ORIGINAL ARTICLE

One-year results of vital pulp therapy in permanent molars with irreversible pulpitis: an ongoing multicenter, randomized, non-inferiority clinical trial

Saeed Asgary • Mohammad Jafar Eghbal • Jamileh Ghoddusi • Shahram Yazdani

Received: 14 October 2011 / Accepted: 4 March 2012 / Published online: 21 March 2012 © Springer-Verlag 2012

Abstract

Objectives Root canal therapy (RCT) and tooth extraction have been conventional treatment options for management of human mature teeth with irreversible pulpitis. Excellent short-term treatment outcomes of vital pulp therapy with calcium-enriched mixture cement (VPT/CEM), as a new treatment option, on postoperative pain relief was demonstrated; if intermediate- and long-term treatment outcomes of the new treatment are also non-inferior compared to RCT, then VPT/CEM may become a viable treatment option for management of mature teeth with irreversible pulpitis. *Materials and methods* In 23 healthcare centers, 407 9- to 65year-old patients were randomly allocated into two study arms including one-visit RCT (reference treatment; n=202) and VPT/CEM (alternative treatment; n=205). Six- and twelvemonth clinical and radiographic successes were assessed.

S. Asgary (🖂)

Iranian Center for Endodontic Research, Shahid Beheshti University of Medical Sciences, Evin, 1983963113 Tehran, Iran e-mail: saasgary@yahoo.com

M. J. Eghbal Dental Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran

J. Ghoddusi Endodontic Department, Dental School, Mashad University of Medical Sciences, Mashad, Iran

S. Yazdani

Educational Development Center (EDC), Shahid Beheshti University of Medical Sciences, Tehran, Iran *Results* Mean follow-up times at 6- and 12-month follow-ups were " 6.70 ± 0.68 and 6.72 ± 0.71 months" and " 12.96 ± 0.67 and 12.90 ± 0.66 months" in the available cases of RCT and VPT/CEM arms, respectively. Favorable clinical success rates in the two study arms did not show statistical difference; however, the radiographic success rate in the VPT/CEM was significantly greater than RCT arm at the two follow-ups (P < 0.001). The patients' age had no effect on the treatment outcomes (P=0.231).

Conclusions Treatment outcomes of VPT/CEM may be superior to RCT in mature molars with irreversible pulpitis. The performance of biomaterials such CEM cement may assist in the shift towards more biologic treatments.

Clinical relevance VPT/CEM may be a realistic alternative treatment for human mature molar teeth with symptoms of irreversible pulpitis; the use of VPT/CEM is highly beneficial for patients as well as general dentists.

Keywords Biomaterial · Calcium-enriched mixture · CEM cement · Endodontics · Human · Molar · Pulpitis · Pulpotomy · Vital pulp therapy

Introduction

Endodontic case–control studies have revealed excellent prognosis for root canal therapy (RCT); this treatment has been regarded as the "gold standard" for treatment of established irreversible pulpitis [1]. However, many epidemiologic surveys demonstrated a high percentage of treatment failure (\approx 24–66 %) due to inadequate RCTs performed chiefly by general dentists [2, 3]. Moreover, RCT is a non-conservative and nonbiological treatment [4] that is expensive, complicated, and time consuming procedure. In the new millennium, endodontology has shifted towards postponing or avoiding non-biological treatment and descending down the restorative spiral, which would significantly reduce the long-term prognosis for tooth retention and function [5]. Recent studies have suggested vital pulp therapy (VPT) as a realistic treatment modality for pulp exposures with supposed irreversible pulpitis. They have recommended VPT as a biologic, conservative, economic, and simple method with a favorable prognosis [6–10].

Calcium-enriched mixture (CEM) cement, a new endodontic filling material, has been developed [11] with good sealing ability [12], antibacterial effect [13], physical and chemical properties [14–16], and biocompatibility [17–21] when compared to mineral trioxide aggregate (MTA) as the gold standard dental biomaterial.

We hypothesized that the outcomes of vital pulp therapy with CEM cement (VPT/CEM) would be non-inferior to one-visit RCT in human mature molar teeth with symptoms of irreversible pulpitis. The recent results of pain relief during 7 days revealed superior treatment outcomes for VPT/CEM in comparison to one-visit RCT [22].

The objectives of this part of trial were to assess the intermediate- and long-term (6- and 12-month) radiographic and clinical success rates of VPT/CEM and RCT.

Materials and methods

Study plan/Ethical approval

This project was evaluated and approved by the Iranian Ministry of Health as well as the Ethics Committee of Iran Center for Dental Research of Shahid Beheshti University of Medical Sciences. The clinical trial on patients that were diagnosed with "irreversible pulpitis" was conducted in compliance with the ethical principles of the Helsinki declaration.

