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Materials used for indirect pulp treatment in primary teeth: a mixed treatment comparisons meta-analysis

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Abstract: This study aimed to systematically review the literature to address the question regarding the influence of different materials in the clinical and radiographic success of indirect pulp treatment in primary teeth. A literature search was carried out for articles published prior to January 2017 in PubMed/MEDLINE, CENTRAL, Scopus, TRIP and ClinicalTrials databases; relevant articles included randomized clinical trials that compared materials used for indirect pulp treatment in primary teeth. Two reviewers independently selected the studies and extracted the data. The effects of each material on the outcome (clinical and radiographic failures) were analyzed using a mixed treatment comparisons meta-analysis. The ranking of treatments according to their probability of being the best choice was also calculated. From 1,088 potentially eligible studies, 11 were selected for full-text analysis, and 4 were included in the meta-analysis. In all papers, calcium hydroxide liner was used as the control group versus an adhesive system, resin-modified glass ionomer cement or placebo. The follow-up period ranged from 24 to 48 months, with dropout rates of 0-25.7%. The material type did not significantly affect the risk of failure of the indirect pulp treatment. However, calcium hydroxide presented a higher probability of failure. In conclusion, there is no scientific evidence showing the superiority of any material used for indirect pulp treatment in primary teeth.

Keywords: Tooth, Deciduous; Review; Calcium Hydroxide.

Introduction

According to the guidelines of the American Academy of Pediatric Dentistry (AAPD), indirect pulp treatment is a procedure recommended for teeth with deep carious lesions without signs or symptoms of pulp degeneration.[1] The main goal of this minimal intervention approach is based on modification of the microenvironment of the contaminated dentin, intentionally left under the restoration, thereby arresting the cariogenic process, while preserving the tooth structure and pulp vitality.[2] Furthermore, indirect pulp treatment is preferable to pulpotomy, because the former has shown higher rates of clinical and radiographic success.[1,3] Several materials have been used for indirect pulp treatment in primary teeth, such as calcium hydroxide liner,[4,5,6] dentin bonding agents[5,7] mineral trioxide aggregate[6], glass ionomer cement,[8] zinc oxide/eugenol,[9] calcium silicate[10] or medical Portland cement.[11]

Despite the indication of using a biocompatible material over the remaining demineralized dentin,[1] it has been shown the arresting caries lesion can be achieved even when inert materials (*i.e.*, gutta-percha) are used as capping materials.[4,12] This finding emphasizes that carious dentin can be arrested if margins of restorations remain sealed. It has been reported that glass ionomer cement or resin composite provide adequate marginal sealing in primary teeth submitted to indirect pulp capping.[8,13]

A recent systematic review found that using a calcium hydroxide liner is unsubstantiated, but solid evidence for omitting a lining is not available.[14] In this sense, doubts have been raised regarding the need for the use of a calcium hydroxide liner for maintaining pulp vitality, particularly if there is a better material to use in the indirect pulp treatment. Direct evidence from high-quality randomized clinical trials should be used wherever possible. Without this evidence, it is necessary to look for indirect comparisons from randomized clinical trials.[15]

Therefore, the aim of this systematic review and mixed treatment comparison (MTC) meta-analysis was to address the question regarding the influence of different materials in the clinical and radiographic success of indirect pulp treatment in primary teeth.

Methodology

This systematic review was written according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement.[16]

The following research question was formulated to address the literature and outline the search strategy: Is there a better material used for indirect pulp treatment in primary teeth?

