

Review

Long-term clinical and radiographic evaluation of the effectiveness of direct pulp-capping materials

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Abstract: The aim of this review was to assess the effectiveness of different direct pulp-capping (DPC) materials for human pulp-exposed teeth. An electronic search was performed on 20 February 2018. Long-term clinical and radiographic evaluations of the effectiveness of different DPC materials for use on human pulp-exposed teeth were included. Risk-of-bias assessment and data extraction were performed. From the 496 identified articles, 15 met the eligibility criteria. Among the studies included in those articles, a total of 1,322 teeth were treated with 12 types of DPC materials, and 1,136 teeth were evaluated at a final follow-up examination. For mineral trioxide aggregate (MTA) and calcium hydroxide (CH), the number of included studies, the number of treated teeth, and the mean follow-up period of studies were almost equal, and the success rates of MTA was superior to CH. Therefore, MTA is likely to be a more effective and predictable material for DPC compared to CH. However, the results were based on the included studies, which were all judged to have a high risk of bias. Therefore, more long-term clinical and radiographic studies designed with lower risk of bias are needed. Moreover, the other 10 materials were only investigated by a small number of studies; therefore, further studies are required.

Keywords: review; direct pulp capping; calcium hydroxide; mineral trioxide aggregate.

Introduction

Historically, pulpectomy was the accepted treatment in dental practice when patients presented with dental pulp exposure, because it was believed that the recovery of the pulp, once exposed, was impossible. However, in 1989, Stanley reported that the regenerative capabilities of dental pulp were far greater than had been traditionally believed. They suggested that dental pulp should be conserved as much as possible in cases without irreversible pulp inflammation. In cases in which pulp exposure occurred due to caries, trauma, or accidents during cavity preparation, vital pulp therapy to preserve and maintain pulp tissue, such as direct pulp capping (DPC), was recommended (1).

Various materials have been used for DPC since it was first performed; however, it is still unclear which material should be selected for DPC. Numerous studies have been conducted with nonrandomized designs or short follow-up periods that are insufficient to determine long-term outcomes with various DPC materials. Therefore, the aim of this review was to summarize the effectiveness of the different DPC materials based on clinical success through selected reliable clinical studies with long-term follow-up periods. From that summary, we will recommend materials that are most suitable for DPC in dental practice. The question addressed according to the participants, interventions, control, and outcomes principle was, "What type of material has been utilized for DPC in high-quality clinical and radiographic studies with long-term follow-up, and how effective are the different DPC materials for pulp-exposed human teeth?"

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Table 1 Search strategy used in PubMed (MEDLINE)

No.	Search terms	No. of articles
#1	“dental pulp capping”[MeSH] OR “pulp capping”[TW]	2374
#2	“randomized”[TW] OR “randomized”[TW]	755399
#3	#1 AND #2	162

Table 2 Eligibility criteria

Inclusion criteria	Exclusion criteria
Language: English	Not RCTs
Pulp exposure with or without caries	Indirect pulp capping, Pulpotomy
Efficacy of pulp-capping materials	Animal studies, <i>in vitro</i> studies
Clinical and radiographic evaluation	Follow-up period: less than 6 months
	Studies comparing the same material but from different companies or with different pretreatments
	Studies comparing test group with negative control group

Materials and Methods

Literature search, study selection, data extraction, and risk of bias assessments were independently performed by two reviewers (T.M. and V.K.S.K.).

Search strategy and study selection

An electronic search was performed on 20 February 2018 in six databases (PubMed, Google Scholar, The Cochrane Library, Scopus, EBSCOhost, and ProQuest). The search terms that were used are shown in Table 1. Furthermore, issues of following journals published between the year 2000 and February 2018 (the last available issue) were manually searched: *Journal of Dental Research*, *Journal of Endodontics*, *Journal of Conservative Dentistry*, and *American Journal of Dentistry*.

Eligibility criteria are described in Table 2. Clinical and radiographic studies that were included had long-term follow-up periods that assessed the effectiveness of DPC materials in the treatment of human teeth with exposed dental pulp with or without caries. Only randomized clinical trials (RCTs) with follow-up periods of more than 6 months were included, because RCTs are the most rigorous study design, and a 3-month follow-up period would be insufficient to guarantee long-term outcomes with various DPC materials. Studies treating either mature or immature teeth were included. The titles and abstracts of the articles were screened for a full-text evaluation. After removing duplicates, reviews, and non-English articles, the full texts were screened for eligibility. Articles that did not meet eligibility criteria were excluded, and articles that fulfilled all the selection criteria were processed for data extraction.

