Restor Dent Endod. 2024 Nov;49(4):e34
https://doi.org/10.5395/rde.2024.49.e34
eISSN 2234-7666

Restorative Dentistry & Endodontics RDE

Review Article

Check for updates

Success rate of direct pulp capping on permanent teeth using bioactive materials: a systematic review and meta-analysis of randomized clinical trials

Karem Paula Pinto,[1] **Gabriela Ribeiro da Silva**,[1] **Cláudio Malizia Alves Ferreira**,[1] **Luciana Moura Sassone**,[1] **Emmanuel João Nogueira Leal da Silva** [1,2*]

[1]Department of Integrated Clinical Procedures, School of Dentistry, Rio de Janeiro State University (UERJ), Rio de Janeiro, RJ, Brazil
[2]Departament of Endodontics, Grande Rio University (UNIGRANRIO), Rio de Janeiro, RJ, Brazil

OPEN ACCESS

Received: Jun 19, 2024
Revised: Jul 11, 2024
Accepted: Jul 28, 2024
Published online: Sep 6, 2024

Citation
Pinto KP, Silva GR, Ferreira CMA, Sassone LM, Silva EJNL. Success rate of direct pulp capping on permanent teeth using bioactive materials: a systematic review and meta-analysis of randomized clinical trials. Restor Dent Endod 2024;49(4):e34.

***Correspondence to**
Emmanuel João Nogueira Leal da Silva, DDS, PhD
Department of Integrated Clinical Procedures, School of Dentistry – Rio de Janeiro State University (UERJ), Boulevard 28 de setembro, 157 – Pavilhão Mario Franco Barroso – 2º andar, Vila Isabel, Rio de Janeiro, RJ, Brazil.
Email: nogueiraemmanuel@hotmail.com

ABSTRACT

This systematic review and meta-analysis aimed to evaluate the success rate of direct pulp capping (DPC) on permanent teeth, comparing the use of MTA with calcium hydroxide and calcium silicate-based cements. A systematic search was carried out in 4 databases until July 2023. The selection was based on PICOS criteria and only randomized clinical trials were included. The risk of bias was assessed using RoB-2 tool, and meta-analyses were performed using RevMan 5.3 software. The overall quality of evidence was determined using the GRADE tool. Thirteen studies were included. Meta-analyses indicated significantly higher success rate for DPC using MTA compared to calcium hydroxide, while no significant difference was observed between MTA and Biodentine, showing a success rate from 80% to 100% even after 3 years of follow-up. Five studies were classified as having high risk of bias and the GRADE assessment revealed low certainty of evidence. DPC is highly effective for permanent teeth when using MTA or Biodentine. There is a need for future well-designed randomized clinical trials to evaluate the efficacy of DPC using newer bioceramic materials.

Keywords: Bioceramics; Calcium hydroxide; Direct pulp capping; Endodontics; Mineral trioxide aggregate

INTRODUCTION

Direct pulp capping (DPC) is a vital pulp therapy performed when small pulp exposure occurs. Its indication is contingent upon factors such as the cause and dimensions of pulp exposure, the presence of inflammation, and whether bleeding at the site of exposure is controlled [1,2]. This procedure involves the application of a dressing material onto the exposed area, with the aim of stimulating reparative dentin formation and the maintenance of pulp vitality [3]. Therefore, the optimal material should cause minimal or no damage to the pulp, demonstrate biocompatibility, possess antimicrobial activity, and exhibit good sealing ability [4].

Conflict of Interest
No potential conflict of interest relevant to this article was reported.

Author Contributions
Conceptualization: Pinto KP, Silva EJNL; Data curation: Pinto KP, Silva GR, Ferreira CMA; Formal analysis: Pinto KP; Investigation: Pinto KP, Silva GR; Methodology: Pinto KP, Silva GR, Ferreira CMA; Project administration: Pinto KP, Sassone LM, Silva EJNL; Resources: Sassone LM, Silva EJNL; Software: Pinto KP; Supervision: Pinto KP, Silva EJNL; Validation: Pinto KP, Silva EJNL; Writing - original draft: Pinto KP, Silva EJNL; Writing - review & editing: Sassone LM, Silva EJNL.

ORCID iDs
Karem Paula Pinto
https://orcid.org/0000-0001-5642-9541
Gabriela Ribeiro da Silva
https://orcid.org/0009-0004-8279-8550
Cláudio Malizia Alves Ferreira
https://orcid.org/0000-0002-4970-3757
Luciana Moura Sassone
https://orcid.org/0000-0002-6181-7490
Emmanuel João Nogueira Leal da Silva
https://orcid.org/0000-0002-6445-8243

For a long time, calcium hydroxide has been regarded as the prime choice for DPC [5]. This material has excellent antibacterial properties attributed to its high pH and prompts superficial necrosis within the exposed pulp. This stimulation facilitates repair and the formation of a dentin bridge, in addition to protecting the pulp from thermoelectric stimuli [6,7]. However, calcium hydroxide displays pronounced solubility in fluids, along with limited sealing capacity and lack of adhesion, which can impair the success of the DPC [8-10].

Calcium silicate-based materials, also known as bioceramics, have been formulated to exceed specific physicochemical requisites in endodontic applications [11]. Such materials also exhibit an alkaline pH and the ability to release calcium ions, thereby contributing to the reparative and mineralization processes in DPC [12]. Mineral trioxide aggregate (MTA) was the initial calcium-silicate material developed specifically for endodontic purposes, recognized for its remarkable physicochemical attributes, including the advantage by providing an excellent seal with the tooth structure by a hydration expansion reaction, antibacterial properties, biocompatibility and the ability to stimulate the release of bioactive proteins from the dentin matrix [13-15]. Several clinical trials have demonstrated an outstanding success rate ranging from 90% to 100% in DPC procedures using MTA, after 1 year of follow-up [16-20].

Recently, new calcium silicate-based cements, such as Biodentine (Septodont, Saint-Maur-des-Fossés, France), have gained prominence attention in the field of endodontology, particularly for vital pulp treatments. These materials are characterized by high biocompatibility, bioactivity, and ability to stimulate dentinogenesis by releasing calcium ions that contribute to dentin bridge formation and pulpal repair [21,22]. Additionally, resin-modified calcium silicate materials, such as TheraCal (Bisco, Inc., Schaumburg, IL, USA), have made their way into the market offering a combination of the benefits of calcium silicate cements with the additional advantage of a resin component, enhancing some of the physical properties and handling characteristics [23]. Both materials have also shown promising results in clinical studies, underscoring their efficacy in DPC procedures [16,17,24].

Recent systematic reviews with meta-analyses assessed the efficacy of DPC on permanent teeth, comparing the use of MTA with using calcium hydroxide or other silicate-based cements [25,26]. However, those reviews only included studies that assessed teeth with cariously exposed pulps and included few randomized clinical trials (RCTs). For this reason, the evidence regarding the success rate of DPC on permanent teeth using the evaluated materials remains inconclusive. In the hierarchy of evidence, systematic reviews of RCTs offer the highest level of certainty [27]. Therefore, the current study aimed to carry out a systematic review of RCTs to answer the following question: what is the success rate of DPC performed on permanent teeth using MTA, compared to DPC performed using calcium hydroxide or other calcium silicate-based material?

