–5} Among the several treatment options, such an emergency pulpotomy or pulp-ectomy is the most reliable way to obtain pain relief.⁶

If there are no time restrictions, then RCT is the treatment of choice.⁷ RCT has an excellent prognosis (success rate \pm 95% CI, $82.8 \pm 1.19\%$).⁸ However, it is expensive, complicated, and time consuming. Unfortunately, in some countries, owing to financial restrictions or the lack of the necessary skills, the only alternative may be extraction of the affected tooth.⁹ Therefore, an economical, simple, and conservative technique such as pulpotomy should be considered.

Preserving the whole or at least the radicular part of the dental pulp is essential when treating pulp exposures, particularly in carious exposures in young permanent teeth or in the complex root canal systems in primary molars.^{10,11} Exposures may result from caries, iatrogenic mishaps, or traumatic injury.¹² In pedodontics, pulpotomy is a popular treatment with well-documented positive results.¹⁰

When the dental pulp of the permanent dentition becomes infected, only the superficial pulp tissue is affected for a considerable period.¹³ A few case series have suggested that pulpotomy is a viable treatment option for carious pulp exposures with irreversible pulpitis,^{11,14–16} because of the healing potential of the remaining radicular pulp of mature permanent molars as well as the biocompatibility of pulpotomy agents, especially mineral trioxide aggregate (MTA),^{11,15,17} but the evidence grade of these reports is low (fourth level).¹⁸

Recently, a novel endodontic cement called Calcium-Enriched Mixture (CEM; BioniqueDent, Iran) cement has been developed.¹⁹ In vitro studies comparing the sealing ability of CEM and MTA (as the gold standard)²⁰ and in vivo vital pulp therapy performed in animals²¹ and humans^{14,15} yielded comparable results, but CEM seems to offer some benefits over MTA. These include a better antibacterial effect,²² improved handling, a shorter setting time, decreased film thickness, and improved flow.¹⁹ CEM has the

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ability to form hydroxyapatite over material in normal saline solution and it exhibits characteristics similar to the surrounding dentin when used as root-end filling material.^{23,24} Moreover, it costs less.

Clinical trials are a safe and efficient way of collecting new data about new forms of treatment. The trials can be designed using one of three major approaches: superiority, equivalence, and noninferiority. The goal of a superiority clinical trial is to determine if a new treatment is superior to similar established treatments. An equivalence clinical trial is used to show that the efficacy of the new treatment is similar to that of the current treatment used as a control. In contrast, a noninferiority trial is appropriate for evaluating the efficacy of a new therapy versus a reference treatment; it is hypothesized that the new therapy may not be superior to a proven effective treatment, but that it is clinically and statistically not inferior in its effectiveness.^{25,26}

No clinical trials have compared pulpotomy as an alternative permanent treatment to RCT in irreversible pulpitis. Hence, the purpose of this randomized clinical trial was to compare pain alleviation of pulpotomy with CEM (PCEM) and one-visit RCT (ORCT) in human molar teeth. We hypothesized that PCEM would not be inferior to ORCT in efficacy in irreversible pulpitis.

Materials and methods

Study design

Our project was evaluated and approved by the Iranian Ministry of Health as well as by the Ethics Committee of the Dental Research Center of Shahid Beheshti University MC, Tehran, Iran. It was also sponsored by the Ministry of Health. The trial was conducted in compliance with the ethical principles of the Helsinki Declaration.

The trial was led by academic professors and managed by the Iranian Center for Endodontic Research (ICER). It was a 12-week multicenter, primary care-based, noninferiority trial with a randomized, parallel-grouped, and open-labeled design conducted by 23 general dentists (GDs).

Hypothesis

We hypothesized that PCEM would be noninferior to ORCT in efficacy. The primary end point for efficacy is long-term clinical and radiographic success (results to be published in a future report) and the secondary end point is pain relief within 1 week postoperatively (this report). In this study, we formally tested the hypothesis at the secondary end point.

Criteria for selection of patients

Subjects were recruited from a pool of patients referred to 23 healthcare centers of five medical universities in four different states of Iran. Subjects were recruited from

both sexes. For standardization, we used inclusion criteria similar to those of the trials that established the efficacy of RCT.^{7,27}

To be included, subjects were required (1) to have a vital molar tooth (i.e., vitality tests were conducted before anesthesia; in particular radicular pulp bleeding after coronal pulp amputation was ascertained to be present); (2) to report pain indicating irreversible pulpitis (i.e., a history²⁸ of spontaneous pain lasting for a few seconds to several hours, exacerbation of pain by hot and cold fluids confirmed with a hot/cold test, and radiating pain); (3) to have opted for extraction for pain relief; (4) to be between 9 and 65 years old; (5) to be prepared to appear for follow-up; and (6) to provide written informed consent.