Data extraction, risk of bias assessment, and statistical analysis

Data were extracted from the included studies for qualitative analysis. The recall rates were the number of treated teeth at the final follow-up examination relative to the number of treated teeth at baseline, calculated as a percentage. The methodological quality evaluation of the included studies was performed as part of the data extraction process. The Cochrane Collaboration’s risk-of-bias assessment tool was used to assess the risk of bias in the included studies. The following criteria were taken into consideration: (1) random sequence generation; (2) allocation concealment; (3) blinding of participants; (4) blinding of operators; (5) blinding of outcome assessment; (6) selective reporting; (7) incomplete outcome data; and (8) other bias. All domains were assessed as low, high, or unclear risk of bias. Studies were considered at low risk of bias if all domains were at low risk of bias. Unclear risk of bias was assigned if one domain was at unclear risk of bias and other domains were at low risk of bias. High risk of bias was assigned if more than one domain was at high risk of bias or more than two domains were at unclear risk of bias.

The descriptive statistics were performed by summarizing the total number of included studies, the total number of treated teeth, the mean follow-up period (and range), and the range of the clinical and radiographic success rates at the final follow-up examination.

Results

Literature identification

A flowchart summarizing the screening process is presented in Fig. 1. The electronic search retrieved 484

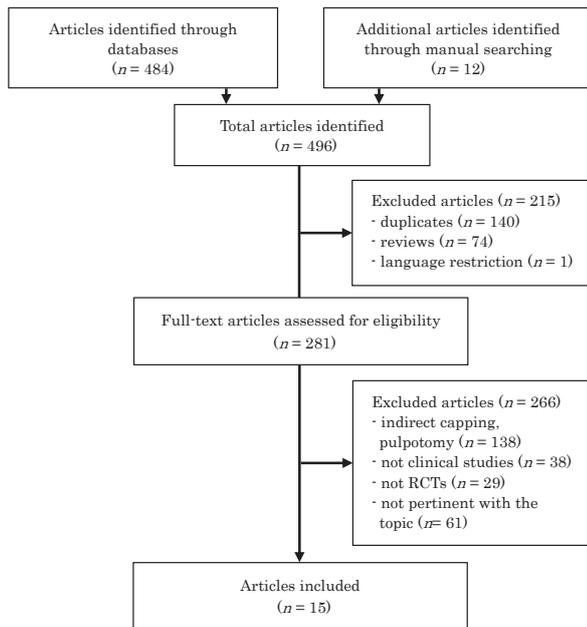


Fig. 1 Flowchart for systematic review

articles, and 12 additional articles were found by manual search. After the first screening of the titles and abstracts, 215 articles were excluded because they were duplicates, reviews, or published in a language other than English. The remaining 281 articles were assessed for eligibility. After evaluation of the full-text version, 266 articles that did not fit the eligibility criteria were excluded, and 15 articles were included in this review (2-16).

Characteristics of the included studies

The characteristics of the included studies are presented in Table 3, and the DPC materials included in this review are summarized in Table 4. A total of 1,322 teeth (529 primary teeth and 793 permanent teeth) were treated with 12 types of DPC materials, and 1,136 teeth (485 primary teeth and 651 permanent teeth) were evaluated at the final follow-up examination. Calcium hydroxide (CH) was used in 10 studies (2-5,7,8,11-13,15), and mineral trioxide aggregate (MTA) was used in nine studies (3,6,7,9,10,13-16). An improved calcium silicate-based cement (Biodentine; Septodont, Saint-Maur-des-Fossés, France) was used in three studies (13,14,16). For the other materials, each was used in one study (2,4-6,8-12). The risk of bias of the included studies is summarized in Table 5. All studies included in this review were found to be at a high risk of bias (2-16).

Calcium hydroxide

CH has been used in dental practice since the 1920s (17). The high pH (approximate pH 12) of OH⁻ ions has an

anti-bacterial function, and CH promotes dentine bridge formation at the site of pulpal exposure with Ca²⁺ ions (18). Although CH had long been considered the gold standard for DPC, it has some disadvantages: (1) high pH irritates the dental pulp, causing inflammation and necrosis on the exposed pulp surface; (2) tunnel defect formation may occur in a formed dentin bridge; and (3) degradation over time leads to failure of the long-term seal. These disadvantages may be responsible for the widely fluctuating success rates.