MATERIALS AND METHODS

Protocol and registration

The protocol for this systematic review was registered in the PROSPERO database (CRD42023432260) and followed the recommendations of the PRISMA (Preferred Reporting Items for Systematic Reviews) 2020 guidelines [28].

Focused question

This systematic review was based on the main question: what is the success rate of DPC performed on permanent teeth using MTA, compared to using calcium hydroxide or other calcium silicate-based material? The null hypothesis tested was that there is no significant difference in the success rate among the different materials.

Search strategy

A systematic search was carried out by 2 independent reviewers (G.R.S. and K.P.P.) in PubMed, Cochrane Library, Scopus and Web of Science databases. The search was conducted without restrictions until July 2023. The search strategy employed a combination of Medical Subject Heading (MeSH) terms and text words related to the study topic, including MTA (MeSH), mineral trioxide aggregate (MeSH), bioceramic, calcium hydroxide, pulp capping (MeSH), vital pulp therapy, permanent teeth, mature teeth, permanent dentition (MeSH), and secondary dentition. The search terms were combined using the Boolean operators 'AND' and 'OR' to create the search strategies for each database (**Supplementary Table 1**). A final screening process involved a manual examination of the references of the selected studies and an additional search on Open Grey.

Study selection

1. Inclusion criteria

The inclusion criteria for this systematic review were established using the PICOS strategy, as follows [28,29]:

- P (population): Mature or immature permanent teeth submitted to DPC due to caries, trauma or restorative procedures.
- I (intervention): DPC using MTA.
- C (comparison): DPC using calcium hydroxide or other calcium silicate-based cements.
- O (Result): Success rate based on clinical and radiographic evaluations with at least 6 months of follow-up.
- S (Study design): RCTs.

The clinical assessment required evaluating at least 2 of the following symptoms: pain, swelling, tenderness to percussion, edema, or increased mobility. For the radiographic assessment, at least 2 of the following indicators needed to be examined: presence of periapical lesions, periodontal ligament widening, root formation continuity, or root resorption.

2. Exclusion criteria

Preliminary studies, non-randomized controlled trials, and articles that were not relevant to the study topic were excluded.

The articles retrieved from the initial search were imported into Endnote X9 software (Thomson Reuters, New York, NY, USA) to remove duplicates. Then, the articles were exported to an Excel sheet and their titles and abstracts were analyzed independently by 2 authors (G.R.S. and K.P.P.). Potential studies were reviewed in full and independently evaluated by the authors (G.R.S. and K.P.P.) to determine their eligibility. In case of discordance, a third author (E.J.N.L.S.) was consulted to make the final decision.

Data extraction

The following information was extracted from each included study by 2 independent authors (G.R.S. and K.P.P.): author and year, teeth, root status (mature or immature teeth), patients age, cause of pulp exposure, pulpal diagnosis, material of comparison, sample size, temporary restorative material, permanent restorative material and time of restoration, follow-up time and success rate, and main findings. Any disagreement was resolved by a third author (E.J.N.L.S.).

Quality assessment

The quality of the included studies was assessed by 2 independent authors (G.R.S. and K.P.P.) using the Cochrane Collaboration tool RoB-2 [30]. The RoB-2 tool assesses the following 5 domains: randomization process, adherence to intended interventions, missing outcome data, outcome measurement, and reported outcome selection. Each domain was classified as having 'low risk,' 'unclear risk' or 'high risk.' The overall risk of bias in a study was considered as 'low risk' if all domains were assessed as 'low risk,' 'unclear risk' if one or more domains were assessed as 'unclear risk' or 'high risk' if one or more domains were classified as 'high risk.' In case of discordance between the 2 evaluators, a third author (E.J.N.L.S.) was consulted.

Meta-analysis

RevMan software (Version 5.3, The Cochrane Collaboration) was used to conduct the meta-analyses, with forest plots generated to compare the success rates of DPC with MTA against calcium hydroxide and calcium silicate-based cements at various follow-up intervals, provided when at least 2 studies were available for data aggregation. Success rates were calculated based on the number of successful cases versus the total cases and were presented as dichotomous data. The effect of the intervention was estimated using odds ratios with corresponding 95% confidence intervals (CIs).

Chi-square test was used to detect statistical heterogeneity with p value set at < 0.10. I^2 statistics was used to assess the degree of heterogeneity with > 25%, > 50%, and > 75% indicating low, moderate, or high degree of heterogeneity, respectively. Fixed-effect models were utilized in case of low heterogeneity, while random-effect models were used in case of moderate or high heterogeneity.

Grading of evidence

The Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) tool (GRADEpro, McMaster University, Hamilton, ON, Canada) was used to evaluate the certainty of evidence in this systematic review. Two reviewers (K.P.P. and E.J.N.L.S.) assessed the 5 domains and each of them was rated as 'not serious,' 'serious,' or 'very serious.' The overall certainty of evidence was categorized into 'very low,' 'low,' 'moderate,' or 'high' based on established criteria [31-35].

RESULTS

Study selection

The initial search resulted in the retrieval of 771 studies (**Supplementary Table 1**, **Figure 1**). After removing duplicate articles, 441 studies underwent title and abstract screening. From these, 19 studies were considered eligible and were read in full. After applying the eligibility

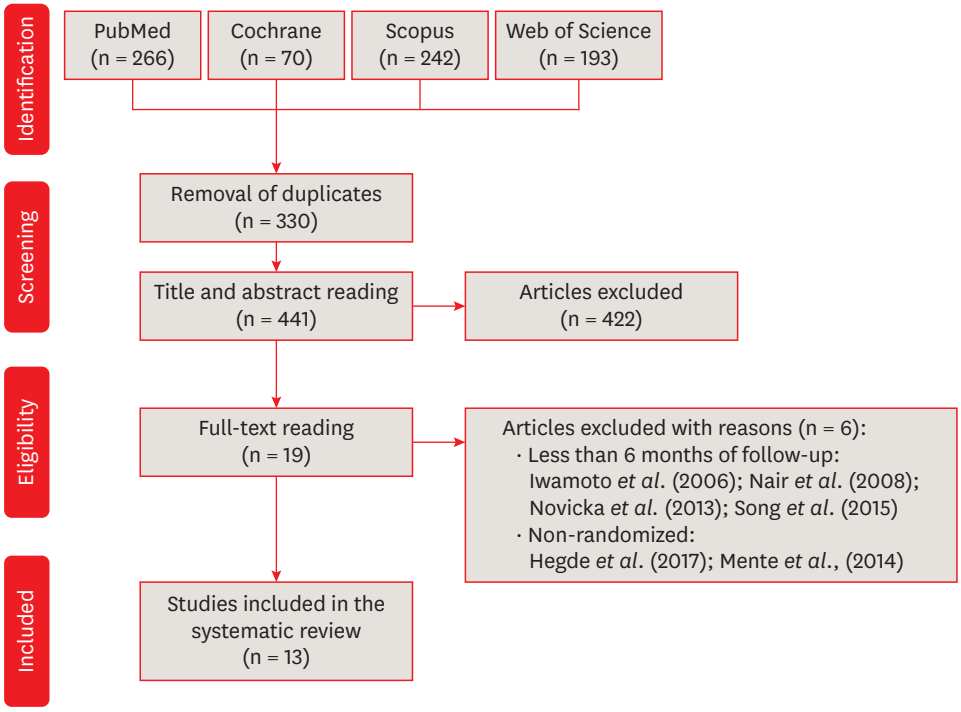

Figure 1. PRISMA flow diagram.

criteria, 6 studies were excluded (**Figure 1**) and 13 studies were included in the present systematic review [16-20,24,36-42]. No additional relevant study was found after screening the references of the selected studies or searching on OpenGray.