Study protocol

This report is part of a larger study, which has been registered at ClinicalTrials.gov (Identifier: NCT00748280). This was a 15-month multicenter, randomized, parallel-grouped, and open-labeled design. Inclusion and exclusion criteria, sample size determination and randomization, general dentists' (GD) attendance, one-visit RCT technique (reference treatment) as well as VPT/CEM method (alternative treatment) were similar to our previous report [22] as follow:

1. Criteria for selection of patients. Study subjects were recruited from a pool of patients (both sexes) referred to 23 health care centers of five Medical Universities in four different states of Iran (Appendix 1). For standardization of the participants in this non-inferiority trial, we used inclusion/exclusion criteria as outlined below:

- 1. Inclusion Criteria. Subjects were required to (a) have a vital molar tooth (visual inspection of pulpal hemorrhage), (b) had reported pain indicating irreversible pulpitis (i.e., a history of spontaneous pain for a few seconds to several hours, pain exacerbating with hot and cold fluids, radiating pain, or reproducible pain with cold testing), (c) have opted for extraction for pain relief, (d) be in the age range of 9–65 years, (e) be prepare for recalls, and (f) provide written informed consent.
- Exclusion Criteria. Subjects with (a) moderate or 2. severe marginal periodontitis (i.e., pocket probe> 3 mm), (b) non-restorable tooth (with amalgam), (c) internal/external root resorption in periapical radiograph, (d) root canal calcification in periapical radiograph, (e) active systemic disease, (f) physical or mental disability, and (g) patients who were pregnant or nursing. Once eligibility was confirmed, the study was carefully explained verbally and in writing to the patients. The subjects were also informed that they may suspend their cooperation at any time, without penalty or loss of benefits to which they would otherwise be entitled. Demographic data, patient code, and the treated teeth were recorded before treatment.
- 2. Sample size. Considering previous studies [1], a primary event rate of 83 % (long-term success rate) was estimated for patients in one-visit RCT and VPT/CEM with an effect size of 15 % and a delta of -0.02. To obtain 90 % power with a two-sided α =0.05, approximately 100 patients per treatment arm were needed to establish the non-inferiority of VPT/CEM compared with RCT. With assuming a 10 % dropout per year during 5-year follow-up, approximately 400 patients were required.
- 3. Randomization. Upon enrollment, patients were randomly assigned by a computer-generated permuted block randomization scheme to receive RCT or VPT/ CEM. The allocation took place on a central basis in the Iranian Center for Endodontic Research (ICER) to ensure concealment. The patient was not aware of the group assignment before participation. Neither the medical universities (health care centers) nor the GDs took part in the randomization procedure.
- 4. General dentists. Thirty GDs attended a training workshop at ICER, which included the demonstration of the study protocol, hands-on training in standardized RCT, and instructions in the pulpotomy treatment. Twentythree GDs passed the final examination and were qualified for the trial. Each dentist was asked to recruit 18

patients with irreversible pulpitis of a permanent molar tooth (nine patients in each of the study arms). All 23 GDs worked in the primary health care centers throughout the country (Appendix 1).

- 5. Reference treatment. Arm 1: RCT. Teeth were anesthetized with 2 % lidocain and 1/80,000 epinephrine (Daroupakhsh, Tehran, Iran). A 0.2 % chlorhexidine rinse (Shahre Daru, Iran) was performed by each patient. Teeth were isolated with rubber dam, and then caries was removed and access cavities were prepared. All procedures were performed with sterilized instruments and meticulous regard for cross-infection. Canal preparation was conducted using step-back technique. The working lengths were determined and confirmed by radiographs. The minimum size file for preparing the working length was size ISO #35 K-file (Mani, Tochigi, Japan) to within 0.5-2 mm of the radiographic apex of the root. During hand instrumentation, canals were frequently irrigated with adequate amount of sterile normal saline solution. The root canals were filled with multiple gutta-percha cones (Ariadent, Tehran, Iran) and AH-Plus resin based sealer (DeTrey Dentsply, Konstanz, Germany) using cold lateral condensation technique. Placing a cotton pellet in the pulp chamber, the access cavity was temporarily filled with Cavit (ESPE, Norristown, PA). The treatments of all samples were performed in one visit. After 7 days, Cavit was replaced with amalgam.
- 6. New treatment. *Arm 2: VPT/CEM.* Anesthetizing and mouth rinsing were the same as in arm 2. Pulpotomy was performed with a diamond round bur in a high-speed handpiece with copious irrigation, removing inflamed pulp tissue to stump level. 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 approximately 2-mm layer of CEM cement (BioniqueDent, Tehran, Iran). A sterile wet cotton pellet was then placed over the CEM cement, and the cavity sealed with Cavit. After 7 days, Cavit was replaced with amalgam.

Outcomes

In the original trial, the primary outcome measures were intermediate (6 months) and long-term (1, 2, and 5 years) clinical and radiographic treatment outcomes of the study arms. In the present study, we reported the intermediate and first long-term (1 year) treatment outcomes. The secondary outcome measure was pain relief achieved during the 7 days (short-term postoperative control) which has been reported previously [22].

Follow-up (clinical and radiographical assessments)

Patients were recalled for clinical examination 6 and 12 months postoperatively. The outcome of clinical success or failure was determined by subjective symptoms and objective observation of inflammation and/or infection. Objective signs including abscess, swelling, sinus tract, redness, and tenderness were recorded by the general dentists at each follow-up.

