Efficacy of alternative medicaments for pulp treatment in primary teeth in the short-term: meta-analysis

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Abstract

Objective: This systematic review and meta-analysis aimed to evaluate the overall, clinical, and radiographical success rates of alternative pulpotomy medicaments in primary teeth.

Methods: A systematic search of five databases was conducted following the PRISMA guidelines. Prospective clinical trials utilising alternative pulpotomy medicaments in children were included. The outcome measures were overall, clinical, and radiographic success, expressed in percentages and converted to odds ratios (OR). Fifteen articles were included in the meta-analysis.

Results: combined OR for overall, clinical, and radiographic success was 0.55 [95% CI: 0.12-2.41; $P=0.42$; $I^2=76\%$], 1.03 [95% CI: 0.57-1.86; $P=0.92$; $I^2=0\%$] and 0.84 [95% CI: 0.54-1.47; $P=0.66$; $I^2=34\%$], respectively. The results suggest an inconclusive outcome in the success rate of alternative medicaments.

Conclusions: There is insufficient evidence to support the efficacy of alternative pulpotomy medicaments for use in primary teeth. Further robust studies are required before such alternative medicaments should be used in clinical practice.

Keywords: Pulpotomy, Primary Teeth, Alternative Medicaments, Evidence-Based

Introduction

The primary tooth pulpotomy was popularised in the early 1900's and to date remains the most commonly used technique for the management of deep dentinal caries in children.^{1, 2}

The aim of a pulpotomy is to amputate the inflamed coronal pulp and preserve the vitality of the radicular pulp, thereby facilitating the normal exfoliation of the primary tooth.

Diagnosing the status of the pulp in a child is challenging and the treatment outcomes are heavily influenced by the clinical and radiographic signs and symptoms as well as the appropriate use of pulpotomy medicaments and/or techniques.^{3, 4}

Over the years numerous pulpotomy medicaments have been described, the most common being calcium hydroxide (CH),⁵ formocresol (FC),⁶ ferric sulphate (FS),⁷ and mineral trioxide aggregate (MTA).⁸ FC was first introduced in 1904 and has long been considered the gold standard of pulpotomy medicaments with reported success rates ranging from 84% to 100%.⁹ However, questions remain around the safety of FC and in particular its constituents formaldehyde and cresol.¹⁰⁻¹² According to the American Academy of Pediatric Dentistry (AAPD) Guideline, FC and FS has been supported by numerous studies for long-term clinical success.¹³ In addition, electrosurgery (ES) has been demonstrated to show a promising clinical success.¹⁴ A recent Cochrane review evaluated the efficacy of commonly used pulpotomy medicaments (CH, FC, FS, and MTA) and found no evidence to identify superiority between materials.¹⁵ However, AAPD believes that MTA could be the medicament of choice in the future.^{13, 16, 17} Nevertheless, the cost of MTA may preclude its clinical use and while FS may be used instead, it confers little additional benefit other than its haemostatic potential.^{15, 18} These issues have led to a shift in the popularity and use of certain pulpotomy agents while sparking interest in the development and investigation of alternative pulpotomy medicaments.^{1, 19}

Alternative medicaments for pulpotomy have been described in the literature such as antioxidant Mix (AM) [consisting of enzymes and non-enzymes],²⁰ allium sativum oil (AS) [garlic extract],²¹ ankaferd blood stopper (ABS) [a medicinal plant extract comprised of a standardised mixture of dried grass and leaf extracts],²² aloe vera (AV),²³ calcium enriched mixture (CEM) [a calcium oxide based endodontic cement],^{24, 25} copaifera langsdorffii oil resin (CLOR) [oleo-resin obtained from the stem bark of *Copaifera langsdorffii* a tropical rainforest tree],²⁶ propolis (P) [a resinous substance produced by honey bees from collected plant products],²⁷ platelet concentrates (PC),²⁸ and thymus vulgaris (TV) [also known as garden thyme, a perennial herb native to Southern Europe].²⁷ All of these medicaments vary in terms of their pharmacological mechanisms of action with most possessing anti-inflammatory, anti-oxidant, anti-microbial, reparative, and/or wound healing properties.