Data extraction

Table 1 displays the data extracted from the 13 studies included in this review. The primary material for comparison was calcium hydroxide, followed by Biodentine, with Endocem (Maruchi, Wonju, Korea) and TheraCal also undergoing evaluation. In relation to the MTA brand, most studies used ProRoot MTA (Dentsply, Tulsa, OK, USA), while 4 studies used MTA Angelus (Angelus, Londrina, Brazil) and 1 study used MTA Plus (Cerkamed, Stalowa Wola, Poland). One study did not mention the MTA's brand [16-18,24,36,42]. Permanent restoration was performed immediately or within timeframes of 24 hours, 7 days, 1 month or 3 months and the most used permanent material was composite resin. The maximum follow-up period was extended up to 72 months.

For direct capping using calcium hydroxide, success rates ranged from 44% to 100% at 6-month follow-up, 69% to 86% at 12-month, and 52% to 69% at 36-month. Regarding DPC with MTA, success rates varied from 81% to 100% at 6-month follow-up, 86% to 100% at 12-month, 84% to 92% at 18-month, 80% to 100% at 24-month, and 85% to 93% at 36-month. For Biodentine, success rates varied from 83% to 100% at 6-month follow-up, 80% to 100% at 12-month, 92% to 96% at 18-month, and 79% to 100% at 36-month follow-up. Endocem demonstrated a success rate of 83% at 12-month follow-up, and Theracal displayed success rates of 81% at 6-month follow-up, 73% at 12-month, and 72% at 36-month. The success rate was based on a combined assessment of clinical and radiographic evaluations. The separate success rates for clinical and radiographic assessments were not analyzed because of insufficient data from various studies.

Restorative Dentistry & Endodontics RDE

Table 1. Data from the included studies

Author and year	Teeth	Mature or immature teeth	Patients age	Cause of pulp exposure	Pulpal diagnosis	Material of comparison	Sample size	Temporary restorative material	Permanent restorative material and time of restoration	Follow-up time and success rate	Main findings
Hilton *et al.* (2013) [38]	ND	ND	7 yr or more	Caries, trauma or mechanical exposure	Excluded spontaneous pain	CH	336 (n = 181 for CH and 195 for MTA)	Resin-modified GIC	Final restorations were performed as deemed appropriate by the dentist	24 mon MTA: 80.3%, CH: 68.5%	The success rate using MTA was significantly higher compared to CH.
Jang *et al.* (2015) [39]	Incisors, premolars and molars	ND	19–79 yr	Trauma or caries	Included only reversible pulpitis	Endocem	46 (n = 23 for each group)	MTA: IRM Endocem: Resin-modified GIC	Direct resin, inlay or overlay or single crown 3 mon after DPC	12 mon MTA: 86.96%, Endocem: 83.33%	There was no statistically significant difference between groups.
Kundzina *et al.* (2017) [40]	Molars	Mature	18–55 yr	Caries	Excluded irreversible pulpitis	CH	70 (n = 33 for MTA and 37 for CH)	GIC	Composite resin 1 wk after DPC	36 mon MTA: 85%, CH: 52%	The success rate using MTA was significantly higher compared to CH.
Brizuela *et al.* (2017) [37]	Molars	Mature or immature	7–16 yr	Caries	Included normal pulp and reversible pulpitis	CH and BD	169 (n = 53 for CH, 56 for MTA and 60 for BD)	ND*	GIC + Composite resin immediately	6 mon CH: 93.11%, MTA: 91,89%, BD: 100% 12 mon CH: 86.36%, MTA: 86.36%, BD: 100%	There was no statistically significant difference between groups.
Katge and Patil (2017) [18]	First molars	ND	7–9 yr	Caries, pulp exposure during caries excavation	Excluded spontaneous pain	BD	42 (n = 21 for each group)	MTA: Resin-modified GIC BD: All cavity filled with BD	Composite resin 3 mon after DPC	6 mon MTA: 100%, BD: 100% 12 mon MTA: 100%, BD: 100%	There was no statistically significant difference between groups.
Linu *et al.* (2017) [41]	Mandibular molars	ND	15–30 yr	Caries	Excluded spontaneous pain	BD	30 (n = 15 for each group)	MTA: Resin-modified GIC BD: All cavity filled with BD	Composite resin 1 wk after DPC	18 mon MTA: 84.6%, BD: 92.3%	There was no statistically significant difference between groups.
Parinyaprom *et al.* (2018) [19]	ND*	Mature or immature	6–18 yr	Caries	Included normal pulp, reversible or irreversible pulpitis	BD	55 (n = 27 for MTA and 28 for BD)	MTA: Resin-modified GIC BD: All cavity filled with BD	Composite resin immediately	18 mon MTA: 92.6%, BD: 96.4%	There was no statistically significant difference between groups.
Awawdeh *et al.* (2018) [16]	Incisors, premolars and molars	Mature	16–51 yr	Caries	Included only reversible pulpitis	BD	68 (n = 34 for each group)	IRM	Amalgam or composite resin 7 days after DPC	6 mon BD: 100%, MTA: 100% 12 mon BD: 100%, MTA: 100% 24 mon BD: 100%, MTA: 100% 36 mon BD: 93.3%, MTA: 100%	There was no statistically significant difference between groups.

(continued to the next page)