Four CH products were included in this review: Life (Kerr, Orange, CA, USA), Dycal (Dentsply, Milford, DE, USA), AnalaR CH powder (Sigma-Aldrich Chemical Company Ltd, Poole Dorset, UK), and CH capsule (Hertz Pharmaceutical, Santiago, Chile). In the included studies, 181 permanent teeth were treated with Life, 185 (133 primary teeth and 52 permanent teeth) were treated with Dycal, 60 primary teeth were treated with AnalaR CH, and 53 permanent teeth were treated with CH capsule. The median follow-up period was 18.0 months (range 6-36 months). At the final follow-up examination, 175 permanent teeth had been treated with Life, 164 (115 primary teeth and 49 permanent teeth) had been treated with Dycal, 60 primary teeth had been treated with AnalaR CH, and 25 primary teeth had been treated with CH capsule. A total of 479 teeth were treated with CH, and 424 of them were evaluated at the final follow-up examination. Success rates ranged from 52% to 100%.

Mineral trioxide aggregate

MTA is a calcium silicate-based cement that was developed in 1993. It is composed of tricalcium silicate, tricalcium aluminate, tricalcium oxide, silicate oxide, and other mineral oxides (19). Histological evaluation of the effectiveness of MTA for DPC in human teeth showed that it resulted in less pulpal inflammation and more predictable hard tissue formation than CH (20). In this review, three MTA products were included: ProRoot MTA (Dentsply, Tulsa, OK, USA), MTA-Angelus (Angelus Soluções Odontológicas, Londrina, Brazil), and white ProRoot MTA (Dentsply) which contained less iron, aluminum, and magnesium than ProRoot MTA for less tooth discoloration (21). Three RCTs that compared the effectiveness of MTA for DPC with that of CH were included in this review. Two of the RCTs showed significant differences, while one showed no difference between the study groups (3,7,15). Sawicki et al. and Iwamoto et al. performed RCTs to compare the effectiveness of MTA to CH for DPC and showed no significant difference between them; however, their follow-up period was less than 6 months (22,23).

Table 3 Characteristics of the included studies (Part 1)

Author (year) (Ref.)	Participants		Types of teeth	Deep caries	Pulp exposure size in diameter	Bleeding controlled within	Group (n) [test (T) and control (C)]	No. of operators
	No.	Age mean (range) in years						
Kundzina et al. (2017) (15)	70	30.6 (18-55)	1st or 2nd permanent molar	+	NA	10 min	T: WMTA (33) C: CH (Dycal) (37)	6
Hilton et al. (2013) (7)	376	37.9 (8-90)	permanent teeth	trauma or caries	less than 1 mm [87.5% (MTA), 81.8% (CH)] more than 1.5 mm [12.6% (MTA), 18.3% (CH)]	until bleeding controlled or operator decided DPC not appropriate	T: ProRoot MTA (195) CH (Life) (181)	35
Tuna et al. (2008) (3)	25	NA (5-8)	primary molar	+	less than 1 mm	2-3 min	T: WMTA (25) C: CH (Dycal) (25)	NA
Parinyaprom et al. (2017) (16)	NA	NA (6-18)	permanent teeth	+	less than 2.5 mm	10 min	T: Biodentine (29) C: ProRoot MTA (30)	8
Brizuela et al. (2017) (13)	169	11.3 (7-16)	permanent teeth	+	less than 2 mm	10 min	T1: Biodentine (60) T2: WMTA (56) C: CH capsule (53)	5
Katge et al. (2017) (14)	50	NA (7-9)	1st permanent molar	+	less than 1 mm	NA	T: Biodentine (29) C: MTA-Angelus (29)	1
Jang et al. (2015) (9,32)	35	42 (19-79)	permanent teeth	trauma or caries	NA	10 min	T: Endocem (23) C: ProRoot MTA (23)	NA
Fallahinejad Ghajari et al. (2013) (65,6)	21	6.9 (5-8)	primary molar	+	less than 1 mm	3 min	T: CEM (21) C: ProRoot MTA (21)	1
Ulusoy et al. (2014) (8)	40	7.3 (5-9)	primary molar	+	less than 2 mm	2 min	T: CS (20) C: CH (Dycal) (20)	1
Garrocho-Rangel et al. (2009) (4)	45	5.7 (NA)	primary molar	+	1 mm (created with a round bur after caries removal)	2 or 3 min	T: Emdogain (45) C: CH (Dycal) (45)	1
Asl Aminabadi et al. (2016) (10)	83	NA (3-6)	primary molar	+	less than 1 mm	5 min	T: 3Mixtatin (40) C: WMTA (40)	1
Songsiripradubboon et al. (2015) (12)	42	NA (7-11)	primary molar	+	less than 1 mm	3 min	T: Acemannan (24) C: CH (Dycal) (23)	1
Asl Aminabadi et al. (2010) (5)	84	4.35 (4-5)	primary molar	+	true pinpoint exposure	no bleeding	T: FC + ZOE (60) C: CH powder (60)	NA
Demir et al. (2007) (2)	67	NA (5-9)	primary molar	+	less than 1 mm	1 min	T1: AS (Prime&Bond NT) (20) T2: AS (Xeno III) (20) C: CH (Dycal) (20)	1
Cengiz et al. (2016) (11)	60	28 (18-41)	permanent teeth	+	between 0.5 and 1.5 mm	3 min	T: TheraCal LC (15) C: CH (Dycal) (15)	1