Subjects who had (1) moderate or severe marginal periodontitis, (2) a nonrestorable tooth, (3) internal or external root resorption, (4) root canal calcification, (5) active systemic disease, (6) physical or mental disability, or were (7) pregnant or nursing were excluded.

Once eligibility was confirmed, the study was thoroughly explained verbally and in writing to the patients by the GDs. The subjects were also informed that they could suspend their cooperation at any time without penalty or loss of benefits. Demographic data, patient numbers, and the teeth to be treated were recorded before treatment.

Randomization

Patients were randomly assigned by a computer-based randomization schedule to receive either ORCT or PCEM. The allocation was performed centrally at ICER to ensure that it was conducted in a blind manner. The patients were not aware of their group assignment before participation. Neither the medical universities (healthcare centers) nor the GDs participated in the randomization procedure.

Sample size

On the basis of previous studies,⁸ a primary event rate of 83% (long-term success rate) was estimated for patients in both treatment groups, with a delta of -0.02 and an effect size of 15%. Even a success rate of 68% for PCEM would be considered noninferior to ORCT. To obtain 90% power with a 2-sided α equal to 0.05, approximately 100 patients per group were considered necessary. With a 10% annual drop-out rate, and assuming an average follow-up of 5 years, approximately 400 patients were thus required.

General dentists

Thirty GDs attended a training workshop at ICER, which included discussion of the study protocol, hands-on training in standardized RCT, and instructions in the pulpotomy treatment. Twenty-three GDs passed the final exam and qualified for the trial. Each dentist was asked to recruit 18 patients with irreversible pulpitis of a permanent molar

tooth (nine patients in each group). All 23 GDs worked in the primary healthcare centers (PHC) throughout Iran.

Reference treatment

Group 1: One-visit root canal therapy

Similar to trials that established the efficacy of RCT,^{7,29} teeth were anesthetized with 2% lidocaine and 1/80000 epinephrine (Daroupakhsh, Tehran, Iran). A 0.2% chlorhexidine rinse was carried out by each patient. Teeth were isolated with a rubber dam and then caries were removed and access cavities prepared. All procedures were carried out with sterile instruments and meticulous care to prevent cross infection. Canal preparation was conducted using the step-back technique. The working lengths were determined and confirmed by radiographs. The minimum size file for preparing the working length was a #25 K-file (Mani, Japan) to within 0.5–2 mm of the radiographic apex. Canals were irrigated with copious amounts of sterile saline solution. They were filled with multiple gutta-percha cones (Ariadent, Tehran, Iran) and AH Plus resin-based sealer (DeTrey Dentsply, Konstanz, Germany) by using the cold lateral condensation technique. The access cavity was temporarily filled with Cavit temporary filling material (ESPE America, Norristown, PA, USA). Treatment was completed during the first visit in all subjects.

Group 2: Pulpotomy treatment with calcium-enriched mixture cement

The teeth were anesthetized and mouth rinse given as above. Under isolation, pulpotomy was performed with a round diamond bur (Diamant D & Z, Goerzallee, Berlin, Germany) in a high-speed handpiece with copious water irrigation; inflamed pulp tissue was removed via the canal orifice. Hemostasis was achieved by irrigation of the cavity with sterile normal saline and application of small pieces of sterile cotton pellets. The blood clot-free pulpal wound was covered with an approximately 2-mm-thick layer of CEM; a sterile wet cotton pellet was then placed over the CEM and the cavity sealed with Cavit.

In both procedures, occlusal adjustment was done after treatment. Cavit was completely removed after 7 days and replaced with amalgam.

Outcomes

The outcome measures in this trial were similar to those of the previous trial that established the efficacy of RCT.⁷ The primary outcome measures were clinical and radiographic success rates of PCEM compared with those of ORCT at 6 months and 1, 2, and 5 years (results to be presented in future clinical reports). The secondary outcome measure was pain relief achieved during the first 7 days (short-term postoperative control).