A recent systematic review assessed the outcome of herbal medicine versus standard pulpotomy medicaments but this was not comprehensive in including the aforementioned medicaments.²⁹ Therefore, the current meta-analysis aims to evaluate the overall, clinical, and radiographical success rates of alternative medicaments for pulpotomies in primary teeth.

Materials and methods

Study selection

The meta-analysis was registered on the PROSPERO database (registration number: CRD42018089660) and conducted according to the PRISMA guidelines.³⁰ Two authors (JP and RA) independently conducted a systematic search of the literature in January 2018. The following digital databases were accessed: PubMed, Web of Science, Medline, Cochrane Library, and CINAHL, in order to assess published studies that reported on alternative

pulpotomy medicaments for use in primary teeth. The search was conducted using the following keyword combination: pulpotomy, pulp therapy, pulp treatment, primary, deciduous, tooth, teeth, dentition, with the prefix 'AND' and 'OR'. No time of publication limit was placed, but only articles published in English were included. In the screening stage, the title and abstracts of publications were reviewed and the duplicated studies were excluded. Subsequently, full text copies were reviewed for eligibility in the meta-analysis. The inclusion criteria were as follows: prospective clinical trials investigating alternative pulpotomy medicaments namely: AM, AS, ABS, AV, CEM, CLOR, P, PC, and TV. Studies that did not meet the inclusion criteria were excluded. A consensus was reached after through discussion if any discrepancies arose between the two examiners.

Data extraction

The following were analysed as variables: study design, study sample (number and age range), length of the follow-up period, and the primary outcome (overall success, clinical success, and radiographic success). The information was extracted as per population (P), intervention (I), comparison (C), and outcome (O) criteria. In order to improve the power the meta-analysis, any studies that had deviated methodologies from previous published studies were excluded.^{22, 31, 32}

Data synthesis

The parameters for the meta-analysis consisted of analysing successful outcomes using the adopted odd's ratio (OR) formula:³³

$$OR = ad / bc$$

a = Number of successes in the intervention group

b = Number of successes in the comparison group

c = Number of failures in the comparison group

d = Number of failures in the intervention group

After obtaining the necessary parameters, a meta-analysis was undertaken in accordance with Review Manager software (RevMan 5.0 for Windows, Last Update - 2014). The statistical parameters were set as follows: Statistical significance ($P < 0.05$), statistical heterogeneity in accordance the Chi-Squared test (P -value of 0.1), and a high degree of heterogeneity classification if inconsistency (I^2) test value is greater than 50%.³⁴

Risk of bias

Cochrane's Collaboration tool for assessing risk of bias was used quality assess each studies.³⁵ The checklist consisted of: random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and researchers (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias), and other potential biases. These domains were assessed by examiners and were categorised as having low, unclear, or high levels of risk. Furthermore, Oxford Centre for Evidence-based Medicine (OCEBM) were utilised to critically evaluate the the evidence.³⁶

Inter-agreement Reliability

Inter-agreement reliability was calculated between the two independent reviewers, in the data extraction (identification, screening, eligibility, and inclusion) stage (%). In addition, during the quality assessment stage (risk of bias), SPSS version 24.0 (IBM Company, Chicago, IL,

USA) was used to compute kappa statistics as a measure to test the inter-agreement reliability amongst the reviewers.³⁷

Results

Study selection

A total of 203 articles were initially identified through database and manual searching. One hundred duplicate citations were and excluded. Based on the title and abstract, 38 articles were considered for inclusion. Further analysis of the full text articles resulted in 23 articles being excluded and fifteen articles fulfilled the inclusion criteria and were included in the meta-analysis.^{20, 22, 23, 25-28, 31, 32, 38-43} Within the fifteen articles, only five reported overall success.^{23, 25, 28, 31, 43} Four articles compared three pulpotomy medicaments,^{26, 27, 41, 42} and an additional article compared four pulpotomy medicaments (Figure 1).³⁹

Study characteristics

All the studies were prospective randomised controlled trials. Participants demographic details in all of the included studies were collated and a summary is outlined in Tables 1, 2 and 3. The countries where the studies were undertaken comprised of: Egypt, India, Iran, and Turkey. None of the studies reported on the socio-economic status of the participants and most studies recruited the participants in a university/teaching hospital setting.