Search strategy and selection criteria

A comprehensive literature search was undertaken using PubMed/MEDLINE, Cochrane Central Register of Controlled Trials (CENTRAL), Scopus, and TRIP databases to identify studies that were related to the research question and that were published prior to January 2017. The search was conducted with no publication year or language limits. The subject search used a combination of controlled vocabulary and text words based on the search strategy for the PubMed/MEDLINE database as follows:

((((((((((((((((((((Dental Pulp Capping[MeSH Terms]) OR Dental Pulp Capping) OR Indirect Pulp Capping) OR Indirect Pulp Treatment) OR Indirect Capping) OR Partial Caries Removal) OR Selective Caries Removal) OR Deep Carious Lesions) AND Tooth, Deciduous[MeSH Terms]) OR Deciduous Tooth) OR Deciduous Teeth) OR Primary Tooth) OR Primary Teeth) OR Primary Dentition) OR Deciduous Dentition) OR Primary Molars) OR Deciduous Molars)) AND ((((((((((((((((((((((((Calcium Hydroxide[MeSH Terms]) OR Calcium Hydroxide) OR mineral trioxide aggregate[MeSH Terms]) OR mineral trioxide aggregate) OR MTA cement) OR MT aggregate) OR Portland cement) OR Glass Ionomer Cements[MeSH Terms]) OR Glass Ionomer Cement*) OR Glass-Ionomer Cement*) OR Glass Polyalkenoate Cement*) OR Resin modified glass ionomer) OR Resin-modified glass ionomer) OR Dentin-Bonding Agents[MeSH Terms]) OR Dentin-Bonding Agent*) OR Dentin Bonding Agent*) OR Adhesive*) OR Gutta-Percha[MeSH Terms]) OR Gutta-Percha) OR Gutta Percha) OR Guttapercha) OR Zinc Oxide-Eugenol Cement[MeSH Terms]) OR Zinc Oxide-Eugenol Cement) OR Zinc Oxide Eugenol Cement) OR Chlorhexidine[MeSH Terms]) OR Chlorhexidine OR Biodentin*)) AND ((((clinical[Title/Abstract] AND trial[Title/Abstract]) OR clinical trials as topic[MeSH Terms] OR clinical trial[Publication Type] OR random*[Title/Abstract] OR random allocation[MeSH Terms] OR therapeutic use[MeSH Subheading]))))

A sensitive search strategy was adapted for the CENTRAL, TRIP and Scopus databases. To reduce publication bias, unpublished documents were searcher for through ClinicalTrials (website). The results of searches of various databases were cross-checked to locate and eliminate duplicates.

Two reviewers (D.P. and P.S.S.) independently assessed the identified publications and selected them by title and abstract based on the following inclusion criteria: clinical trials comparing different materials used for protection of dentin-pulp complex in primary teeth submitted to indirect pulp capping. When only a relevant title without a listed abstract was available, a full copy of the article was used for evaluation. The reviewers were previously trained and calibrated for

paper selection (Kappa = 0.91). Any discrepancies were solved through discussion and consensus with a third reviewer (T.L.L.). To retrieve all relevant papers, the same reviewers also screened the reference lists of the included papers and their related reviews.

A final decision about inclusion of potentially relevant studies was made based on a full-text evaluation. Exclusion criteria were as follows: non-random allocation of subjects or less than 2 arms; not a longitudinal clinical trial with minimum follow-up of 6 months; a dropout rate higher than 30%[17]; an absence of similar follow-up for subjects of both groups, as evaluated in the same way; did not report computable data for both groups; did not assess clinical and radiographic success as the outcome. In the case of studies reporting the same sample, we included those that presented more available information.

Data extraction

A protocol for data extraction was defined. Two reviewers (D.P. and P.S.S.) independently collected the data of the eligible studies. For each paper, the following data were systematically extracted: publication details (title, authors and year), sample characteristics (number of participants and age, sample size), study methodology (commercial brand and manufacturer of the materials for protection of dentin-pulp complex and restorative procedures, operators' number) and outcome information (clinical and radiographic success, follow-up and dropout).