https://rde.ac
https://doi.org/10.5395/rde.2024.49.e34

Restorative Dentistry & Endodontics RDE

Table 1. (Continued) Data from the included studies

Author and year	Teeth	Mature or immature teeth	Patients age	Cause of pulp exposure	Pulpal diagnosis	Material of comparison	Sample size	Temporary restorative material	Permanent restorative material and time of restoration	Follow-up time and success rate	Main findings
Suhag *et al*. (2019) [20]	Molars	Mature	15–40 yr	Caries	Included only reversible pulpitis	CH	64 (n = 32 for each group)	MTA: IRM	MTA: Resin-modified GIC after 24 hr CH: Resin-modified glass ionomer + Composite resin immediately	12 mon MTA: 93%, CH: 69%	The success rate using MTA was significantly higher compared to CH.
Peskersoy *et al*. (2021) [24]	Molars	ND	18–42 yr	Caries	Included only reversible pulpitis	BD, Theracal LC, conventional CH and light-cured CH (LC Calcihyd)	525 (n = 105 for each group)	ND	Composite resin immediately	6 mon MTA: 86%, BD: 84%, Theracal LC: 81%, CH: 76%, LC Calcihyd: 66% 12 mon MTA: 86%, BD: 80%, Theracal LC: 73%, CH: 72%, LC Calcihyd: 64% 36 mon MTA: 86.3%, BD: 79.4%, Theracal LC: 72.1%, CH: 69.4%, LC Calcihyd: 61%	The success rate using all calcium silicate-based cements was significantly higher than CH cements.
Agrawal Aanchal *et al*. (2021) [36]	Molars	ND	15–52 yr	Caries	Excluded irreversible pulpitis	CH	45 (n = 15 for each group)	MTA: IRM	Policarboxilate liner + Silver amalgam CH: immediately MTA: 24 hr after DPC	6 mon MTA: 100%, CH: 100%	There was no statistically significant difference between groups.
Holiel *et al*. (2021) [17]	Premolars and molars	ND	18–40 yr	Accidental traumatic pulp exposure	Excluded spontaneous pain	BD	45 (n = 15 for each group)	ND	Resin-modified GIC + Composite resin immediately	24 mon MTA: 100%, BD: 100%	There was no statistically significant difference between groups.
Selvendran *et al*. (2021) [42]	Molars	ND	19–40 yr	Caries	Included healthy pulp or reversible pulpitis	CH and BD	36 (n = 12 for each group)	IRM	After 1 mon	6 mon BD: 91.67%, MTA: 81.82%, CH: 44.44%	The success rate using MTA or BD was significantly higher than CH.

ND, no data; CH, calcium hydroxide; MTA, mineral trioxide aggregate; GIC, glass ionomer cement; BD, Biodentine; DPC, direct pulp capping; IRM, immediate restorative material.

https://rde.ac

https://doi.org/10.5395/rde.2024.49.e34

Quality assessment

The risk of bias for the 13 included studies is depicted in **Figure 2**. Five studies were considered as having high risk of bias in the domain of "deviations from intended interventions" [18,24,37,41,42]. The high-risk studies failed to consider potential dropouts during follow-up when calculating sample size or failed to assess how these dropouts could impact the study outcome. In addition, 1 study was considered as having high risk of bias and 2 studies were considered as having unclear risk of bias in the domain "randomization process" [24,39,41]. In these studies, the randomization was not described or performed by one of the study organizers at random. The other 7 studies were considered as having low risk of bias, as none of the evaluated biases was detected [16,17,19,20,36,38,40].

Meta-analysis

Different meta-analyses were performed to compare the success rate of DPC using MTA with different materials of comparison. Calcium hydroxide and Biodentine were the only materials evaluated in at least 2 studies. Endocem and TheraCal were evaluated in only 1 study each and, therefore, could not be included in the meta-analyses. **Figures 3** illustrate the meta-analyses for the MTA x calcium hydroxide comparison at 6-, 12- and 36-month follow-ups, respectively. Notably, the success rate for direct capping in permanent teeth using MTA was

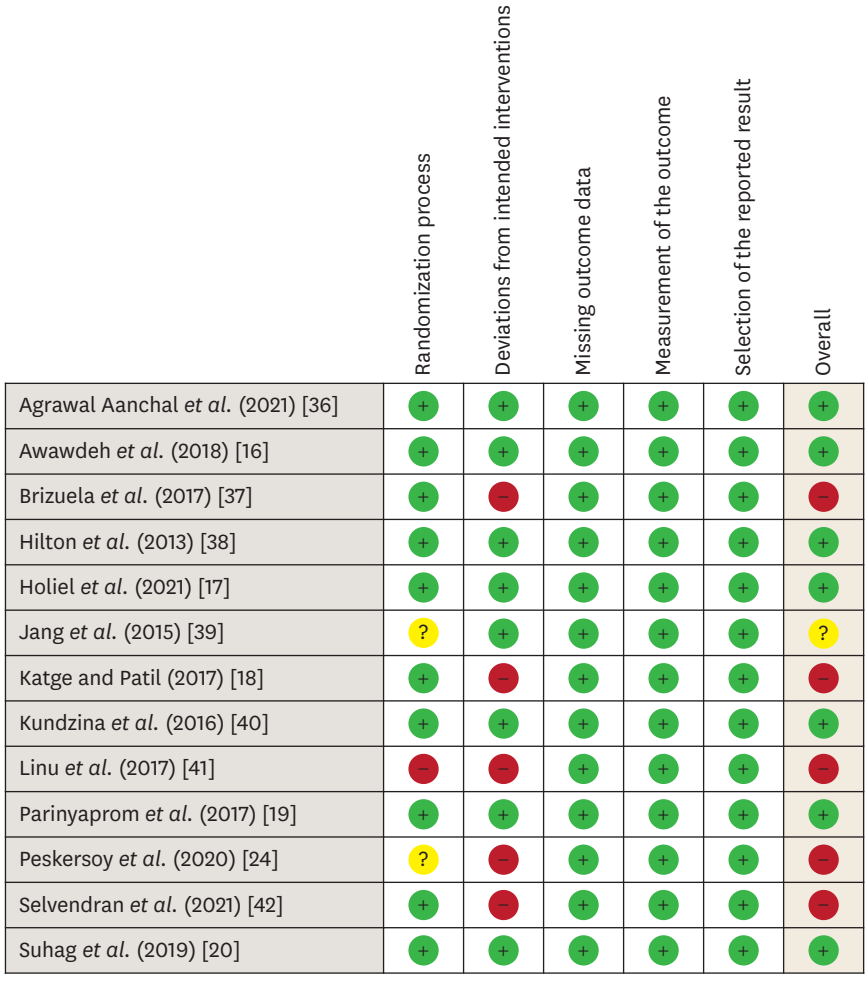

Figure 2. Risk of bias assessment.