The outcome of radiographic success was classified by using a modification of the Strindberg criteria [23]. Teeth with normal contour and width of periodontal ligament (PDL) were judged as "healed", teeth with a clearly decreased size of the periapical radiolucency were judged as "healing", and teeth with unchanged, increased, or new periapical radiolucency were judged as "failed". The radiographic outcome assessments were made by a total of four independent experienced endodontists and oral radiologists of two each. All examiners were calibrated prior to their assessment through individual evaluation of 20 radiographs independent from this trial.

Statistics

Statistical analysis of the results related to clinical and radiographic evaluations between two study arms was completed using Chi square test. Inter- and intra-rater agreement was measured for the radiographic criteria using Cohen's unweighted kappa statistic. The effect of the patients' age on the treatment outcomes was evaluated using the generalized estimating equations (GEE). Statistical error type I was considered as 0.05. Statistical analysis was set up using SPSS version 13.

Results

The two groups of patients and teeth were well-balanced, without differences in the baseline data and type, respectively [22]. There were no noted side effects in each study arm.

Distribution of tooth type in the RCT and VPT/CEM were 152 and 144 for 1st molar, 47 and 56 for 2nd molar, and 3 and 5 for 3 rd molar teeth, respectively, without any significant differences (P=0.548).

Forty-five (RCT; n=18, VPT/CEM; n=27) and sixty-five (RCT; n=27, VPT/CEM; n=38) participants did not attend 6- and 12-month follow-ups, resulting in 362 (88.94 %) and 342 (84.71 %) cases for intermediate- and long-term outcome analysis, respectively (Fig. 1).

Mean follow-up times at 6-month and 1-year were " 6.70 ± 0.68 and 6.72 ± 0.71 months" and " 12.96 ± 0.67 and 12.90

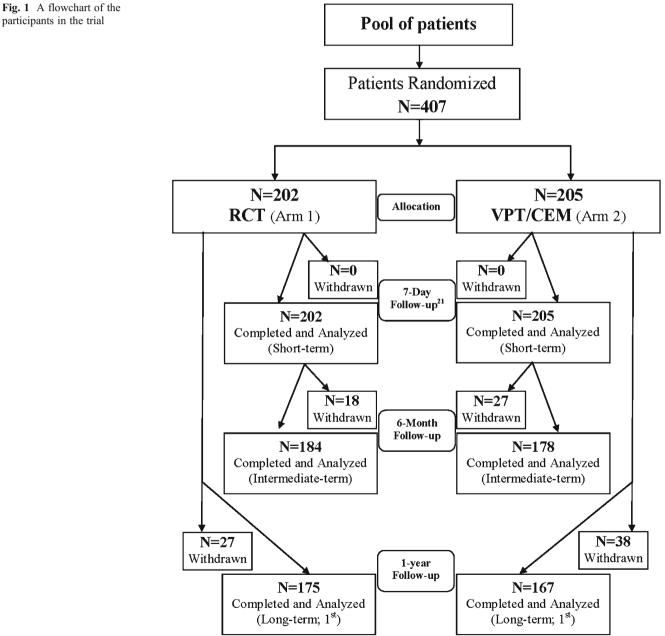
 ± 0.66 months" in RCT and VPT/CEM arms, respectively; a statistical difference was not observed (P > 0.05).

Clinical success in the two study arms at 6- and 12-month follow-up were "94.4 % and 91.3 %" and "98.3 % and 97.6 %" in RCT and VPT/CEM arms, respectively; there was no statistical difference (P>0.05) (Table 1).

The radiographic intra-rater reliabilities were $\kappa = 0.79$, $\kappa =$ 0.85, κ =0.89, and κ =0.91 for raters 1–4, respectively. The inter-rater reliabilities were raters 1/2=0.79, raters 1/3=0.88, raters 1/4=0.77, raters 2/3=0.89, raters 2/4=0.86, and raters 3/4=0.91. The results of radiographic evaluation by the four examiners after 6-month and 1-year follow-ups illustrated that the success rates between the two study arms was statistically different (P=0.001) (Table 2).

Preoperative periapical involvement were present at baseline in 128 patients (31 %) in the two study arms [RCT (n=65) and VPT/CEM (n=63)]; no statistically significant difference was observed (P=0.779) [22]. Interestingly, in cases with preoperative periapical involvement, RCT produced more failures than VPT/CEM at the 6- and 12-month follow-ups (P=0.001) (Table 3).