Risk of bias assessment

Two reviewers (D.P. and P.S.S.) independently assessed (Kappa = 0.97) the risk of bias, based on the published specific study design-related risk bias assessed forms (*Cochrane Handbook for Systematic Reviews of Interventions* 5.0.1).[18] The criteria were divided into seven domains as follows: selection bias (sequence generation, allocation concealment), performance and detection bias (blinding of participants, personnel, outcome assessment), attrition bias (incomplete outcome data), and reporting bias (selective outcome reporting). Evaluation of the studies was performed by rating each domain as low, high or unclear risk of bias (no information or uncertainty over the potential for bias). For the final classification of risk of bias, disagreements between the reviewers were solved by consensus. Authors were contacted via e-mail (at least twice) for missing or unclear information.

Statistical analyses

We performed a per-protocol analysis (analysis of participants based on the intervention they received and their availability for follow-up). The effects of each material used for indirect pulp treatment in primary teeth on the outcome (clinical and radiographic failures) were analyzed using MTC meta-analysis. MTC is a generalization of a traditional pairwise meta-analysis that allows all evidence from multiple treatments to be taken into account simultaneously in a single model, combining direct and indirect evidence.[19] As MTC is based on a Bayesian hierarchical framework, the estimates (a posteriori) were obtained by Markov-Chain Monte Carlo simulations and expressed as Risk Relative (RR), with 95% confidence intervals (95%CI). For the analysis, we choose the R statistical software using the GeMTC-package, version 0.8, and the rJAGSpackage to estimate the models.

The choice between fixed and random effects was made by comparing the competing models using the deviance information criteria (DIC). For each model, goodness-of-fit to the data was evaluated using residual deviance.[20] Each chain used 30,000 interactions with a burn-in of 60,000 and a thinning interval of 25. Vague prior distributions were used for all models. The fixed effect model showed the best fit according to the values of DIC. The expected ranking of efficacy for all treatments based on the posterior probabilities of all treatment rankings (*i.e.*, the probability of being the best, the probability of second best, and so on)[19] was also calculated. A node splits analysis for inconsistency was not performed, because most parts of the treatment did not present direct comparisons, except for calcium hydroxide.