AM: amalgam; AS: adhesive system; CEM: calcium enriched mixture; CH: calcium hydroxide; CHX: chlorhexidine; CR: composite resin; CS: calcium sulfate; MTA: mineral trioxide aggregate; NA: not available; SS: sterile saline; SSC: stainless steel crown; WMTA: white ProRoot MTA; ZOE: zinc oxide eugenol.

In the included studies, 269 teeth (65 primary teeth and 204 permanent teeth) were treated with ProRoot MTA, 154 (21 primary teeth and 133 permanent teeth) were treated with white ProRoot MTA, and 29 permanent teeth were treated with MTA-Angelus. The median follow-up period was 19.0 months (range 6-36). At the final follow-up examination, 252 teeth (19 primary teeth

and 233 permanent teeth) had been treated with ProRoot MTA, 107 (54 primary teeth and 53 permanent teeth) had been treated with white ProRoot MTA, and 21 had been treated with MTA-Angelus. A total of 452 teeth were treated with MTA, and 380 were evaluated at the final follow-up examination. Success rates ranged from 76.36% to 100%.

Table 3 Characteristics of the included studies (Part 2)

Author (year) (Ref.)	Rubber dam isolation	Disinfection or hemostasis with NaOCl	Final restoration	Final follow-up (months)	At final follow-up		Statistical analysis
					Recall rate (n/N)	Clinical and radiographic success rate (success/total) [test (T) and control (C)]	
Kundzina et al. (2017) (15)	±	+	CR	36	T: 93.9% (31/33) C: 91.9% (34/37)	T: 85% (NA) C: 52% (NA)	significant difference
Hilton et al. (2013) (7)	±	92.3% (MTA group) 82.9% (CH group)	none (36.9%) AM (35.2%) CR (21.5%) other (6.4%)	24	T: 93.8% (183/195) C: 96.7% (175/181)	Kaplan-Meier estimate T: 77.6%, C: 68.5% Crude success rate T: 86.4% (158/183), C: 75.4% (132/175)	significant difference
Tuna et al. (2008) (3)	+	-	AM	24	T: 88% (22/25) C: 80% (20/25)	T: 100% (22/22) C: 100% (20/20)	not performed
Parinyaprom et al. (2017) (16)	+	+	CR (70.9%) AM (1.8%) SSC (27.3%)	18.9 ± 12.9	T: 96.6% (28/29) C: 90% (27/30)	T: 96.4% (27/28) C: 92.6% (25/27)	no significant difference
Brizuela et al. (2017) (13)	+	-	CR	12	T1: 41.7% (25/60) T2: 44.6% (25/56) C: 47.2% (25/53)	T1: 100% (25/25) T2: 76.36% (19/22) C: 76.36 (19/22)	no significant difference
Katge et al. (2017) (14)	+	+ (when bleeding persisted after pressure application)	CR	12	T: 72.4% (21/29) C: 72.4% (21/29)	T: 100% (21/21) C: 100% (21/21)	no significant difference
Jang et al. (2015) (9,32)	+	+	CR, inlay, onlay, single crown	12	T: 78.3% (18/23) C: 100% (23/23)	T: 83.33% (15/18) C: 86.96% (20/23)	no significant difference
Fallahinejad Ghajari et al. (2013) (65,6)	- (cotton rolls & suction)	-	AM	20	T: 90.5% (19/21) C: 90.5% (19/21)	T: 89% (17/19) C: 95% (18/19)	no significant difference
Ulusoy et al. (2014) (8)	+	-	AM	12	T: 85% (17/20) C: 80% (16/20)	T: 70.58% (12/17) C: 81.25% (13/16)	no significant difference
Garrocho-Rangel et al. (2009) (4)	+	- (washed with alternate irrigations of SS and CHX)	metallic crown	12	T: 100% (45/45) C: 100% (45/45)	T: 97.8% (44/45) C: 97.8% (44/45)	no significant difference
Asl Aminabadi et al. (2016) (10)	+	+	AM	12	T: 92.5% (37/40) C: 80% (32/40)	T: 91.9% (34/37) C: 93.8 (30/32)	no significant difference
Songsiripraduboon et al. (2015) (12)	+	+	SSC	6	T: 91.7% (22/24) C: 87.0% (20/23)	T: 72.73% (16/22) C: 70% (14/20)	no significant difference
Asl Aminabadi et al. (2010) (5)	+	-	SSC	24	T: 100% (60/60) C: 100% (60/60)	Clinical outcome T: 90% (54/60), C: 61.7% (37/60) Radiographic outcome T: 85% (51/60), C: 53.3% (32/60)	significant difference
Demir et al. (2007) (2)	NA	+	T1: CR T2: CR C: AM	24	T1: 85% (17/20) T2: 100% (20/20) C: 70% (14/20)	T1: 100% (17/17) T2: 95% (19/20) C: 100% (14/14)	no significant difference
Cengiz et al. (2016) (11)	+	-	CR	6	T: 100% (15/15) C: 100% (15/15)	T: 66.6% (10/15) C: 73.3% (11/15)	no significant difference