Using GEE model, the influence of the patients' age on the treatment outcomes did not show statistical significance (P=0.231; Odd ratio=1.018).



participants in the trial

Table 1 Number and percentage of clinical success and fail-	Follow-up (month)	Group	Clinical Outcome		Total	P value
ures in the two study arms at 6- and 12-month follow-up			Success	Failure		
<i>VPT-CEM</i> Vital pulp therapy with calcium enriched mixture cement ^a One-visit root canal therapy	6	RCT ^a VPT/CEM	168 (91.3) 168 (94.4)	16 (8.7) 10 (5.6)	184 (100) 178 (100)	0.257
	12	RCT VPT/CEM	172 (98.3) 163 (97.6)	3 (1.7) 4 (2.4)	175 (100) 167 (100)	0.718

Discussion

Irreversible pulpitis can significantly impact quality of life of patients. It was shown that 97 % of patients reported improved quality of life and satisfaction with their decision to have RCT rather than extraction [24]. Unfortunately, many individuals may prefer tooth extraction due to financial restrictions, unavailability of complex dental treatment and/or lack of education. On the other hand, considering the recent progress in tissue management/wound healing, it is time to reassess whether all diseased vital pulps require pulpectomy for optimal healing and success. Therefore, an alternative treatment that would promote oral health, tooth retention, pulp healing and therefore quality of life would be hugely beneficial. It was hypothesized that VPT may be a reasonable alternative [7, 8].

Moreover, the outcomes of RCT in case-controlled studies performed in controlled clinical environments by endodontists have demonstrated success rates of up to 98 % [25]. RCT is one of the most technically challenging clinical procedures and the quality of treatment provided by general dentists has been questioned worldwide. Epidemiologic studies conducted in various parts of the globe have demonstrated \approx 24–66 % prevalence of apical periodontitis after endodontic treatment chiefly performed by general dental practitioners; the high frequency of technically defective RCT's were shown to have a strong correlation with the presence of apical periodontitis [2, 3, 26]. An effective, technically simple, affordable, and conservative treatment option such as VPT/CEM may improve the outcomes of endodontic treatments performed by majority of general dentists.

Furthermore, VPT for mature permanent teeth with irreversible pulpitis and/or carious pulp exposure remains one of the most challenging/controversial areas in dentistry. Endodontists have a preference to remove entire diseased pulp tissue and many endodontic textbooks do not recommend VPT. A growing body of evidence from recent studies have revealed that permanent teeth with irreversible pulpitis contain putative stem cells [27] and can be managed successfully by VPT [28]. Consequently, the concept of VPT is included in the latest edition of current endodontic textbooks [29]. Carious exposure results from progressive destruction of the tooth by acids/proteolytic enzymes that have been synthesized during microbial activity; in such cases the underlying pulp becomes inflamed to a varying degree but it is not possible to precisely agree on the state of pulpitis on the basis of indirect diagnostic methods [30]. The generally accepted terms for pulpitis refer to reversible and irreversible, although clinical differentiation is largely carried out on an empirical basis [31]. It is recognized that the degree/ characteristic of pain does not precisely represent the pulpal state [32]; there is no information to indicate which symptom is the main cause of pulp incompetency to heal. Lingering pain exacerbated with hot/cold fluids dictated clinicians to classify pulpitis as irreversible; hence, from a practical/clinical point of view, carious pulp exposure may be carried out, and from a histological point of view, such an inflamed pulp is vital; if the circulating blood flow is sufficient, this pulp is capable of healing, provided that suitable treatment is carried out. Beside, the inflammatory process should be reexamined to identify its positive effect on pulpal healing/regeneration. Recent reports have revealed successful outcome of VPT in cariously exposed pulps with signs/symptoms of irreversible pulpitis even with

 Table 2
 Consensus treatment
outcome [number (percentage)] in the two study arms at 6- and 12-month follow-ups

VPT/CEM Vital pulp therapy with calcium enriched mixture cement

^aOne-visit root canal therapy

Group	Follow-up (month)	Radiographic O	Total, <i>n</i> (%)	P value		
		Healed, n (%)	Healing, n (%)	Failure, n (%)		
RCT ^a VPT/CEM	6	101 (54.9) 149 (83.7)	41 (22.3) 14 (7.9)	42 (22.8) 15 (8.4)	184 (100) 178 (100)	0.001
RCT VPT/CEM	12	123 (70.3) 154 (92.2)	19 (10.9) 1 (0.6)	33 (18.9) 12 (7.2)	175 (100) 167 (100)	0.001

Table 3 Distribution of radio- graphic outcome in relation to	Study arm	Radiographic outcome	Periapical involvement before treatment			
periapical involvement [number (percentage)] in the two study			6-Month follow-up		12-Month follow-up	
arms at 6- and 12-month follow-ups			Absent	Present	Absent	Present
	RCT ^a	Healed, n (%)	83 (67.5)	18 (29.5)	99 (81.8)	24 (44.4)
		Healing, n (%)	19 (15.4)	22 (36.1)	6 (5.0)	13 (24.1)
		Failure, n (%)	21 (17.1)	21 (34.4)	16 (13.2)	17 (31.5)
<i>VPT/CEM</i> Vital pulp therapy with calcium enriched mixture cement ^a One-visit root canal therapy	VPT/CEM	Healed, n (%)	115 (89.8)	34 (68.0)	128 (96.2)	42 (91.3)
		Healing, n (%)	7 (5.5)	7 (14.0)	0 (0.0)	0 (0.0)
		Failure, n (%)	6 (4.7)	9 (18.0)	5 (3.8)	4 (8.7)

apical lesions [10, 33, 34]; such findings have reinforced the high capacity of pulpal connective tissue to heal. Furthermore, in the sight of these recent data, there is a need for reclassification of pulpal diseases.