Results

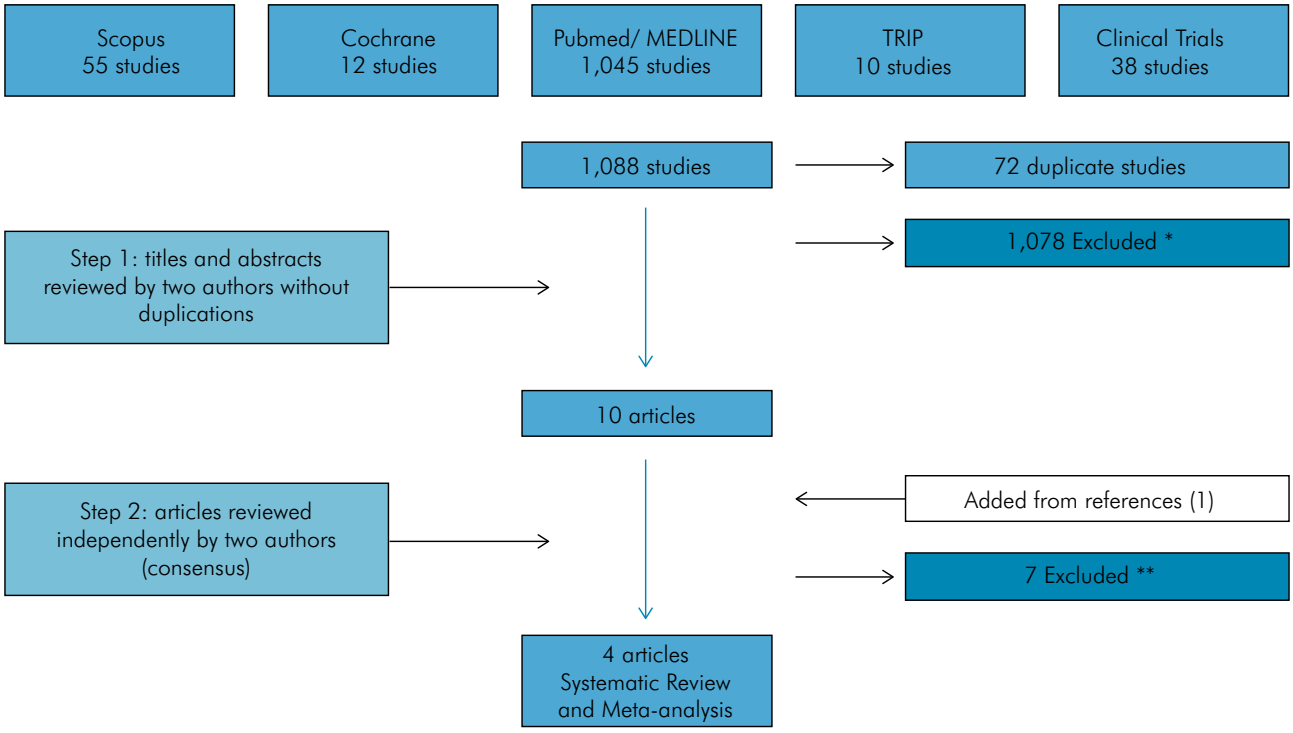
Study selection

The search strategy identified 1,088 potentially relevant records, excluding duplicates. After screening titles and abstracts, 10 studies were retrieved for more detailed information. Another study was identified in

reference lists of related reviews. From the 11 full-text articles, 2 randomized clinical trials were published in 2 reports with different follow-up periods. For one study[7], the paper with a longer follow-up[21] was excluded because of a reported dropout rate higher than 30%. For another trial,[5,22] the paper with a lower follow-up was excluded.[22] Finally, 4 papers met the eligibility criteria and were included in the systematic review, totaling 133 cases divided into 4 different materials for indirect pulp treatment. A flow chart summarizes the process of studies selection and the reasons for exclusions (Figure 1).

Characteristics of the included studies

The main characteristics of the included studies are presented in Table 1. All studies[5,7,8,13] were performed in secondary care in Brazil and used a calcium hydroxide liner for the control group. In two studies,[5,7] the experimental group used an adhesive system; one paper[8] tested a resin-modified glass ionomer cement; and another study[13] used a placebo layer (gutta-percha). Resin composite restorations were performed in the majority of the studies.[5,7,13]. In one paper,[8] resin-modified glass ionomer cement was used as a material for dentin-pulp complex protection and direct restoration, and it was compared with resin



*** Exclusions (a study could have fulfilled more than one criteria):**
No comparison of materials for indirect pulp treatment in primary teeth (n=5); Review (n=116); Other area of interest (n=957).

**** Exclusions:**
Non-random allocation of subjects (n=1); Follow-up lower than 6 months (n=2); Dropout higher than 30% (n=1); Did not assess clinical and radiographic success as outcome (n=4); Duplicate data (n=2); Did not evaluate only deep caries lesions (n=1); Did not remove caries infected dentin in the control group (n=1)

Figure 1. Flow diagram of the study selection according to the PRISMA statement.

Table 1. Detailed chart related to studies included in the systematic review.