AM: amalgam; AS: adhesive system; CEM: calcium enriched mixture; CH: calcium hydroxide; CHX: chlorhexidine; CR: composite resin; CS: calcium sulfate; MTA: mineral trioxide aggregate; NA: not available; SS: sterile saline; SSC: stainless steel crown; WMTA: white ProRoot MTA; ZOE: zinc oxide eugenol.

MTA was associated with major improvements in DPC outcomes; however, it had some disadvantages, including a long setting time, poor handling, and discoloration. Various studies have been performed to find ways to improve MTA, and four RCTs included in

this review evaluated the effectiveness of two improved calcium silicate-based cements for DPC: Biodentine and Endocem (Maruchi, Wonju, Korea) (9,13,14,16).

Table 4 Summary of the pulp-capping materials included in this review

Material	No. of RCTs	No. of teeth at baseline & final follow-up		Follow-up mean (range) (months)	Range of success rate (%)
CH	10	479	424	18.0 (6-36)	52-100
Dycal	7	185	164	–	–
Life	1	181	175	–	–
CH capsule	1	53	25	–	–
AnalaR CH	1	60	60	–	–
MTA	9	452	380	19.0 (6-36)	76.36-100
ProRoot MTA	4	269	252	–	–
WMTA	4	154	110	–	–
MTA-Angelus	1	29	21	–	–
Biodentine	3	118	74	14.3 (6-31.8)	96.4-100
Endocem	1	23	18	12	83.33
CEM	1	21	19	20	89
CS	1	20	17	12	70.58
Emdogain	1	45	45	12	97.8
Acemannan	1	24	22	6	72.73
3Mixtatin	1	40	37	12	91.9
ZOE	1	60	60	24	85
TheraCal LC	1	15	15	6	66.6
AS	1	40	37	24	85-100
Prime&Bond NT	1	20	17	–	–
Xeno III	1	20	20	–	–
Total	15	1,322	1,136	17.0 (6-36)	52-100

AS: adhesive system; CEM: calcium enriched mixture; CH: calcium hydroxide; CS: calcium sulfate; MTA: mineral trioxide aggregate; WMTA: white ProRoot MTA; ZOE: zinc oxide eugenol.

Biodentine

Biodentine is an improved calcium silicate-based cement that was introduced in 2009. The powder components include tricalcium silicate, calcium carbonate, and zirconium oxide. The liquid contains calcium chloride, which is used as a setting accelerator and water-reducing agent. It sets in approximately 12 min and causes significantly less tooth discoloration than white ProRoot MTA (24). Histological evaluation of the effectiveness of Biodentine for DPC in human teeth demonstrated that Biodentine promoted a significantly higher amount of dentine bridge formation without any pulpal inflammation in comparison to CH, like white ProRoot MTA (25-27). Biodentine was used in three studies that were included in this review (13,14,16). In the included studies, 118 permanent teeth were treated with Biodentine. The median follow-up period was 14.3 months (range 6-31.8). A total of 74 permanent teeth that had been treated with Biodentine were evaluated at the final follow-up examination, and the success rate ranged from 96.4% to 100%. All three articles compared the effectiveness of Biodentine to MTA for DPC. No significant differences were observed between the study groups in the clinical or radiographic success rates at the final follow-up examination.