Consequently, this non-inferiority randomized clinical trial was designed to evaluate the treatment outcomes of VPT/CEM in permanent molar teeth with established irreversible pulpitis, compared with RCT (gold standard). Non-inferiority trials determine whether a new treatment is not worse than, or is at least equal to the reference treatment, but with some added advantages [35]. In our trial, the advantages were reduced spent time and cost, greater availability, less invasivity and tooth destruction, fewer side effects, easier chair-side application, and safety (i.e., maintain tooth vitality, increase survival rate, less pain killer/anti-inflammatory, and less x-ray). This multicenter trial demonstrated that VPT/CEM was statistically non-inferior to RCT when considering their radiographic success at 6-month and 1-year follow-ups.

The methodological limitation of this clinical trial concerns the blindness of the patients/clinicians/raters, which were open-labeled due to the nature of the treatment options.

The radiographic reliability in our trial scored at least 0.77 with Cohen's kappa statistic. Though the sensitivity, specificity, and reliability of radiographs of posterior teeth are not sufficiently accurate to permit consistent diagnosis [36], they have great clinical significance in routine dental practice. It was suggested that the levels of agreement of less than 0.45 represents poor agreement, values between 0.45 and 0.75 represent fair to good agreement, and values over 0.75 represent excellent agreement [37].

It is reported that failure of direct pulp capping is most likely to occur within the first 5 years [38]. On the other hand, the most relevant articles regarding full pulpotomy have revealed that the overall success rates from 6 months to 3 years were almost invariable [28]. Comparison of our results revealed that radiographic success rates after VPT was similar at 6- and 12-months follow ups, concurring with other researchers who reported similarity between 3- and 18-months results [33]. Therefore it seems that 3- to 6month follow up is an adequate time for assessing the results of VPT. However, in the RCT arm, the probability of healed cases \approx 15 % increased during the period of 1 year. This finding agrees with other studies that demonstrated the increasing success rate of RCT over time [39]. In some cases, the process of "healing" might require a long time following initial RCT [40]; we plan to carry out up to 5-year follow-ups, if feasible.

Based on the clinical outcome measures, our study had \approx 98 % clinical success in both arms at 1-year follow-up. These findings concur with other follow-up studies demonstrating that the probability of endodontically treated teeth to remain functional over time is up to 97 % [25]. This rate is \approx 6–18 % more than our obtained radiographic success rates after 1-year follow-up, demonstrating the asymptomatic nature of post-treatment apical periodontitis. However, the scientific and academic point of view would argue that the absence of clinical symptoms is an inadequate measure of ultimate success in a case-controlled trial, but from an epidemiological point of view, the absence of clinical symptoms and retention/function of the tooth in the oral cavity can form the grounds for treatment success [41].

Currently, replacing the vital dental pulp with endodontic filling material is not classified as a biological approach [4]; however, clinicians are routinely performing nonconservative RCT treatment in teeth with vital pulps in developed nations [42]. Favorable success of VPT as a biologic treatment is based on the healing potential of the remaining so called "irreversibly inflamed" pulp as well as biocompatibility of pulp capping agents [43]. A pulp with irreversible pulpitis contains dental pulp stem cells (DPSCs-IPs) with immense tissue regenerative potential [27, 44]. DPSCs-IPs will allow the pulp to heal after appropriate treatment [7-10]. Besides, biomaterials can play an imperative role in regenerative endodontics and their success in endodontics may entirely modify endodontic treatment philosophy. Endodontics seems to be on the brink of an era that is shifting towards saving a diseased dental pulp, rather than removing it [45].

Vital pulp therapy in teeth with apical lesions is not "state-of-the-art" in many countries world-wide; however, the 1-year radiographic outcomes show that in periapical involvement cases, removing the etiologic factor will create favorable conditions for periapical healing by ≈ 91 % in the VPT/CEM arm after 1-year follow-up. The key factor in success of VPT is the sealing ability of the material; on the other word, the most important cause of failure is bacterial recontamination during the healing process [46]. An in vitro study showed that CEM and MTA, as root-end filling materials, have similar sealing ability which was superior to IRM [12]. Moreover, CEM cement was an effective antibacterial agent [13]. An interesting recent study reported successful results following regenerative endodontic treatment (revascularization) of necrotic immature molars with CEM cement [47]. Recent interesting randomized clinical trials have demonstrated favorable clinical outcomes for CEM pulpotomy of human primary as well as immature permanent molars [48, 49]. The precise biological mechanism by which CEM cement promotes healing/regeneration is currently unclear. This characteristic is likely to be the result of several properties such as its sealing ability [12], biocompatibility [17-22, 47, 50-52], high alkalinity and sustained calcium hydroxide release [14, 53], antibacterial effect [13, 54], and/ or hydroxyapatite formation [15, 16].

While it has been recommended that VPT should be performed only in young permanent teeth [55], patients up to 70 years of age were treated successfully with VPT [28, 33, 56]. The age of the patients in our study ranged from 9 to 65 years. Our results demonstrated that age did not have an influence on the treatment outcomes; this was also confirmed in a retrospective study of DPC [56]. Besides, the relevant literature confirms our results by illustrating the weakness of evidence regarding the effects of age and status of the root apex on outcomes of VPT" [28].