Author	Country	Participants N (age), teeh (n)	Intervention	Control	Operator	Follow-up (months)	Dropout (%)	Failure – Protocol analysis		Overall success (%)
								Clinical	Radiographic	
Falster et al. (2002)[7]	Brazil	3–5 year-old children 48 primary molars with active carious lesion in deep dentin limited to the occlusal surface without symptoms of irreversible pulpitis	Scotchbond Multipurpose Adhesive (3M ESPE, St. Paul, MN, USA) and RC Z100 (3M ESPE, St. Paul, MN, USA) (n = 25)	CH (Dycal, Dentsply, Milford, DE), Scotchbond Multipurpose Adhesive (3M ESPE, St. Paul, MN, USA) and RC Z100 (3M ESPE, St. Paul, MN, USA) (n = 23)	1	24	0	AD: 0/25 CH: 0/23	AD: 1/25 CH: 4/23	96 83
Marchi et al. (2006)[8]	Brazil	17 children (4–9 year-old) 27 primary molars with active carious lesion in deep dentin in occlusal/ proximal surfaces without symptoms of irreversible pulpitis	GIC (Vitremer; 3M ESPE, St. Paul, MN, USA) (n = 15)	CH (Dycal, Dentsply, Milford, DE), Scotchbond Multipurpose Adhesive (3M ESPE, St. Paul, MN, USA) and RC Z100 (3M ESPE, St. Paul, MN, USA) (n = 12)	1	48	14.8	GIC: 0/15 CH: 0/9	RMGIC: 1/15 CH: 1/9	93 89
Franzon et al. (2007)[13]	Brazil	20 children (4–7 year-old) 39 primary molars with active carious lesion in deep dentin in occlusal/ proximal surfaces without symptoms of irreversible pulpitis	Gutta-percha, Scotchbond Multipurpose Adhesive (3M ESPE, St. Paul, MN, USA) and RC Z250(3M ESPE, St. Paul, MN, USA) (n = 19)	CH (Hydro C, Dentsply, Rio de Janeiro, RJ, BR), Scotchbond Multipurpose Adhesive (3M ESPE, St. Paul, MN, USA) and RC Z250 (3M ESPE, St. Paul, MN, USA) (n = 20)	Not reported	36	25.7%	GP: 0/14 CH: 0/15	GP: 2/14 CH: 4/15	86 73

Continue

Table 1. Detailed chart related to studies included in the systematic review. Continuation

		21 children (4–8 year-old)	Clearfil SE Bond (Kuraray,	CH (Dycal, Dentsply, Milford, DE), Scotchbond Multipurpose Adhesive (3M ESPE, St. Paul, MN, USA) and RC Z250 (3M ESPE, St. Paul, MN, USA)				AD: 0/17	AD: 3/17	82
Casagrande et al. (2010)[5]	Brazil				Not reported	48	20.0			
		40 primary molars with active carious lesion in deep dentin in occlusal/proximal surfaces without symptoms of irreversible pulpitis	Toquio, Japan) and RC Z250 (3M ESPE, St. Paul, MN, USA)	(n = 21)				CH: 0/15	CH: 4/15	73

AD: adhesive system; CH: calcium hydroxide; RC: resin composite; GIC: resin-modified glass ionomer cement; GP: gutta-percha.

composite restoration. The follow-up period ranged from 24 to 48 months, with a dropout rate of 0 –25.7%.

The criteria used for determination of clinical and radiographic success were as follows: absence of spontaneous pain and/or sensitivity to pressure, absence of fistula, edema, and/or abnormal mobility, absence of radiolucencies at the interradicular and/or periapical regions, as determined by periapical radiographs, absence of increase of the periodontal space, and absence of internal and/or external dentin resorption that was not compatible with the expected resorption due to the exfoliation process.

Risk of bias assessment

The final assessment for the risk of bias for the included studies is displayed in Table 2. A statement of the randomization method was reported in all evaluated papers; however, the method used to generate the random sequence was not reported. Moreover, a lack of information about the allocation concealment was verified in the studies. Regarding the blinding method, only one study[5] reported blinding of outcome assessment. All included papers were free of incomplete outcome data.

MTC meta-analysis

The evidence comparing the four materials included in this systematic review is displayed in Figure 2. Nine possible direct and indirect pair-wise comparisons were performed between the four materials.

The results of the MTC meta-analysis are summarized in Table 3. In the direct evidence, only comparisons between calcium hydroxide and other materials tested could be made. Using indirect comparisons, we could also assess comparisons among other possibilities of indirect treatment, apart from the calcium hydroxide treatment. There were no differences comparing calcium hydroxide and adhesive system, resin-modified glass ionomer cement or gutta-percha, both in direct and indirect comparisons. However, the analysis produced narrower confidence intervals for those cases in which some other treatment was compared to calcium hydroxide.