Data recording

On completion of the treatments, pain assessments were carried out using the pain Numerical Rating Scale (NRS) (Fig. 1) with ratings from 0 to 9 within four grades (pain-free, mild, moderate, and severe). Pain assessments were made at baseline and after 6, 12, 18, 24, 36, 48, and 60 h, and also at 3, 4, 5, 6, and 7 days postoperatively. One NRS form was given to each patient to complete at home at the specified times. Patients were taught how to correctly complete the form, and the GDs stressed to the patients that they were required to complete each section at the appropriate times. Data were recorded in a trials database with appropriate validation procedures.

Statistics

Statistical analyses were performed with SPSS Version 13 (SPSS, Chicago, IL, USA). In addition to reporting the two-sided confidence interval (CI), data were analyzed to determine whether the pain-relieving effects of PCEM were noninferior to those of ORCT. In the two study groups, means of pain intensity (PI) at baseline were compared with Student's *t* test, and the PI trend during 7 days was analyzed by repeated measures analysis of variance (ANOVA). As the NRS comprised four grades, pain duration of each of the three pain grades (mild, moderate, and severe) was determined for each patient and the average was evaluated with a *t* test and Kaplan-Meier (log-rank) tests. The sum of pain intensity (SPI) was calculated by adding all PIs from 6 h to 7 days after treatment. All 6- and 12-h scores were multiplied by 0.25 and 0.5, respectively before the addition. Mean SPI was compared between the two groups by *t* test.

Because subjects were allowed to take analgesics as needed, the data were subjected to two-way ANOVA with treatment and analgesic use as factors. Means of percussion pain (PP) at 1 and 7 days were compared between the two groups using analysis of covariance (ANCOVA), by taking PP at baseline as the covariate. We did not perform an intention-to-treat analysis, as in noninferiority trials this often increases the risk of type I error.³⁰ First type statistical error was considered as ($P < 0.05$).

Results

Patient demographics

A total of 407 patients that met the inclusion criteria consented to participate in the trial. They were recruited from 23 healthcare centers in four states and five medical universities of Iran between April and September 2008 and randomized into the two groups. All subjects completed the 7-day follow-up. The most frequently treated teeth were the mandibular and maxillary first molars (73%). There was no difference in the distribution of treated teeth between the two groups. All patients were included in the analysis population.

Fig. 1. Numerical rating scale used in the trial



Patient code:

Pain Questionnaire

Please rate any discomfort at the various time intervals indicated by marking the appropriate number:

- 0 = No pain
 1-3 = Mild pain, recognizable but not discomforting
 4-6 = Moderate pain, discomforting but bearable
 7-9 = Severe discomfort difficult to bear

	None		Mild			Moderate		Severe		
Time Intervals (Hrs)	0	1	2	3	4	5	6	7	8	9
Before appointment	0	1	2	3	4	5	6	7	8	9
6 Hrs. after app.	0	1	2	3	4	5	6	7	8	9
12 Hrs. after app.	0	1	2	3	4	5	6	7	8	9
18 Hrs. after app.	0	1	2	3	4	5	6	7	8	9
24 Hrs. after app.	0	1	2	3	4	5	6	7	8	9
36 Hrs. after app.	0	1	2	3	4	5	6	7	8	9
48 Hrs. after app.	0	1	2	3	4	5	6	7	8	9
60 Hrs. after app.	0	1	2	3	4	5	6	7	8	9
3 days after app.	0	1	2	3	4	5	6	7	8	9
4 days after app.	0	1	2	3	4	5	6	7	8	9
5 days after app.	0	1	2	3	4	5	6	7	8	9
6 days after app.	0	1	2	3	4	5	6	7	8	9
7 days after app.	0	1	2	3	4	5	6	7	8	9

Table 1. Patient demographics and baseline characteristics

	ORCT	PCEM	<i>P</i> value
Age (years) ± SD	26 ± 8	27 ± 8	0.568
Age category, <i>n</i> (%)			
9 ≤ age < 18	36 (17.8)	37 (18.0)	0.978
18 ≤ age < 50	154 (76.3)	155 (75.7)	
50 ≤ age < 65	12 (5.9)	13 (6.3)	
Sex - <i>n</i> (%)			
Male	82 (40.6)	72 (35.1)	0.272
Female	120 (59.4)	133 (64.9)	
PI (cm; mean ± SD)	4.18 ± 2.09	4.03 ± 1.87	0.450

ORCT, one-visit root canal therapy; PCEM, pulpotomy with calcium-enriched mixture cement; PI, pain intensity

The two groups were well balanced with regard to baseline data (Table 1), with no significant differences in demographic characteristics.