Retrospective and controlled prospective clinical trials on humans have been highly recommended to determine longterm biocompatibility of dental/endodontic (bio)materials i.e., CEM cement and MTA [57, 58]. Throughout all efforts and team working on our survey, this prospective, multicenter, randomized, and non-inferiority clinical trial aimed to follow and meet the horizon of stated recommendation.

In conclusion, it is apparent that treatment outcomes of VPT/CEM is not only non-inferior but also may be superior to RCT in mature molars with irreversible pulpitis. Furthermore, our data suggests that VPT/CEM is a predictable procedure with an excellent intermediate- and long-term (6 and 12 months) prognosis and it may be considered a realistic alternative therapy to extraction/RCT. Moreover, the use of VPT/CEM in the treatment of irreversible pulpitis is highly beneficial for patients as well as general dentists. The performance of biomaterials such CEM cement in endodontics/dentistry may assist in the shift towards more biologic treatments.

Acknowledgment The authors thank the study participants and dentists (Drs. S. Niknam, H. Abdolmaleki, M. Shahriari, B. Sepehri, M. Zarei, H. Mohadesi, L. Kochmeshki, N. Shirzaei, S.H. Hoseini, M.R. Naderi, A.R. Torkamanzadeh, N. Sahranavard, J. Mohebi, A. Naseri, M. Forozanfar, A. Razavi, A. Izadi, H. Fadaei, K. Khorshidian, H.A. Taheri, M.H. Bagheri-Atabak, M. Zareshahi, and M. Pahlevan-Shamsi) for their enthusiastic contributions; as well as Drs. K. Bagheri-lankarani, S.H. Emami-Razavi, S.M. Alavian, A.R. Mesdaghinia, M.M. Goya, M.H. Khoshnevisan, S.M. Tabatabaei, K Etemad, M.M. Vardi, M. Sourosh, and H. Hesary, who provided the national supervision of and support for this trial; Dr S.M.R. Safavi for critical review; Drs. A.R. Zali, S. Mohamad-Sadeghi, M.R. Razzaghi, M. Piriaei, and S. Kheirieh for administrative help; Drs. A. Akbarzadeh and M.J. Kharazi-Fard, who helped to develop the original statistical design/analysis; Drs. R.A. Taheri, F. Rahnama, A. Heravi, G.A. Dehghani, and H. Fotohi, who monitored the trial in different states; Dr. E. Soheilipour, M. Ghorbanpour, B. Shadman, O. Hosseini, and Z. Khademi, who entered and checked the data; Drs. H. Nazarinia and S. Goorang, who interpreted the x-rays; and Dr. L. Alim Marvasti for the English editing of the manuscript.

This work was supported by the Iranian Ministry of Health and Medical Education (Health Deputy, Oral Health Office) and Shahid Beheshti University of Medical Sciences [grant number p/25/17/1/tm/103].

Conflict of interest The authors report no conflicts of interest.

Appendix

Table 4 Healthcare centers of five Medical Universities

State	University	Healthcare center	General Dentist	
Tehran	Shahid	Ashrafi Isfahani	S. Niknam	
	Beheshti	Number 2	H. Abdolmaleki	
		Vali Asr	M. Shahriari	
	Iran	Shams	B. Sepehri	
		Rast Ravesh	M. Zarei	
		Safa Dasht	H. Mohaddesi	
		Valfajr	L. Kochmeshki	
Khorasan	Mashad	Imam Reza	N. Shirzaei	
Razavi		Number 8	SH. Hoseini	
		Imam Hasan Mojtaba	MR. Naderi	
		Imam Khomeini	AR. Torkamanzadeh	
		Imamat	N. Sahranavard	
		Imam Hadi	J. Mohebi	
		Number 4 Shahri	A. Naseri	
Fars	Shiraz	Shahid Soltani	M. Forozanfar	
		Golestan	A. Razavi	
		Number 1	A. Izadi	
		Istahban	H. Fadaei	
		Mamasani	K. Khorshidian	
		Marvdasht	HA. Taheri	
Yazd	Shahid Sadoghi	Abrandabad	MH. Bagheri Atabak	
		Number 4	M. Zareshahi	
		Ahmadabad	M. Pahlevan Shamsi	