Data extraction

One outcome was derived as a result; percentage of success (overall, clinical, and radiographic). The studies in the meta-analysis consisted of parameters analogous to the PICO criteria namely, Population: country of the study conducted, sample size (patient / tooth), age range; Intervention: type of alternative pulpotomy medicament; Comparison: type

of pulpotomy medicament; Outcome: clinical success (%) defined by: lack of soft tissue pathologies, lack of pain, and lack of pathologic mobility, and radiographic success (%) defined by: lack of furcation, periapical radiolucency, and lack of external and internal root resorption.

Risk of bias

The quality assessment outcomes of the selected studies using the Cochrane Collaboration's tool for assessing the risk of bias are outlined in Figure 2. Approximately 87% (13 out of 15) of studies were deemed to have an unclear risk of selection bias due to allocation concealment. 87% (13 out of 15) of the studies stated the randomisation procedure within the methods; however, 13% (2 out of 15) of the studies did not provide this information hence, was only assumed that they were randomised appropriately.^{23, 31} All studies had a high risk of performance bias as blinding of the participants and researchers was not conducted. Approximately 13% (2 out of 15) of studies were deemed to have a high risk of attrition bias with incomplete outcome data, and this was attributed to greater than 20% loss of follow-up after treatment. Furthermore, 47% (7 out of 15) of studies had a low-risk of reporting bias, which was primarily due to including all the outcomes stated in the meta-analysis such as, overall clinical and radiographic success.^{22, 26, 27, 38, 39, 41, 42} According to OCEBM standards, all studies included in the meta-analysis achieved an evidence level of 2B, which was primarily due to being low quality randomised controlled trials.

Inter-agreement Reliability

The inter-agreement reliability between the two reviewers was 95.8% (200 out of 203 studies), 92.1% (35 out of 38 studies), 92.1% (35 out of 38 studies), and 100% (15 out of 15 studies) at the identification, screening, eligibility, and inclusion stages, respectively. Any

discrepancies were resolved through discussion, until a consensus was reached. Each domains provided in Cochrane Collaboration's tool for assessing the risk of bias had a strong to almost perfect inter-agreement reliability between the independent reviewers, with a kappa score of: 0.820 (Random sequence generation), 0.822 (Allocation concealment), 0.913 (Blinding of participants and researchers), 0.800 (Blinding of outcome assessment), 0.921 (Incomplete outcome data), 0.890 (Selective reporting), and 0.900 (Other biases) respectively.

Meta-analysis: Overall success

Studies reporting the overall success based on prospective clinical trials are summarised in Table 1 and Figure 3. The age of the participants included in these studies ranged from 4 years to 10 years with a follow-up period ranging from 6 to 24 months. The overall success ranged from 6.9% to 90% for the intervention group. The overall success ranged from 71.4% to 92% for the comparator group. Only one study reported a statistically significant overall success.²³ The combined OR was 0.55 [95% CI: 0.12-2.41; P = 0.42] with a substantial heterogeneity ($I^2 = 76\%$) - see Figure 3.

Meta-analysis: Clinical success

The prospective clinical trials reporting on clinical success rates are summarised in Table 2 and Figure 4. The age of the participants included in these studies ranged from 3 years to 10 years with a follow-up period ranging from 3 to 24 months. The overall success ranged from 84% to 100% for the intervention group. The overall success ranged from 80% to 100% for the comparator group. Only two studies reported a statistically significant clinical success.^{28,}

⁴¹ The combined OR was 1.03 [95% CI: 0.57-1.86; P= 0.92] and no evidence of heterogeneity was observed ($I^2 = 0\%$) - see Figure 4. Furthermore, as illustrated in the forest

plot (Figure 4), it was impossible to estimate the odds ratio for all as seven out of the eighteen groups had similar success rates.

Meta-analysis: Radiographic success

The prospective clinical trials reporting on radiographic success rates are summarised in Table 3 and Figure 5. The age of the participants included in these studies ranged from 3 years to 10 years with a follow-up period ranging from 3 to 24 months. The overall success ranged from 0% to 100% for the intervention group. The overall success ranged from 40% to 100% for the comparator group. Only one study reported a statistically significant radiographic success.^{28, 41} The combined OR was 0.84 [95% CI: 0.54-1.47; P=0.66] and moderate evidence of heterogeneity ($I^2 = 34\%$) - see Figure 5. Furthermore, as illustrated in the forest plot (Figure 5), it was impossible to estimate the odds ratio for all as two out of the eighteen groups had similar success rates.