Table 4 presents the ranking of treatments according to their probability of being the best choice. The order of the probability of failure was: resin-modified glass

Table 2. Methodological assessment of risk of bias of included studies.

Study	Methodological quality item						
	Selection bias		Detection bias			Attrition bias	Reporting bias
	Random sequence generation	Allocation concealment	Blinding of participants	Blinding of personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting
Falster et al. (2002)[7]	Unclear	High	Unclear	High	Unclear	Low	Unclear
Marchi et al. (2006)[8]	Unclear	High	Unclear	High	Unclear	Low	Unclear
Franzon et al. (2007)[13]	Unclear	High	Unclear	High	Unclear	Low	Unclear
Casagrande et al. (2010)[5]	Unclear	High	Unclear	High	Low	Low	Unclear

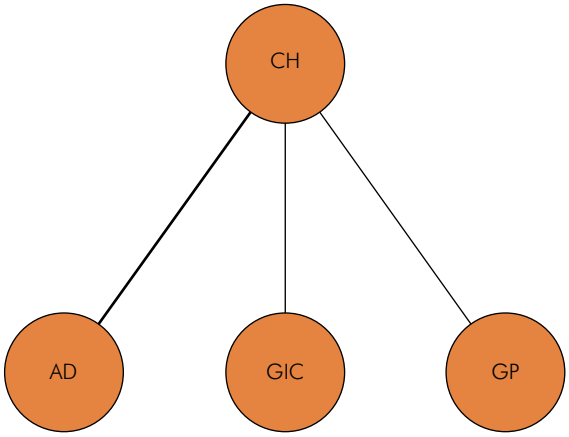


Figure 2. Network of the comparisons of materials used for indirect pulp treatment in primary teeth. The width of lines connecting each pair of treatments is proportional to the number of trials comparing the treatments. CH: calcium hydroxide; AD: adhesive system; GIC: resin-modified glass ionomer cement; GP: gutta-percha.

Table 3. Mixed treatment comparison (MTC) model comparing all materials used for indirect pulp treatment in primary teeth.

Pair-wise comparison	Direct comparison	MTC
	RR(95%CI)	RR(95%CI)
CH-AD	0.49 (0.16–1.51)	0.38 (0.11–1.10)
CH-GIC	0.60 (0.04–8.46)	0.29 (0.01–3.00)
CH-GP	0.54 (0.12–2.48)	0.41 (0.06–1.70)
AD-GIC	-	0.76 (0.02–11.00)
AD-GP	-	1.10 (0.12–7.20)
GIC-GP	-	1.40 (0.06–52.00)

CH: calcium hydroxide; AD: adhesive system; GIC: resin-modified glass ionomer cement; GP: gutta-percha; RR: Relative risk; 95% CI: confidence of interval of 95%

Table 4. Ranking of probabilities of presenting failures among materials.

Materials	Position 1*	Position 2	Position 3	Position 4†
CH	0.0006	0.0228	0.2405	0.7166
AD	0.2638	0.4235	0.2858	0.0256
GIC	0.4688	0.2187	0.1705	0.1085
GP	0.2666	0.3337	0.2960	0.0900

*Smaller percentage of outcomes; †Larger percentage of outcomes. CH: calcium hydroxide; AD: adhesive system; GIC: resin-modified glass ionomer cement; GP: gutta-percha.

ionomer cement, adhesive system, gutta-percha and calcium hydroxide. The resin-modified glass ionomer cement was the material with the lowest probability of occurrence of outcomes (0.4688) and calcium hydroxide was the treatment most likely to present an outcome (0.7166).