https://doi.org/10.5395/rde.2024.49.e34

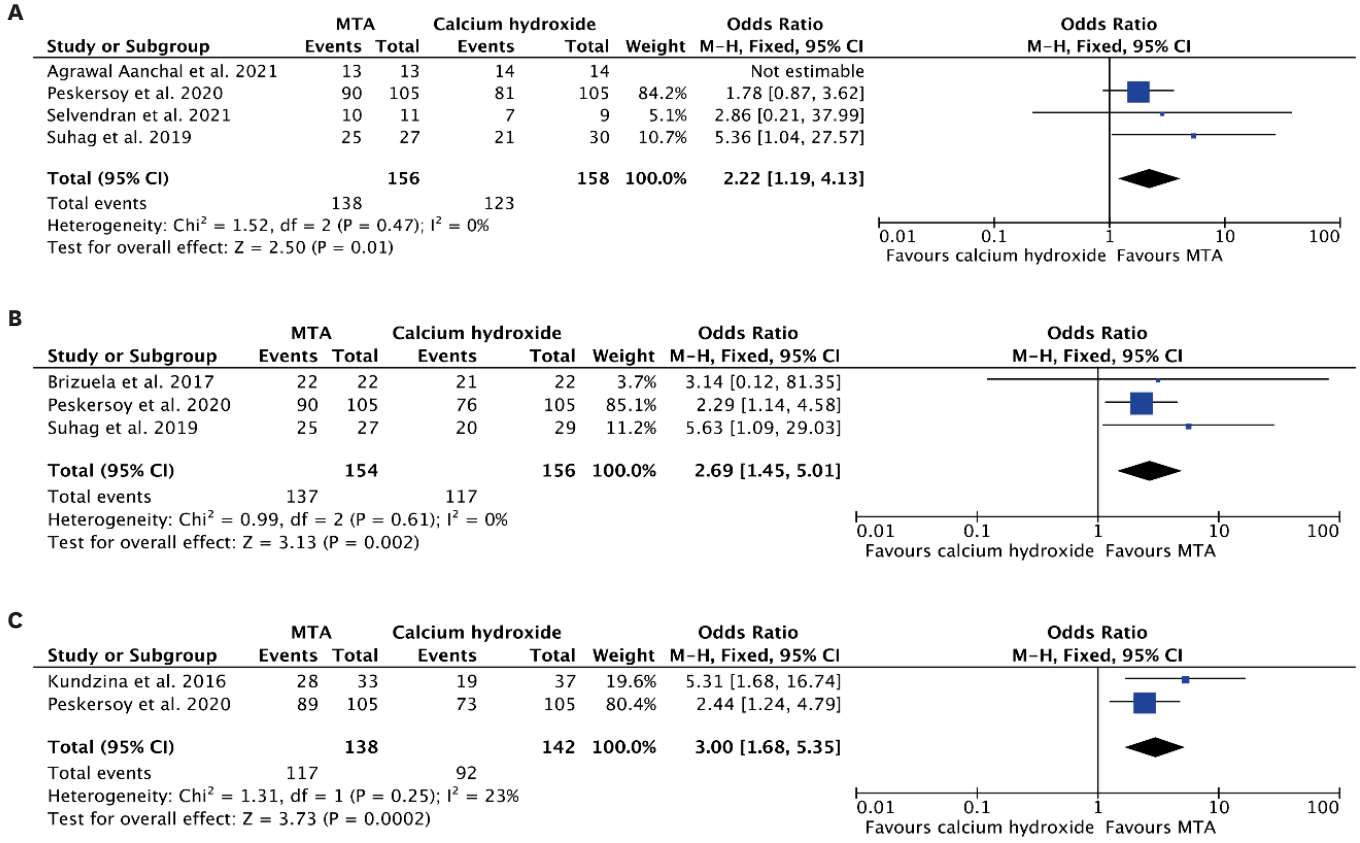

Figure 3. Forest plots of success cases of pulpotomy with MTA and calcium hydroxide at (A) 6-months follow-up, (B) 12-months follow-up and (C) 36-month follow-up showing that the success rate of pulpotomy on permanent teeth was significantly higher when using MTA compared to calcium hydroxide.
MTA, mineral trioxide aggregate; CI, confidence interval.

significantly higher than that of calcium hydroxide at all time points (6-months: $p = 0.01$; 12-month: $p = 0.002$; 36-month: $p = 0.0002$). **Figure 4** exhibit the meta-analyses of the comparison MTA and Biodentine at 6-, 12-, 18- and 36-month follow-ups, respectively. No statistically significant differences were observed between MTA and Biodentine (6-months: $p = 0.72$; 12-month: $p = 0.21$; 18-month: $p = 0.39$; 36-month: $p = 0.23$).

While the etiology of pulp exposure, root maturation level, and restoration methods are recognized as variables that could impact the efficacy of DPC, it was not possible to perform statistical analysis on their influence on success rate. This is due to the fact that only 1 study exclusively assessed accidental traumatic pulp exposure, no study focused solely on immature teeth, and considerable diversity existed in restorative approaches among the included studies [17].

Grading of evidence

The certainty of evidence for the included studies was rated low (**Table 2**). The 'risk of bias' domain was rated as 'serious' due to some studies having limited control over confounding factors in both their design and statistical analysis [31]. Conversely, the 'inconsistency' domain was rated as 'not serious,' given that the results were consistent and free from unexplained heterogeneity [33]. The 'indirectness' domain was also rated as 'not serious' because the studied populations were representative of those who would receive the recommended interventions and relevant patient outcomes were assessed [34]. The 'imprecision' domain