Endocem

Endocem is also an improved calcium silicate-based cements, composed of calcium oxide, aluminum oxide, silicate oxide, magnesium oxide, and bismuth trioxide (28). It sets in approximately 4 min, because it contains small-particle pozzolan cement. Some *in vitro* and *in vivo* studies showed that Endocem caused less tooth discoloration and had similar biological effects when compared to ProRoot MTA (29-31); however, Endocem produced a significantly lower level of osteopontin, a bone mineralization marker, in comparison to ProRoot MTA (28). Endocem was used in one study included in this review (9,32). In that study, 23 teeth were treated with Endocem, and 23 were treated with ProRoot MTA as a control. At the 12-month follow-up examination, 18 teeth that had been treated with Endocem and 23 treated with ProRoot MTA were evaluated. The success rates of Endocem and ProRoot MTA were 83.33% and 86.96%, respectively. No significant differences were observed in the clinical or radiographic success rates of the study groups.

Table 5 Risk of bias of the included studies

Author (year) (Ref.)	Random sequence generation	Allocation concealment	Blinding of			Selective reporting	Incomplete outcome data	Other bias	Overall
			patients	operators	outcome assessment				
Kundzina et al. (2017) (15)	Low (Envelop method)	Low (Central randomization)	Low	High	Low	Low	Low	Low	High
Hilton et al. (2013) (7)	Low (R 2.15) (Randomization was done by practice)	Low (Central randomization)	Unclear	High	High (Operator assessed radiograph)	Low	Low	Low	High
Tuna et al. (2008) (3)	Unclear	Unclear	Low	High	Low	Low	Low	Low	High
Parinyaprom et al. (2017) (16)	Low (Randomization number table)	Unclear	Low	High	Low	Low	Low	Low	High
Brizuela et al. (2017) (13)	Low (Excel table)	Unclear	Unclear	High	Unclear	Low	High (Missing data can influence the result)	Low	High
Katge et al. (2017) (14)	Unclear	Unclear	Low	High	Unclear	Low	Low	Low	High
Jang et al. (2015) (9,32)	Unclear	Low (Independent coordinator)	Low	High	Low	Low	High (Missing data can influence the result)	Low	High
Fallahinejad Ghajari et al. (2013) (65,6)	Unclear	Unclear	Low	Low	Low	Low	Low	Low	High
Ulusoy et al. (2014) (8)	Unclear	Unclear	Unclear	High	Low	Low	Unclear *	Low	High
Garrocho-Rangel et al. (2009) (4)	Low (R 2.4.0)	Low (Independent blinded observer)	Low	High	Low	Low	Low	Low	High
Asl Aminabadi et al. (2016) (10)	Low (Randomization software)	Unclear	Low	High	Low	Low	Low	Low	High
Songsiripraduboon et al. (2015) (12)	Unclear	Unclear	Unclear	High	Low	Low	Low	Low	High
Asl Aminabadi et al. (2010) (5)	Low (Coin tossing)	Unclear	Unclear	High	Unclear	Low	Low	Low	High
Demir et al. (2007) (2)	Unclear	Unclear	Unclear	High	Low	Low	Low	Low	High
Cengiz et al. (2016) (11)	Unclear	Unclear	Unclear	High	Low	Low	Low	Low	High

Low: low risk of bias; Unclear: unclear risk of bias; High: high risk of bias.

*: The total success rate in abstract (24/32) and table (25/33) did not match and the reasons for missing data (3/4) in the CH group were not described.

Calcium enriched mixture

Calcium enriched mixture (CEM) (BioniquDent, Tehran, Iran) was developed in 2008. It is composed of different calcium compounds including calcium hydroxide, calcium oxide, calcium phosphate, calcium sulfate, calcium silicate, and calcium carbonate (33). Histological evaluation of the effectiveness of CEM for DPC in human teeth showed that it promoted dentin bridge

formation and did not induce inflammation, similar to MTA (34,35). CEM was only used in one study included in this review (6). In that study, 21 teeth were treated with CEM, and 21 were treated with ProRoot MTA as a control. At the 20-month follow-up examination, 19 teeth that had been treated with CEM and 19 teeth that had been treated with ProRoot MTA were evaluated, and the success rates of CEM and ProRoot MTA were 89%

and 95%, respectively. No significant differences were observed in the clinical or radiographic success rates of the study groups.