References

- Kojima K, Inamoto K, Nagamatsu K, Hara A, Nakata K, Morita I, Nakagaki H, Nakamura H (2004) Success rate of endodontic treatment of teeth with vital and nonvital pulps. A meta-analysis. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 97:95–99
- Siqueira JF, Rôças IN, Riche FNSJ, Provenzano JC (2008) Clinical outcome of the endodontic treatment of teeth with apical periodontitis using an antimicrobial protocol. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 106:757–762
- Asgary S, Shadman B, Ghalamkarpour Z, Shahravan A, Ghoddusi J, Bagherpour A, Akbarzadeh Baghban A, Hashemipour M, Ghasemian Pour M (2010) Periapical status and quality of root canal fillings and coronal restorations in Iranian population. Iranian Endodontic J 5:74–82
- 4. Goldberg M, Schmalz G (2011) Toward a strategic plan for pulp healing: from repair to regeneration. Clin Oral Investig 1–2
- Caplan DJ, Cai J, Yin G, White BA (2005) Root canal filled versus non-root canal filled teeth: a retrospective comparison of survival times. J Public Health Dent 65:90–96
- McDougal RA, Delano EO, Caplan D, Sigurdsson A, Trope M (2004) Success of an alternative for interim management of irreversible pulpitis. J Am Dent Assoc 135:1707–1712
- Eghbal MJ, Asgary S, Baglue RA, Parirokh M, Ghoddusi J (2009) MTA pulpotomy of human permanent molars with irreversible pulpitis. Aust Endod J 35:4–8
- 8. Asgary S, Ehsani S (2009) Permanent molar pulpotomy with a new endodontic cement: a case series. J Conserv Dent 12:31–36
- Nosrat A, Asgary S (2010) Apexogenesis of a symptomatic molar with calcium enriched mixture. Int Endod J 43:940–944
- Asgary S (2011) Calcium-enriched mixture pulpotomy of a human permanent molar with irreversible pulpitis and condensing apical periodontitis. J Conserv Dent 14:90–93
- 11. Asgary S. Endodontic filling material, USA. 7,942,961, 2011 May 17
- Asgary S, Eghbal MJ, Parirokh M (2008) Sealing ability of a novel endodontic cement as a root-end filling material. J Biomed Mater Res A 87:706–709
- Asgary S, Kamrani FA (2008) Antibacterial effects of five different root canal sealing materials. J Oral Sci 50:469–474
- Asgary S, Shahabi S, Jafarzadeh T, Amini S, Kheirieh S (2008) The properties of a new endodontic material. J Endod 34:990–993
- Asgary S, Eghbal MJ, Parirokh M, Ghoddusi J (2009) Effect of two storage solutions on surface topography of two root-end fillings. Aust Endod J 35:147–152
- 16. Asgary S, Eghbal MJ, Parirokh M, Ghoddusi J, Kheirieh S, Brink F (2009) Comparison of mineral trioxide aggregate's composition with Portland cements and a new endodontic cement. J Endod 35:243–250
- Asgary S, Eghbal MJ, Parirokh M, Ghanavati F, Rahimi H (2008) A comparative study of histologic response to different pulp capping materials and a novel endodontic cement. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 106:609–614
- Parirokh M, Mirsoltani B, Raoof M, Tabrizchi H, Haghdoost AA (2011) Comparative study of subcutaneous tissue responses to a novel root-end filling material and white and grey mineral trioxide aggregate. Int Endod J 44:283–289
- Asgary S, Eghbal MJ, Ehsani S (2010) Periradicular regeneration after endodontic surgery with calcium-enriched mixture cement in dogs. J Endod 36:837–841
- Samiee MEM, Parirokh M, Abbas FM, Asgary S (2009) Repair of furcal perforation using a new endodontic cement. Clin Oral Investig 14:653–658
- Tabarsi B, Parirokh M, Eghbal M, Haghdoost A, Torabzadeh H, Asgary S (2010) A comparative study of dental pulp response to different pulpotomy agents. Int Endod J 43:565–571