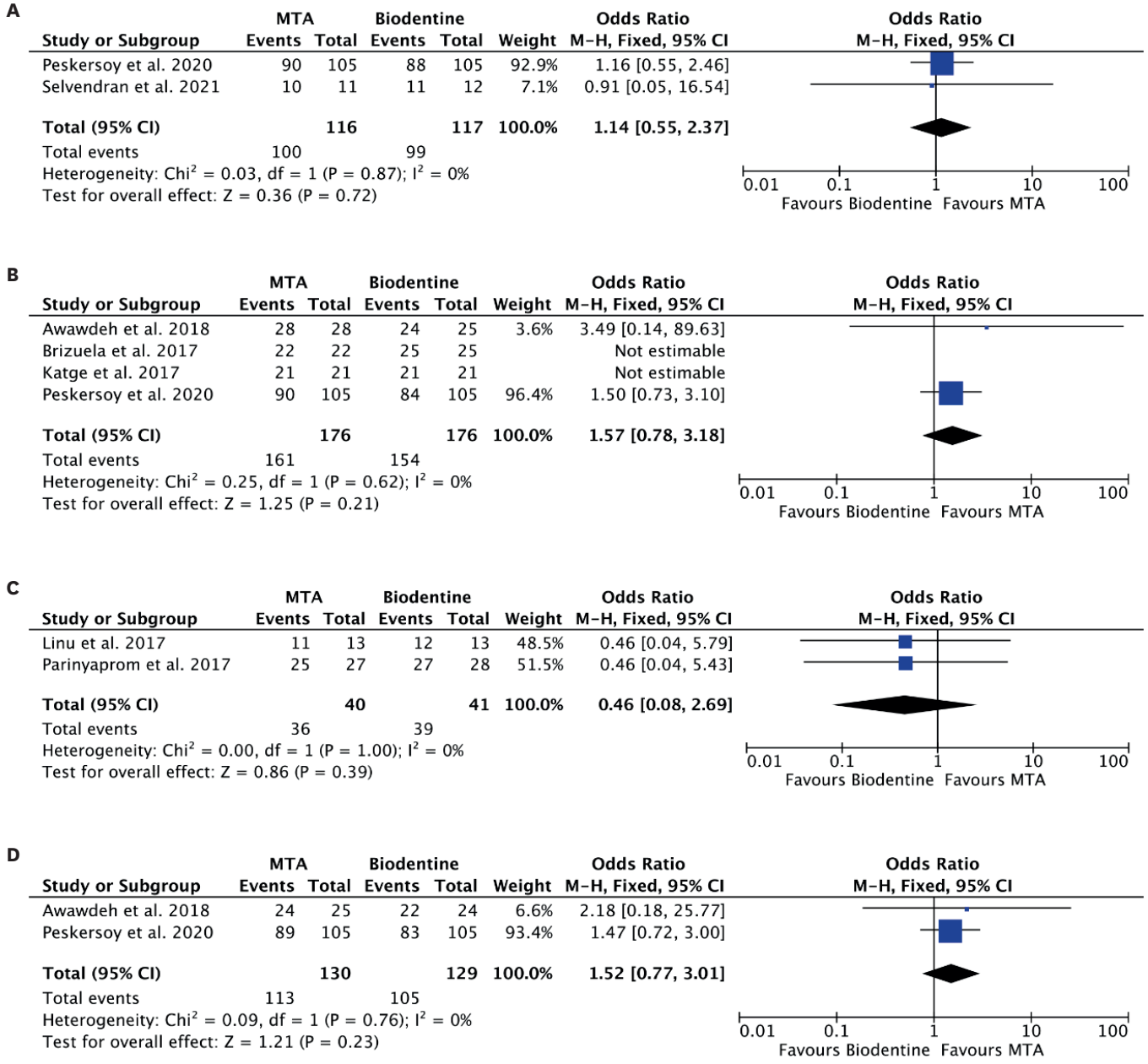

Figure 4. Forest plots of success cases of pulpotomy with MTA and Biodentine at (A) 6-months follow-up, (B) 12-month follow-up, (C) 18-month follow-up and (D) 36-month follow-up showing no significant differences in the success rate between the 2 materials.
MTA, mineral trioxide aggregate; CI, confidence interval.

was rated as 'very serious' due to the pooled sample size in most meta-analyses being under 300, with 95% confidence intervals including both significant benefit and harm (OR under 0.75 or over 1.25) [32]. While there were not enough studies for a quantitative assessment of publication bias using funnel plots or regression tests, publication bias was not deemed significant enough to lower the quality of evidence. This assessment was supported by the inclusion of studies from indexed and non-indexed journals and without any funds from the private sector [35].

Table 2. Assessment of the quality of evidence

Certainty assessment						
Participants (studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence
1,531 (13 RCTs)	Serious[a]	Not serious[b]	Not serious[c]	Very serious[d]	None[e]	⊕⊕◯◯ LOW

RCT, randomized clinical trial.
[a]Several studies exhibited shortcomings in controlling confounding factors within the study design or statistical analysis.
[b]All studies showed consistent results and was not observed unexplained heterogeneity.
[c]Populations were representative of the patients for whom the interventions are recommended and patient-important outcomes were assessed.
[d]In most meta-analyses, the pooled sample size was less than 300 and the 95% confidence interval of the effect estimate included significant benefit or harm (odds ratio under 0.75 or over 1.25).
[e]The possibility of publication bias was not excluded but it was not considered sufficient to downgrade the quality of evidence, as no study was funded by industry.

DISCUSSION

The primary aim of this systematic review was to assess the success rate of DPC on permanent teeth using MTA, in comparison to both calcium hydroxide and other calcium silicate-based cements. The studies included in the present systematic review demonstrated success rates exceeding 80% for MTA and over 70% for the calcium silicate-based cements Biodentine, Endocem and TheraCal, even after 3 years of follow-up. This indicates the effectiveness of these materials used in vital pulp therapy on permanent teeth. In contrast, the studies revealed a significantly lower success rate when using calcium hydroxide, a finding confirmed by the meta-analyses. Therefore, the null hypothesis was rejected.

Over the last decades, calcium hydroxide has been considered the gold standard material for DPC, given its excellent physicochemical properties that stimulate pulp repair [43]. Despite its extensive application in DPC, studies have shown that calcium hydroxide has weak bonding to dentin, low mechanical strength, and high solubility and degradation over time, resulting in suboptimal sealing [8,10]. In fact, the present meta-analyses indicated that the difference in success rates between MTA and calcium hydroxide increased overtime, with odds ratios of 2.22 at 6 months, 2.69 at 1 year and 3.00 at 3 years. Moreover, several studies show tunnel-like defects in calcium hydroxide-induced reparative dentin formation [8,10,44]. In contrast, MTA has shown promising results for DPC. Unlike calcium hydroxide, MTA has excellent sealing ability, long-term stability and low solubility, in addition to resulting in less pulpal inflammation and better dentin bridge formation [44-46].

The outcomes of this systematic review revealed no significant difference in the success of DPC on permanent teeth when comparing the use of MTA with Biodentine. Both MTA and Biodentine yielded success rates ranging from 80% to 100%, even after a 3-year span of DPC [16,24]. A recent systematic review has also demonstrated a similar success rate when employing either MTA or Biodentine in pulpotomy procedures on permanent teeth [47]. Biodentine shows excellent physio-chemical properties, including biocompatibility, bioactivity, and adhesion to dentin. Furthermore, its simpler manipulation and handling, facilitated by automatic mixing using a capsule amalgamator, obviates the likelihood of manipulation and proportion errors that commonly occur with other materials [48].

Endocem and TheraCal, other calcium silicate-based cements, underwent an examination in only 1 study each included in the present review. Consequently, they could not be included in

the conducted meta-analyses. However, the results of the included studies also demonstrated no statistically significant difference in the outcomes when comparing the use of MTA with Endocem [39]. However, MTA showed a significantly better success rate compared to TheraCal after 1 and 3 years of follow-up [24]. Thus, more long-term studies are needed to evaluate the effectiveness of these materials for DPC on permanent teeth.

In the present systematic review, it was not possible to perform statistical analysis to assess the influence of factors such as the cause of pulp exposure, root maturity status, and restoration procedures on the success rate of DPC. This limitation arises because only 1 study exclusively examined accidental traumatic pulp exposure, none of the studies focused solely on immature teeth, and there was considerable variability in restorative procedures [17]. In fact, most of the studies included in this review did not differ between permanent teeth with open or closed apex, although some studies included children and teenagers. It is well-established that young teeth with open apex possess greater blood supply, ensuring greater resistance to pulp infection [49]. However, the consistently high success rate observed in DPC studies, even when considering age groups suggests that this procedure can be highly effective regardless of the stage of root development.

Most studies included in this review did not provide relevant data concerning factors that may influence both the indication and outcome of DPC, such as the location and dimensions of pulp exposure, as well as the extent of bleeding at the exposure site [1,2]. In carious-exposed pulps, a higher frequency of pulp exposures, larger pulp exposures and pronounced bleeding have been linked to a worse prognosis for DPC [1,2]. These variables are predictive of more extensive pulp damage and underscore the critical nature of accurate clinical diagnosis. One of the included studies showed that pulpal exposure in class V cavities resulted in a significantly higher failure rate (50%) compared to class I, II, and III cavities (5.3%) [39]. Regarding the size of pulpal exposure, only 2 studies specified that exposures were up to 2 mm^2, while the others did not assess this parameter [17,42]. Two studies reported homeostasis times up to 3 minutes and 4 minutes, both showing high success rates for DPC using MTA or Biodentine, exceeding 92% [16,19]. Studies indicating homeostasis time of approximately 10 minutes showed success rates for MTA, Biodentine, or Endocem of over 80% [20,36,37,39-42]. These high success rates highlight the importance of an accurate diagnosis, as nearly all studies excluded patients with signs and symptoms of irreversible pulpitis.