Pain assessment

Data collected during the first 7 postoperative days (407 patients) from both groups were assessed. Table 1 shows the mean baseline PI scores, which were confirmed statistically ($P = 0.45$) to be comparable between the two groups.

The distributions of postoperative PI during 7 days in the two study groups are summarized in Table 2. Overall, PI showed significant changes during the 7 days ($P < 0.001$).

PI throughout the 7 days (mean ± standard deviation) was 1.26 ± 0.08 and 0.67 ± 0.05 in ORCT and PCEM, respectively, which were significantly different ($P < 0.001$).

The mean duration of continuous severe pain was 14.14 h in ORCT (95% CI, 6.03–22.26 h) and 8.00 h in PCEM (95% CI, 6.39–9.61 h); this difference was not statistically significant ($P = 0.138$). Mean total duration of continuous severe or moderate pain was 27.91 h (95% CI, 22.60–33.23 h) in the ORCT group and 14.40 h (95% CI, 10.95–17.85 h) in the PCEM group, a significant difference ($P < 0.001$) (Fig. 2).

The median time to pain-free status (NRS = 0) of 36.00 h (95% CI, 27.00–45.00 h) in the ORCT was significantly higher than that of 18.00 h (95% CI, 15.00–21.00 h) in the PCEM group ($P < 0.01$) (Fig. 3).

The proportion of patients taking postoperative analgesics (Table 3) was greater in the ORCT group ($P < 0.001$) than in the PCEM group. Estimated marginal means of SPI of the two groups with and without use of analgesics were significantly different ($P < 0.001$) (Fig. 4).

At the 1 and 7-day follow-ups, soft tissue inspection and palpation of alveolar areas over the roots revealed no swelling, redness, tenderness, or discomfort in either group. In contrast, the distribution of PP between 1 and 7 days was significantly different in both groups, with ANCOVA used to control for baseline differences ($P < 0.001$ in both cases) (Table 4).

Table 2. Distribution of PI during 7 postoperative days in the two study arms

Day	Arm	PI Category				Patients reporting pain (%)
		Pain-free	Mild	Moderate	Severe	
Baseline	ORCT	0	80	94	28	100
	PCEM	0	82	96	27	100
Day 1	ORCT	97	77	25	3	51.98
	PCEM	150	47	8	0	26.82
2	ORCT	128	52	18	4	36.63
	PCEM	173	28	4	0	15.60
3	ORCT	149	41	10	2	26.23
	PCEM	173	30	2	0	15.60
4	ORCT	156	32	12	2	22.77
	PCEM	174	28	3	0	15.12
5	ORCT	167	30	5	0	17.32
	PCEM	177	26	2	0	13.65
6	ORCT	174	27	1	0	13.86
	PCEM	180	23	2	0	12.19
7	ORCT	181	20	1	0	10.39
	PCEM	184	21	0	0	10.24

Table 3. Patients taking analgesics for postoperative pain in the two study arms during the first 24 h

Arm	Ibuprofen (400 mg)	Acetaminophen (325 mg) with codeine (15 mg)	Mefenamic acid (250 mg)	None
Arm 1: ORCT ^a	86 (42)	24 (11)	12 (6)	85 (41)
Tablets ^b	191 (2.2)	43 (1.8)	32 (2.6)	0 (0)
Arm 2: PCEM ^a	49 (24)	19 (9)	7 (3)	130 (64)
Tablets ^b	98 (2)	25 (1.3)	10 (1.4)	0 (0)

^aNo. of patients (%)

^bNo. of tablets (average no. of tablets/patient)

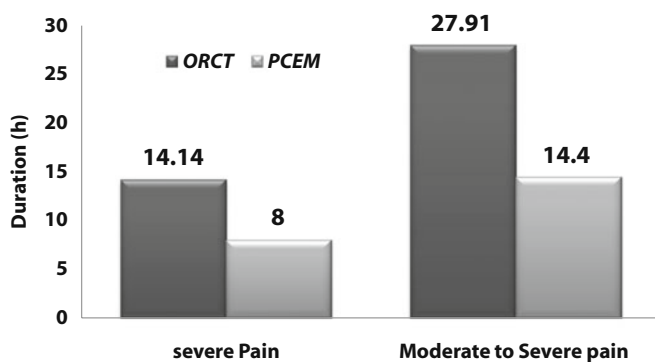


Fig. 2. Mean duration of “severe” and “moderate to severe” pain in the two study arms PCEM, pulpotomy with calcium-enriched mixture cement; ORCT, one-visit root canal therapy