Discussion

Based on this review, evidence for the superiority of any material used to maintain pulpal vitality when performing indirect pulp treatment in primary teeth was not found. It should also be highlighted that calcium hydroxide, being the resin despite an absence of superiority, has been used as a control in all of the included studies. Calcium hydroxide has been traditionally used for cavity lining of the cavity floor in proximity to the pulp because of its antibacterial effect.[23] Because of that, new alternatives often have been compared to it. However, other options of treatment have not been regularly compared in a pairwise manner. Indirect comparisons permitted,

in the present systematic review, an estimation of the relationship among other available materials that were not tested by direct comparisons.[24]

The use of cavity lining was based on the ability for reduction of the number of viable bacteria remaining, remineralization of demineralized hard tissues, induction of the reactionary dentin and protection of the integrity of the pulp.[25] Nevertheless, a similar success rate in indirect pulp treatment in primary teeth was found when calcium hydroxide or a placebo liner (gutta-percha) were used under resin composite restorations.[13] Moreover, calcium hydroxide has been found to hydrolyze over time and to reduce the area available for bonding.[1] Both could potentially jeopardize the integrity of the restoration. Despite the absence of a significant difference, calcium hydroxide showed a higher probability of failure. It should be noted that failures of pulp origin were considered as an outcome in this review. Therefore, compromised restoration integrity due to a reduced bonding area might have an indirect influence on pulpal failure. In all studies, resin composite restorations were placed over calcium hydroxide lining. Composite fillings are prone to shrinkage and present only limited biocompatibility compared to other materials, such as glass ionomer cement, both of which could be detrimental to pulpal health.[26] The use of adhesive systems also might affect post-operative pulp conditions. Conversely, it recently has been reported that the type of adhesive strategy (etch-and-rinse or self-etch) for posterior resin composite restorations does not influence the risk and intensity of post-operative sensitivity.[27] The indirect evidence analysis shows no difference between adhesive systems and resin-modified glass ionomer cement, but the latter presented a lower probability of occurrence of pulp failure. A similar survival rate of resin composite and resin-modified glass ionomer cement restorations has been shown in primary molars.[28] Taking into account the advantages, such as fluoride release, less technically demanding and lower post-operative sensitivity, resin-modified glass ionomer cements could be a good option for indirect pulp treatment in primary teeth.

Even when using indirect comparisons and evaluating different materials, our findings did not increase the scientific evidence presented in a previous systematic review,[14] where the liner material used (calcium hydroxide or bonding agents) had no effect on the success of indirect pulp treatment in primary molars.

The small number of included trials and the small sample size in each of the included studies might have exerted an influence on the absence of significant differences among materials used for pulp-complex protection found in this review. Even after increasing the sample size using the MCT compared to direct comparisons, we could not find differences among the treatments. Although an adjustment in confidence intervals has been observed, their limits seem to be far from significance.

Despite the rank probabilities estimated using a Bayesian framework, we should be cautious about drawing conclusions on treatment efficacy, since the results can be highly influenced by the data included and the statistical models employed.[29] These findings could be pointing an actual absence of differences among the materials used after partial caries removal as indirect pulp treatment. Considering similar efficacies among the treatments, other parameters could be considered in using the different strategies, such as patient-centered outcomes, availability or simplicity/time for execution. Calcium hydroxide, despite traditionally being used for indirect pulp treatment, demands an additional step apart from the restorative procedures, while the other options, such as resin composite and glass ionomer cements, fulfill both functions at the same time. It is important to emphasize that the findings are affected by the underlying quality of the evidence. Only one study[5] used blinded assessments, and allocation concealment was not performed in all trials. All studies were performed in secondary care by a single research team, which limits the external validity of the results. Furthermore, studies[6,10,30] published so far comparing other materials, such as mineral trioxide aggregate or calcium silicate, were not included in this review because they did not fulfill the selection criteria. Therefore, there is a need for further well-designed and well-reported randomized controlled clinical investigations assessing other relevant outcomes for longevity of restorations after indirect pulp treatment.

Conclusions

The current evidence does not support a recommendation for any one of the materials over the other for indirect pulp treatment in primary molars, since they all present similar efficacies in the included studies. There is also no evidence that the use of a liner, as recommended in the AAPD Guidelines,[1] is more efficacious than restoring cavities directly using other adhesive materials.

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