Discussion

To our knowledge, this meta-analysis is the first to both qualitatively and quantitatively evaluates the evidence supporting the use of alternative pulpotomy medicaments in primary teeth. AM,²⁰, ABS,²² AS,³¹ CEM,²⁵, P,³⁹ PC,³² and TV³⁹ had a greater percentage of either overall, clinical, and/or radiographic success in comparison to the traditional pulpotomy medicaments. Within the meta-analysis only two of the studies showed statistical significant outcomes, but these were considered to be of a high risk of bias.^{23, 41} The remaining studies concluded that the alternative pulpotomy medicaments did not show significantly better outcomes when compared to the traditional medicaments.

Furthermore, within the forest plot, it was impossible to estimate the OR for several studies for clinical^{23, 25, 26, 39, 40, 43} and radiographic^{25, 43} success rates as both the intervention and comparison had the same percentage outcome.

It is important to note that most of these studies were conducted in Egypt, India, Iran, and Turkey hence, further clinical trials from different countries are required to extrapolate the results. Nevertheless, moderate to high risk of bias was evident in the published studies, which was primarily due to lack of blinding. The OR values provided in the meta-analysis do not support the use of alternative medicaments in the overall, clinical, and/or radiographic success (OR = 0.55 vs. 1.03 vs. 0.84, respectively). Nevertheless, as the results are not statistically significant, the efficacy of these alternative medicaments remains questionable.

In addition, only the overall success generated a large heterogeneity in comparison to clinical and radiographic success ($I^2 = 76\%$ vs. 0% vs. 34% , respectively). The clinical heterogeneity can be attributed to patient selection, disease severity and variations in the restorative management, which explains the wide range in the odds ratio. However, it is also important to note that most of the studies included in this review have a short duration, with the longest follow-up time being 24 months. Therefore, there is a need for high quality RCTs conducted in accordance with the CONSORT statement, with longer follow-up to make definitive conclusions.⁴⁴

On a global scale, untreated dental caries in the primary dentition affects an estimated 621 million children and is the 10th most prevalent disease affecting children.⁴⁵ Untreated dental caries has the potential to adversely impact a child's oral health related quality of life (OHRQoL).^{46, 47} Untreated dental caries affects several quality of life domains including

orofacial pain, psychosocial impact, orofacial appearance, and oral function.⁴⁸ There is evidence to support an improvement in OHRQoL following comprehensive dental rehabilitation under general anaesthesia.^{49, 50} To date, there are no published studies that comprehensively assess dental patient-reported outcomes (dPRO) after the use of alternative pulp medicaments in primary teeth.⁴⁸ However, from the available published studies, the absence of soft tissue pathology and pain is used as a measure of clinical success.^{20, 22, 23, 25-28, 31, 32, 38-43} Since it is not specific enough, there is a need for high quality dPRO studies to be able to highlight the importance of patient-perceived impact after using alternative pulp medicaments.⁵¹

None of the alternative medicaments namely (AM, AS, ABS, AV, CEM, CLOR, P, PC, and TV) when used for primary molar pulpotomies demonstrated any significant difference when compared with the traditional medicaments (CH, FC, FS, MTA, ZOE). These findings could suggest them to be prospective alternative pulpotomy medicaments. Alternatively, it well demonstrates that the medicament is not a significant factor in the final outcome of a pulpotomy procedure in primary teeth.

Conclusion

There is insufficient evidence to support the efficacy of alternative pulpotomy medicaments for use in primary teeth. Future high quality RCTs are essential before such medicaments can be considered suitable alternatives to mainstream pulpotomy medicaments.

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Conflict of interest

The authors declare they have no potential conflicts of interest.