Discussion

This multicenter trial of >400 participants demonstrated that pulpotomy treatment with CEM was statistically non-inferior to one-visit RCT for relieving pain. In many developing or developed countries, dental caries or their sequelae are the most common reasons for tooth extraction.^{9,31} The deprived or possibly uneducated section of this population needs an alternative form of treatment to discourage

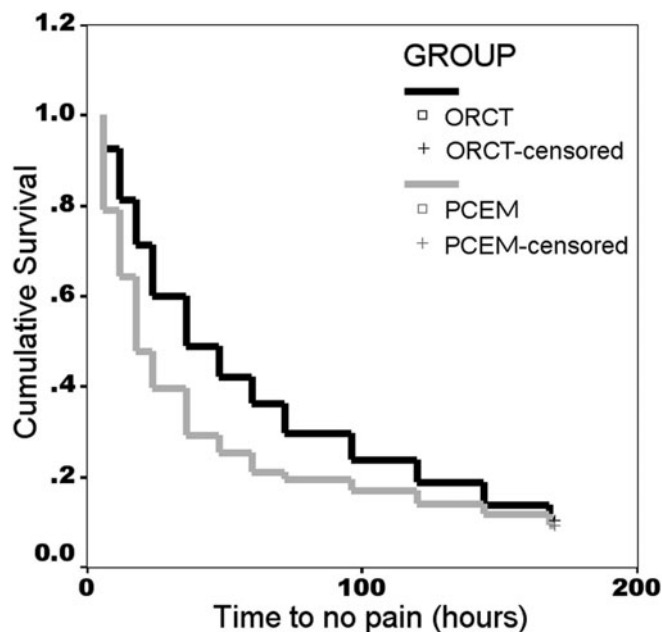


Fig. 3. Time with no pain in the two study arms

treatment avoidance and encourage the preservation of teeth.

A number of options are available for a painful tooth with established irreversible pulpitis, including RCT, treat-

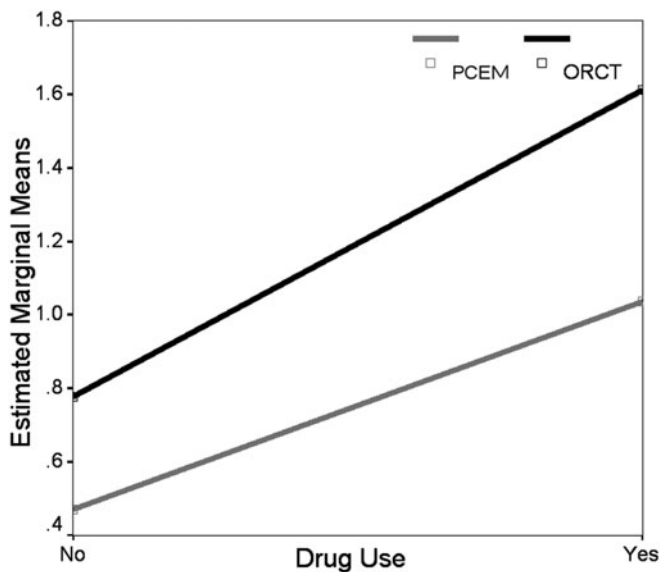


Fig. 4. Sum of the estimated marginal means of pain intensity in the two study arms with and without analgesic use

Table 4. Distribution of percussion pain in the two study arms

Interval	Arm	Sensitivity to percussion			
		Severe	Moderate	Mild	None
Baseline	ORCT	13	47	88	54
	PCEM	5	35	87	78
1 day	ORCT	9	61	73	59
	PCEM	0	4	48	153
7 day	ORCT	2	6	50	144
	PCEM	0	3	21	181

ment avoidance with pain killers, and tooth extraction (a serious option in some countries).³⁻⁵ Although RCT is the treatment of choice, for economic reasons, extraction may be a more attractive treatment option. In some instances patients use self-prescribed analgesics to delay tooth extraction. We hypothesized that pulpotomy treatment might be able to play an important role in such cases.¹⁴

This study is the first randomized clinical trial of pulpotomy treatment in human permanent teeth with irreversible pulpitis; also, it was designed as a noninferiority trial. Noninferiority trials determine whether a new treatment is equivalent to, or not worse than, the reference treatment, but with some added advantages.²⁵ In our trial, the advantages were reduced time and cost, greater availability, less invasiveness and tooth destruction, fewer side effects, and easier chair-side application.