The solutions used to achieve hemostasis with moistened cotton pellets also varied widely among the included studies. Sodium hypochlorite was the most commonly used solution, with concentrations ranging from 0.5%, 2.5%, 3%, 5%, to 5.25% [16,19,20,36,38-41]. Saline was also used in some studies, and 1 study managed pulpal bleeding with 2% lidocaine with adrenaline [17,18,24,37,42]. No differences in success rates were observed among the calcium-silicate-based cements based on the solution used, but the study that employed anesthetic reported the lowest success rate with calcium hydroxide among all studies. Furthermore, a pivotal factor influencing the success of DPC is the restorative procedure. A recent study observed that the main variable impacting the outcome of DPC using calcium hydroxide was the quality of the coronal restoration [2]. In the present review, a lack of standardized methodology in restorative procedures was observed in the included RCTs. Several studies employed a temporary restoration, followed by permanent restoration at intervals of 7 days, 1 month or 3 months [10,16,18,39,41,42]. However, the latest position statements from both the European Society of Endodontology [3] and the American Association of Endodontists (AAE) [50] concerning vital pulp therapies advocate for the

immediate restoration of the tooth after DPC. This recommendation is aimed at averting microleakage, protecting the biomaterial and reducing post-operative sensitivity and thermal conductivity [50].

The present systematic review and meta-analysis has some limitations. The high risk of bias identified in 5 out of the 13 studies included in the present review, the high heterogeneity in methodologies and follow-up times among the included studies, and the lack of control over confounding factors, along with the absence of relevant data, can influence the outcome of DPC within the reviewed studies. Moreover, GRADE analysis indicates an overall low certainty of the evidence, underscoring the need for a cautious interpretation of the present findings. Therefore, the present review highlights the necessity for well-designed future randomized clinical trials focused on evaluating the long-term results of direct capping using newer bioceramic materials.

CONCLUSIONS

The present findings showed that DPC is highly effective for permanent teeth when using MTA or Biodentine. The certainty of the evidence was low and there is a need for future well-designed randomized clinical trials to evaluate the efficacy of DPC using newer bioceramic materials.

SUPPLEMENTARY MATERIAL

Supplementary Table 1
Databases search

REFERENCES

1. Matsuo T, Nakanishi T, Shimizu H, Ebisu S. A clinical study of direct pulp capping applied to carious-exposed pulps. J Endod 1996;22:551-556. PUBMED | CROSSREF
2. Ricucci D, Rôças IN, Alves FR, Cabello PH, Siqueira JF Jr. Outcome of direct pulp capping using calcium hydroxide: a long-term retrospective study. J Endod 2023;49:45-54. PUBMED | CROSSREF
3. Duncan HF, Galler KM, Tomson PL, Simon S, El-Karim I, Kundzina R, *et al.* European Society of Endodontology position statement: management of deep caries and the exposed pulp. Int Endod J 2019;52:923-934. PUBMED | CROSSREF
4. Liu S, Wang S, Dong Y. Evaluation of a bioceramic as a pulp capping agent *in vitro* and *in vivo*. J Endod 2015;41:652-657. PUBMED | CROSSREF
5. Komabayashi T, Zhu Q, Eberhart R, Imai Y. Current status of direct pulp-capping materials for permanent teeth. Dent Mater J 2016;35:1-12. PUBMED | CROSSREF
6. Leye Benoist F, Gaye Ndiaye F, Kane AW, Benoist HM, Farge P. Evaluation of mineral trioxide aggregate (MTA) versus calcium hydroxide cement (Dycal(®)) in the formation of a dentine bridge: a randomised controlled trial. Int Dent J 2012;62:33-39. PUBMED | CROSSREF
7. Lu Y, Liu T, Li H, Pi G. Histological evaluation of direct pulp capping with a self-etching adhesive and calcium hydroxide on human pulp tissue. Int Endod J 2008;41:643-650. PUBMED | CROSSREF
8. Cox CF, Sübay RK, Ostro E, Suzuki S, Suzuki SH. Tunnel defects in dentin bridges: their formation following direct pulp capping. Oper Dent 1996;21:4-11. PUBMED
9. Mohammadi Z, Dummer PM. Properties and applications of calcium hydroxide in endodontics and dental traumatology. Int Endod J 2011;44:697-730. PUBMED | CROSSREF

10. Nowicka A, Wilk G, Lipski M, Kołecki J, Buczkowska-Radlińska J. Tomographic evaluation of reparative dentin formation after direct pulp capping with Ca(OH)2, MTA, biodentine, and dentin bonding system in human teeth. J Endod 2015;41:1234-1240. PUBMED | CROSSREF
11. Nasseh A. The rise of bioceramics. Endod Prac 2009;2:21-26.
12. Han L, Okiji T. Bioactivity evaluation of three calcium silicate-based endodontic materials. Int Endod J 2013;46:808-814. PUBMED | CROSSREF
13. Lee SJ, Monsef M, Torabinejad M. Sealing ability of a mineral trioxide aggregate for repair of lateral root perforations. J Endod 1993;19:541-544. PUBMED | CROSSREF
14. Camilleri J. The chemical composition of mineral trioxide aggregate. J Conserv Dent 2008;11:141-143. PUBMED | CROSSREF
15. Tomson PL, Lumley PJ, Smith AJ, Cooper PR. Growth factor release from dentine matrix by pulp-capping agents promotes pulp tissue repair-associated events. Int Endod J 2017;50:281-292. PUBMED | CROSSREF
16. Awawdeh L, Al-Qudah A, Hamouri H, Chakra RJ. Outcomes of vital pulp therapy using mineral trioxide aggregate or biodentine: a prospective randomized clinical trial. J Endod 2018;44:1603-1609. PUBMED | CROSSREF
17. Holiel AA, Mahmoud EM, Abdel-Fattah WM. Tomographic evaluation of direct pulp capping using a novel injectable treated dentin matrix hydrogel: a 2-year randomized controlled clinical trial. Clin Oral Investig 2021;25:4621-4634. PUBMED | CROSSREF
18. Katge FA, Patil DP. Comparative analysis of 2 calcium silicate-based cements (biodentine and mineral trioxide aggregate) as direct pulp-capping agent in young permanent molars: a split mouth study. J Endod 2017;43:507-513. PUBMED | CROSSREF
19. Parinyaprom N, Nirunsittirat A, Chuveera P, Na Lampang S, Srisuwan T, Sastraruji T, *et al*. Outcomes of direct pulp capping by using either proroot mineral trioxide aggregate or biodentine in permanent teeth with carious pulp exposure in 6- to 18-year-old patients: a randomized controlled trial. J Endod 2018;44:341-348. PUBMED | CROSSREF
20. Suhag K, Duhan J, Tewari S, Sangwan P. Success of direct pulp capping using mineral trioxide aggregate and calcium hydroxide in mature permanent molars with pulps exposed during carious tissue removal: 1-year follow-up. J Endod 2019;45:840-847. PUBMED | CROSSREF
21. Andrei M, Vacaru RP, Coricovac A, Ilinca R, Didilescu AC, Demetrescu I. The effect of calcium-silicate cements on reparative dentinogenesis following direct pulp capping on animal models. Molecules 2021;26:2725. PUBMED | CROSSREF
22. Loison-Robert LS, Tassin M, Bonte E, Berbar T, Isaac J, Berdal A, *et al*. *In vitro* effects of two silicate-based materials, Biodentine and BioRoot RCS, on dental pulp stem cells in models of reactionary and reparative dentinogenesis. PLoS One 2018;13:e0190014. PUBMED | CROSSREF
23. Arandi NZ, Rabi T. TheraCal LC: from biochemical and bioactive properties to clinical applications. Int J Dent 2018;2018:3484653. PUBMED | CROSSREF
24. Peskersoy C, Lukarcanin J, Turkun M. Efficacy of different calcium silicate materials as pulp-capping agents: randomized clinical trial. J Dent Sci 2021;16:723-731. PUBMED | CROSSREF
25. Alsubait S, Aljarbou F. Biodentine or mineral trioxide aggregate as direct pulp capping material in mature permanent teeth with carious exposure? A systematic review and meta-analysis. Oper Dent 2021;46:631-640. PUBMED | CROSSREF
26. Cushley S, Duncan HF, Lappin MJ, Chua P, Elamin AD, Clarke M, *et al*. Efficacy of direct pulp capping for management of cariously exposed pulps in permanent teeth: a systematic review and meta-analysis. Int Endod J 2021;54:556-571. PUBMED | CROSSREF
27. da Costa BR, Juni P. Systematic reviews and meta-analyses of randomized trials: principles and pitfalls. Eur Heart J 2014;35:3336-3345. PUBMED | CROSSREF
28. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, *et al*. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. PUBMED | CROSSREF
29. Maia LC, Antonio AG. Systematic reviews in dental research. A guideline. J Clin Pediatr Dent 2012;37:117-124. PUBMED | CROSSREF
30. Sterne JA, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, *et al*. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ 2019;366:l4898. PUBMED | CROSSREF
31. Guyatt G, Oxman AD, Akl EA, Kunz R, Vist G, Brozek J, *et al*. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. J Clin Epidemiol 2011;64:383-394. PUBMED | CROSSREF
32. Guyatt GH, Oxman AD, Kunz R, Brozek J, Alonso-Coello P, Rind D, *et al*. GRADE guidelines 6. Rating the quality of evidence--imprecision. J Clin Epidemiol 2011;64:1283-1293. PUBMED | CROSSREF