Calcium sulfate (Dentogen)

Calcium sulfate (CS) was first used as a void filler for bony defects in 1892, and it has been used in various medical and dental procedures for many years (36,37). CS was used in one of the studies included in this review (8). In that study, 20 teeth were treated with the CS Dentogen (Orthogen, Springfield, NJ, USA), and 20 were treated with Dycal as a control. At the 12-month follow-up examination, 20 teeth were evaluated that had been treated with Dentogen, and 20 were evaluated that had been treated with Dycal. The success rates of Dentogen and Dycal were 75.75% and 70.58%, respectively. No significant differences were observed in the clinical or radiographic success rates of the study groups.

Emdogain

Emdogain (Biora AB, Malmö, Sweden) is an enamel matrix derivative (EMD) that is harvested from developing porcine tooth buds. It was introduced in 1997 as a product to restore periodontal ligament, cementum, and alveolar bone in the treatment of intra-bony defects (38,39). It has long been used in the treatment of severe periodontitis (40). In 2001, Nakamura et al. used EMD for DPC in adult miniature swine teeth. Their results showed that EMD induced a significantly larger amount of hard tissue formation in comparison to CH (41). Olsson et al. showed that in human teeth treated with EMD, postoperative symptoms were less frequent, and the amount and pattern of hard tissue formation were markedly superior to those seen in teeth treated with CH (42). They showed that EMD induced the odontoblasts and endothelial cells of pulp capillary vessels to produce a hard tissue barrier on the exposed pulp (42). EMD was adopted in one study included in this review (4). In that study, 45 teeth were treated with Emdogain, and 45 were treated with Dycal as a control. At the 12-month follow-up examination, 44 teeth that had been treated with Emdogain and 44 treated with Dycal were evaluated, and the success rates were 100% for both Emdogain and Dycal. No significant differences were observed in the clinical or radiographic success rates of the study groups.

Acemannan

Acemannan is a long-chain polydispersed β -(1,4)-acetylated polymannose extracted from Aloe vera (*Aloe barbadensis miller*), which is a medicinal plant that is commonly grown in tropical regions. Aloe vera has long

been used as an herbal medicine for healing skin wounds (43). An *in vitro* study showed that acemannan promoted the differentiation of human primary dental pulp cells into osteoblast-like cells as well as mineral deposition when used as a DPC agent. Acemannan also reduced inflammation and enhanced more reparative dentin formation on the exposed pulp of rat teeth in comparison to CH (44). Acemannan was used in one study included in this review (12). In that study, 24 teeth were treated with acemannan, and 23 were treated with Dycal as a control. At the 6-month follow-up examination, 22 teeth that had been treated with acemannan and 20 that had been treated with Dycal were evaluated. The success rates of acemannan and Dycal were 72.73% and 70.0%, respectively. No significant differences were observed in the clinical or radiographic success rates of the study groups.

3Mixtatin

3Mix antibiotic and simvastatin were combined to use as the DPC product called 3Mixtatin (10). 3Mix is a combination of metronidazole, minocycline, and ciprofloxacin, which can sterilize carious and endodontic lesions (45). Simvastatin is an HMG-CoA reductase inhibitor, which is a type of statin used in the treatment of hyperlipidemia. Statins have multiple functions including anti-inflammation, induction of angiogenesis, improvement of the vascular endothelial cell function, bone formation, and induction of odontogenic differentiation of human dental pulp stem cells (46). 3Mixtatin was used in one study included in this review (10). In that study, 40 teeth were treated with 3Mixtatin, and 40 were treated with white ProRoot MTA as a control. At the 12-month follow-up examination, 37 teeth that had been treated with 3Mixtatin and 32 that had been treated with white ProRoot MTA were evaluated. The success rates of 3Mixtatin and white ProRoot MTA were 91.9% and 93.8%, respectively. No significant differences were observed in the clinical or radiographic success rates of the study groups.

Zinc oxide eugenol

Zinc oxide eugenol (ZOE) has been reported as a DPC material. It has bactericidal effects like CH. ZOE was adopted in one study included in this review (5). In that study, 60 teeth were treated with ZOE after placing formocresol on the exposed pulp for 5 min, and 60 were treated with AnalR CH powder as a control. At the 24-month follow-up examination, 60 teeth that had been treated with ZOE and 60 that had been treated with CH were evaluated, and the success rates of ZOE and CH were

90.0% and 61.7%, respectively. The radiographic and clinical success rates of the ZOE group were significantly superior to those of the CH group. However, formocresol is known to be associated with toxicity, carcinogenicity, and genotoxicity, and ZOE releases substantial amounts of eugenol, which has a highly cytotoxic effect on dental pulp cells (47,48). Therefore, this method may not be recommended for DPC.