- 22. Asgary S, Eghbal MJ (2010) 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. Odontology 98:126–133
- 23. LZ S (1965) The dependence of the results of pulp therapy on certain factors. Acta Odontol Scand 14 (suppl 21):
- Dugas NN, Lawrence HP, Teplitsky P, Friedman S (2002) Quality of life and satisfaction outcomes of endodontic treatment. J Endod 28:819–827
- Friedman S, Mor C (2004) The success of endodontic therapy healing and functionality. J Calif Dent Assoc 32:493–503
- 26. Dugas NNLH, Teplitsky PE, Pharoah MJ, Friedman S (2003) Periapical health and treatment quality assessment of root-filled teeth in two Canadian populations. Int Endod J 36:181–192
- Wang Z, Pan J, Wright JT, Bencharit S, Zhang S, Everett ET, Teixeira FB, Preisser JS (2010) Putative stem cells in human dental pulp with irreversible pulpitis: an exploratory study. J Endod 36:820–825
- Aguilar P, Linsuwanont P (2011) Vital pulp therapy in vital permanent teeth with cariously exposed pulp: a systematic review. J Endod 37:581–587
- Bogen G, Chandler N (2008) Vital pulp therapy. In: Ingle (ed) Ingle's endodontics, 6th edn. BC Decker INC, Lewiston, pp 1310–1329
- Bjorndal L (2008) Indirect pulp therapy and stepwise excavation. Pediatr Dent 30:225–229
- Levin LG, Law AS, Holland GR, Abbott PV, Roda RS (2009) Identify and define all diagnostic terms for pulpal health and disease states. J Endod 35:1645–1657
- 32. Seltzer S, Bender IB, Ziontz M (1963) The dynamics of pulp inflammation: correlations between diagnostic data and actual histologic findings in the pulp. Oral Surg Oral Med Oral Pathol 16:969–977
- Matsuo T, Nakanishi T, Shimizu H, Ebisu S (1996) A clinical study of direct pulp capping applied to carious-exposed pulps. J Endod 22:551–556
- Caliskan MK (1995) Pulpotomy of carious vital teeth with periapical involvement. Int Endod J 28:172–176
- Piaggio G, Elbourne DR, Altman DG, Pocock SJ, Evans SJ (2006) Reporting of noninferiority and equivalence randomized trials: an extension of the CONSORT statement. JAMA 295:1152–1160
- Bohay RN (2000) The sensitivity, specificity, and reliability of radiographic periapical diagnosis of posterior teeth. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 89:639–642
- Landis JR, Koch GG (1977) The measurement of observer agreement for categorical data. Biometrics 33:159–174
- Dammaschke T, Leidinger J, Schafer E (2010) Long-term evaluation of direct pulp capping—treatment outcomes over an average period of 6.1 years. Clin Oral Investig 14:559–567
- Orstavik D (1996) Time-course and risk analyses of the development and healing of chronic apical periodontitis in man. Int Endod J 29:150–155
- Fristad I, Molven O, Halse A (2004) Nonsurgically retreated root filled teeth—radiographic findings after 20–27 years. Int Endod J 37:12–18
- Salehrabi R, Rotstein I (2004) Endodontic treatment outcomes in a large patient population in the USA: an epidemiological study. J Endod 30:846–850
- Bjørndal L, Laustsen M, Reit C (2006) Root canal treatment in Denmark is most often carried out in carious vital molar teeth and retreatments are rare. Int Endod J 39:785–790
- Asgary S, Eghbal M (2012) Treatment outcomes of pulpotomy in permanent molars with irreversible pulpitis using biomaterials: a multicenter randomized controlled trial. Acta Odontol Scand. doi:10.3109/ 00016357.2011.654251
- 44. Alongi DJ, Yamaza T, Song Y, Fouad AF, Romberg EE, Shi S, Tuan RS, Huang GT (2010) Stem/progenitor cells from inflamed human dental pulp retain tissue regeneration potential. Regen Med 5:617–631

- Ranly DM, Garcia-Godoy F (2000) Current and potential pulp therapies for primary and young permanent teeth. J Dent 28:153–161
- Massler M (1978) Preserving the exposed pulp: a review. J Pedod 2:217–227
- 47. Nosrat A, Seifi A, Asgary S (2011) Regenerative endodontic treatment (revascularization) for necrotic immature permanent molars: a review and report of two cases with a new biomaterial. J Endod 37:562–567
- Malekafzali B, Shekarchi F, Asgary S (2011) Treatment outcomes of pulpotomy in primary molars using two endodontic biomaterials. A 2-year randomised clinical trial. Eur J Paediatr Dent 12:189–193
- 49. Nosrat A, Seifi A, Asgary S (2012) Pulpotomy in caries-exposed immature permanent molars using calcium-enriched mixture cement or mineral trioxide aggregate: a randomized clinical trial. Int J Paediatr Dent. doi:10.1111/j.1365-263X.2012.01224.x
- Asgary S (2010) Furcal perforation repair using calcium enriched mixture cement. J Conserv Dent 13:156–158
- Zarrabi MH, Javidi M, Jafarian AH, Joushan B (2010) Histologic assessment of human pulp response to capping with mineral trioxide aggregate and a novel endodontic cement. J Endod 36: 1778–1781

- 52. Nosrat A, Asgary S (2010) Apexogenesis treatment with a new endodontic cement: a case report. J Endod 36:912–914
- Asgary SNA, Seifi A (2011) Management of inflammatory external root resorption using calcium-enriched mixture cement. J Endod 37:411–413
- 54. Hasan Zarrabi M, Javidi M, Naderinasab M, Gharechahi M (2009) Comparative evaluation of antimicrobial activity of three cements: new endodontic cement (NEC), mineral trioxide aggregate (MTA) and Portland. J Oral Sci 51:437–442
- Ward J (2002) Vital pulp therapy in cariously exposed permanent teeth and its limitations. Aust Endod J 28:29–37
- 56. Mente J, Geletneky B, Ohle M, Koch MJ, Friedrich Ding PG, Wolff D, Dreyhaupt J, Martin N, Staehle HJ, Pfefferle T (2010) Mineral trioxide aggregate or calcium hydroxide direct pulp capping: an analysis of the clinical treatment outcome. J Endod 36: 806–813
- Geurtsen W (2001) Biocompatibility of root canal filling materials. Aust Endod J 27:12–21
- Schmalz G (2009) Determination of biocompatibility. In: Schmalz G, Arenholt-Bindslev D (eds) Biocompatibility of dental materials. Springer, Verlag Berlin Heidelberg, pp 13–44

Copyright of Clinical Oral Investigations is the property of Springer Science & Business Media B.V. and its content may not be copied or emailed to multiple sites or posted to a listserv without the copyright holder's express written permission. However, users may print, download, or email articles for individual use.