Pain perception is highly subjective and modulated by many factors, and pain reporting is influenced by factors other than the experimental procedures. Pain assessment is also fraught with hazards and opportunities for error. Pain scales are based on the theory that pain intensity is continu-

ous, without jumps or intervals.³⁰ The NRS is suitable for research use and has been extensively utilized within medicine and dentistry. NRS simplifies pain rating by allowing patients to quantify the extent of their pain by rating it from 0 to 9 in one the four grades.

Preoperative (baseline) pain is related to inflammatory reactions initiated by bacterial invasion, and lasts from several minutes to several days.³² The baseline means of PI in the two groups (ORCT = 4.18 and PCEM = 4.03) were at the moderate pain level. These pain scores suggest that these patients with irreversible pulpitis might have opted for tooth extraction. To achieve meaningful comparisons between treatment effectiveness in providing pain relief, the baseline recordings in the two groups should be similar. This condition was met in this trial, no significant difference being present in the baseline means of PI.

Our data showed that the mean postoperative PI scores decreased significantly in both groups following treatment; however, there were significant differences between ORCT and PCEM. Postoperative pain is defined as pain developed in a patient with no preoperative pain, or with an increase in pain after treatment.³³ Definitive treatment combined with optional pain medication led to pain-free status in 24 h in >73% of patients in the ORCT group and >48% of those in the PCEM group. However, among patients initially seeking treatment for toothache, approximately 90% in both groups were asymptomatic after 1 week. These results agree with the consensus that pulpectomy or pulpotomy is probably the most important factor in reducing post-treatment pain, regardless of other variables.^{6,34} Effective treatment strategies for painful vital teeth should include definitive dental treatment when possible; furthermore, according to our results, pulpotomy is a superior treatment option.

Previous researchers have reported that patients with preoperative pain experience a significantly higher incidence of postoperative pain and that intense pain is more likely to occur during the first 24 h postoperatively.^{34,35} Genet et al.³⁵ demonstrated that 65% of patients reporting with preoperative pain had postoperative pain, whereas only 23% of those with no preoperative pain had postoperative pain. As in previous studies, in this study the incidence of postoperative pain was greatest during the first 24 h and decreased thereafter in both groups. Our results for patients in the ORCT group (>51% had postoperative pain at 24 h) are consistent with the findings of Genet et al.³⁵ In contrast, a minority of patients in the PCEM group reported postoperative pain (<25%). However, the exact mechanism of pain reduction in this group is unknown; it may be attributable to the characteristics of CEM or to the absence of filing in the pulpotomy technique.

The literature supports a direct cause-and-effect relationship between microorganisms and their by-products and postoperative pain.³⁶ Ideal endodontic materials should be antibacterial, biocompatible, and nontoxic. An interesting study demonstrated that CEM and calcium hydroxide showed similar favorable results against four bacterial species, even better than MTA.²² An in vivo study demonstrated that CEM and MTA, as pulp capping materials,

have similar biocompatibility and are superior to calcium hydroxide.²¹ Moreover, the cytotoxicity of CEM is similar to that of MTA.^{37,38} It seems reasonable to consider CEM as a promising material for management of endodontic pain.

After the treatment session, patients were permitted to take over-the-counter (OTC) medications if needed without being excluded from the trial. GDs recorded the number of analgesics taken over the first 24 h, as postoperative PP and PI scores would be affected by painkillers. The most common OTC analgesic taken in this trial was ibuprofen, in agreement with other studies.³⁹ The number of tablets taken in ORCT group was approximately double that taken in the PCEM group. While this difference must be considered when evaluating the pain scores recorded by the patients in the two groups, overall, the PCEM group reported significantly lower PP and mean PI scores after 24 h than the ORCT group, reflecting the more effective pain relief preceded by pulpotomy.

A greater number of women ($n = 254$) than men ($n = 154$) were recruited. Variability of the human pain response may in part be a result of sex. Because of biological differences, women are more likely to report severe pain and seek treatment more readily than men.⁴⁰ It is possible that, because of the larger number of women treated and the basic biological differences between men and women, sex played a role in the reaction to the treatments, thereby affecting the overall result. However, this is difficult to assess.

We conclude that PCEM significantly reduced postoperative and percussion pain as well as the number of analgesics taken compared with one-visit RCT. Therefore, pulpotomy with CEM may be superior to RCT in permanent dentition with established irreversible pulpitis. The clinical ease of pulpotomy and the promising reduction in cost of CEM are important features of this novel treatment method.

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