Adhesive system

In 1996, an adhesive system was first adopted for DPC to treat fractured teeth, and a number of studies have been performed to investigate its effectiveness (49). Six RCTs were reviewed that evaluated the effectiveness of an adhesive system for DPC (2,50-54); however, the follow-up periods of most of these studies were short. Only one of these studies was included in the present review (2). In that study, 20 teeth were treated with an acetone-based single-bottle adhesive Prime&Bond NT (Dentsply, DeTrey, Konstanz, Germany), 20 were treated with a self-etch adhesive Xeno III (Dentsply), and 20 were treated with Dycal as a control. At the 24-month follow-up examination, 17 teeth that had been treated with Prime&Bond NT, 19 that had been treated with Xeno III, and 14 that had been treated with Dycal were evaluated. The success rates of Prime&Bond NT, Xeno III, and Dycal were 100%, 95%, and 100%, respectively. No significant differences were observed in the clinical or radiographic success rates of the study groups. There were several other studies that compared Prime&Bond NT with two different types of pretreatments, but those studies were excluded from this review. Some of the features that may be required for a DPC material include biocompatibility, bactericidal function, function of dentin bridge formation, and long-time sealing ability. However, histological evaluation of the effectiveness of an adhesive system Single Bond Universal (3M ESPE, St Paul, MN, USA) for DPC in human teeth showed that it promoted less dentin bridge formation than either MTA or Biodentine (26). Additionally, adhesive systems were acidic and did not have a bactericidal function.

TheraCal LC

TheraCal LC (Bisco, Schaumburg, IL, USA) is a light-cured resin-modified calcium silicate-filled material composed of resin, calcium silicate particles, radiopaque component, hydrophilic fumed silica, calcium oxide, strontium glass, and light cure initiator that was invented in 2008 (55). *In vitro* studies revealed that TheraCal LC had a higher calcium-releasing ability and lower solubility than either ProRoot MTA or Dycal; however, it

was also observed to have lower cytocompatibility with odontoblast-like cells than either Biodentine or MTA-Angelus (56,57). TheraCal LC was adopted in one study included in this review (11). In that study, 15 teeth were treated with TheraCal LC, and 15 were treated with Dycal as a control. At the 6-month follow-up examination, 15 teeth that had been treated with TheraCal LC and 15 that had been treated with Dycal were evaluated. The success rates of TheraCal LC and Dycal were 66.6% and 73.3%, respectively. No significant differences were observed in the clinical or radiographic success rates of the study groups. The same study evaluated the efficiency of laser irradiation; however, the results were excluded from this review.

Other materials

For the RCTs that were excluded from this review, some of the DPC materials that were evaluated for effectiveness included bioactive glass (58), light-curing calcium hydroxide (Ultradent Plus; Ultradent Products, Inc., South Jordan, UT, USA) (59), calcium hydroxide injectable paste (Multi-Cal; Pulpdent Corporation, Watertown, MA, USA) (60), nano hydroxyapatite (35,61), betamethasone/gentamicin cream (62), and PropolisPaste (63).

Discussion

The present review has some limitations. First, studies in other languages and studies with less than 3 months of follow-up are excluded; therefore, there is a risk of selection bias. Second, in most of the included studies, blinding of operators is impossible because materials require different clinical handling; therefore, the risk of bias in this domain may be unavoidable. Third, in some studies, the research protocol is not consistent. The methods used for restoration vary among the experimental groups. Additionally, different restorative materials have different sealing abilities. Fourth, the true condition of the dental pulp tissue after DPC cannot be evaluated based on clinical symptoms or a radiographic analysis. Histological evaluation is the only way to assess the true dental pulp condition (64). However, in almost all studies in which histological evaluations are, the follow-up period is less than 6 months. With such a short follow-up period, it is impossible to ensure the long-term outcomes for teeth treated with the different DPC materials. Moreover, even follow-up periods of 6 months or one year cannot truly be described as long-term. In the present review, only five articles have a follow-up period of greater than 2 years (2,3,5,7,15).

In conclusion, many materials have been studied, and some may perform better than CH; however, in contrast

to CH, almost all materials are supported by only a small number of studies. Also, they do not have a long-term track record of clinical success as a DPC material like CH. For MTA, the number of included studies, the number of treated teeth, and the mean follow-up period of studies are very similar to those same parameters for CH, and the success rates of MTA are superior to those of CH. Therefore, MTA is likely to be a more effective and predictable DPC material than CH. Yet, the results of this review are based on the included studies that are judged at high risk of bias. Consequently, further clinical and radiographic RCTs with long-term follow-up periods are required to confirm which material is most suitable for DPC.

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Conflict of interest

The authors declare no conflict of interest associated with this report.

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