33. Guyatt GH, Oxman AD, Kunz R, Woodcock J, Brozek J, Helfand M, *et al*. GRADE guidelines: 7. Rating the quality of evidence--inconsistency. J Clin Epidemiol 2011;64:1294-1302. PUBMED | CROSSREF

34. Guyatt GH, Oxman AD, Kunz R, Woodcock J, Brozek J, Helfand M, *et al*. GRADE guidelines: 8. Rating the quality of evidence--indirectness. J Clin Epidemiol 2011;64:1303-1310. PUBMED | CROSSREF

35. Guyatt GH, Oxman AD, Sultan S, Glasziou P, Akl EA, Alonso-Coello P, *et al*. GRADE guidelines: 9. Rating up the quality of evidence. J Clin Epidemiol 2011;64:1311-1316. PUBMED | CROSSREF

36. Agrawal Aanchal MA, Shenoy VU, Sumanthini VM, Satpute Tanvi S. Comparative evaluation of resin-modified glass ionomer cement, mineral trioxide aggregate, and calcium hydroxide when used as a direct pulp capping material on carious pulp exposures of human permanent teeth: a randomized clinical trial. World J Dent 2021;12:381-385. CROSSREF

37. Brizuela C, Ormeño A, Cabrera C, Cabezas R, Silva CI, Ramírez V, *et al*. Direct pulp capping with calcium hydroxide, mineral trioxide aggregate, and biodentine in permanent young teeth with caries: a randomized clinical trial. J Endod 2017;43:1776-1780. PUBMED | CROSSREF

38. Hilton TJ, Ferracane JL, Mancl L, Baltuck C, Barnes C, Beaudry D, *et al*. Comparison of CaOH with MTA for direct pulp capping: a PBRN randomized clinical trial. J Dent Res 2013;92 Supplement:16S-22S. PUBMED | CROSSREF

39. Jang Y, Song M, Yoo IS, Song Y, Roh BD, Kim E. A randomized controlled study of the use of ProRoot mineral trioxide aggregate and Endocem as direct pulp capping materials: 3-month versus 1-year outcomes. J Endod 2015;41:1201-1206. PUBMED | CROSSREF

40. Kundzina R, Stangvaltaite L, Eriksen HM, Kerosuo E. Capping carious exposures in adults: a randomized controlled trial investigating mineral trioxide aggregate versus calcium hydroxide. Int Endod J 2017;50:924-932. PUBMED | CROSSREF

41. Linu S, Lekshmi MS, Varunkumar VS, Sam Joseph VG. Treatment outcome following direct pulp capping using bioceramic materials in mature permanent teeth with carious exposure: a pilot retrospective study. J Endod 2017;43:1635-1639. PUBMED | CROSSREF

42. Selvendran KE, Ahamed AS, Krishnamurthy M, Kumar VN, Raju VG. Comparison of clinical success between three different materials- direct pulp capping of carious molars- an in-vivo stud. J Pharm Res Int 2021;33:192-200. CROSSREF

43. Baume LJ, Holz J. Long term clinical assessment of direct pulp capping. Int Dent J 1981;31:251-260. PUBMED

44. Li Z, Cao L, Fan M, Xu Q. Direct pulp capping with calcium hydroxide or mineral trioxide aggregate: a meta-analysis. J Endod 2015;41:1412-1417. PUBMED | CROSSREF

45. Ferk Luketić S, Malcić A, Jukić S, Anić I, Segović S, Kalenić S. Coronal microleakage of two root-end filling materials using a polymicrobial marker. J Endod 2008;34:201-203. PUBMED | CROSSREF

46. Okiji T, Yoshiba K. Reparative dentinogenesis induced by mineral trioxide aggregate: a review from the biological and physicochemical points of view. Int J Dent 2009;2009:464280. PUBMED | CROSSREF

47. Silva EJ, Pinto KP, Belladonna FG, Ferreira CM, Versiani MA, De-Deus G. Success rate of permanent teeth pulpotomy using bioactive materials: a systematic review and meta-analysis of randomized clinical trials. Int Endod J 2023;56:1024-1041. PUBMED | CROSSREF

48. Camilleri J, Sorrentino F, Damidot D. Investigation of the hydration and bioactivity of radiopacified tricalcium silicate cement, Biodentine and MTA Angelus. Dent Mater 2013;29:580-593. PUBMED | CROSSREF

49. Camp JH. Diagnosis dilemmas in vital pulp therapy: treatment for the toothache is changing, especially in young, immature teeth. Pediatr Dent 2008;30:197-205. PUBMED | CROSSREF

50. AAE. AAE position statement on vital pulp therapy. J Endod 2021;47:1340-1344. PUBMED | CROSSREF