ACCEPTED MANUSCRIPT

References

1. Monteiro J, Ni Chaollai A, Duggal M. The teaching of management of the pulp in primary molars across Europe. *Eur Arch Paediatr Dent*. 2017;18:203-208.
2. Sweet CA. Treatment and Maintenance of Pulpless Deciduous Teeth. *J Am Dent Assoc*. 1935;22:1972-1975.
3. Aminabadi NA, Parto M, Emamverdizadeh P, Jamali Z, Shirazi S. Pulp bleeding color is an indicator of clinical and histohematologic status of primary teeth. *Clin Oral Investig*. 2017;21:1831-1841.
4. Waterhouse PJ, Nunn JH, Whitworth JM, Soames JV. Primary molar pulp therapy - histological evaluation of failure. *Int J Paediatr Dent*. 2000;10:313-321.
5. Zurn D, Seale NS. Light-cured calcium hydroxide vs formocresol in human primary molar pulpotomies: a randomized controlled trial. *Pediatr Dent*. 2008;30:34-41.
6. Loh A, O'Hoy P, Tran X, et al. Evidence-based assessment: evaluation of the formocresol versus ferric sulfate primary molar pulpotomy. *Pediatr Dent*. 2004;26:401-409.
7. Smith NL, Seale NS, Nunn ME. Ferric sulfate pulpotomy in primary molars: a retrospective study. *Pediatr Dent*. 2000;22:192-199.
8. Holan G, Eidelman E, Fuks AB. Long-term evaluation of pulpotomy in primary molars using mineral trioxide aggregate or formocresol. *Pediatr Dent*. 2005;27:129-136.
9. Anthonappa RP, King NM, Martens LC. Is there sufficient evidence to support the long-term efficacy of mineral trioxide aggregate (MTA) for endodontic therapy in primary teeth? *Int Endod J*. 2013;46:198-204.

10. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. Formaldehyde, 2-butoxyethanol and 1-tert-butoxypropan-2-ol. *IARC Monogr Eval Carcinog Risks Hum.* 2006;88:1-478.
11. Myers DR, Pashley DH, Whitford GM, McKinney RV. Tissue changes induced by the absorption of formocresol from pulpotomy sites in dogs. *Pediatr Dent.* 1983;5:6-8.
12. Swenberg JA, Kerns WD, Mitchell RI, Gralla EJ, Pavkov KL. Induction of squamous cell carcinomas of the rat nasal cavity by inhalation exposure to formaldehyde vapor. *Cancer Res.* 1980;40:3398-3402.
13. American Academy of Pediatric Dentistry (AAPD). Guideline on Pulp Therapy for Primary and Immature Permanent Teeth. *Pediatr Dent.* 2016;38:280-288.
14. Dean JA, Mack RB, Fulkerson BT, Sanders BJ. Comparison of electrosurgical and formocresol pulpotomy procedures in children. *Int J Paediatr Dent.* 2002;12:177-182.
15. Smail □Faugeron V, Glenny AM, Courson F, Durieux P, Muller □Bolla M, Fron Chabouis H. Pulp treatment for extensive decay in primary teeth. *Cochrane Database Syst Rev.* 2018;5:CD003220.
16. Ng FK, Messer LB. Mineral trioxide aggregate as a pulpotomy medicament: a narrative review. *Eur Arch Paediatr Dent.* 2008;9:4-11.
17. Seale NS, Glickman GN. Contemporary perspectives on vital pulp therapy: views from the endodontists and pediatric dentists. *J Endod.* 2008;34:S57-61.
18. Ranly DM. Pulpotomy therapy in primary teeth: new modalities for old rationales. *Pediatr Dent.* 1994;16:403-409.
19. Avram DC, Pulver F. Pulpotomy medicaments for vital primary teeth. Surveys to determine use and attitudes in pediatric dental practice and in dental schools throughout the world. *ASDC J Dent Child.* 1989;56:426-434.

20. Kathal S, Gupta S, Bhayya DP, Rao A, Roy AP, Sabhlok A. A comparative evaluation of clinical and radiographic success rate of pulpotomy in primary molars using antioxidant mix and mineral trioxide aggregate: An in vivo 1-year follow-up study. *J Indian Soc Pedod Prev Dent*. 2017;35:327-331.
21. Mohammad SG, Baroudi K. Assessment of the potential of Allium sativum oil as a new medicament for non-vital pulpotomy of primary teeth. *J Int Soc Prev Community Dent*. 2015;5:314-320.
22. Odabaş ME, Cinar C, Tulunoğlu O, Işık B. A new haemostatic agent's effect on the success of calcium hydroxide pulpotomy in primary molars. *Pediatr Dent*. 2011;33:529-534.
23. Kalra M, Garg N, Rallan M, Pathivada L, Yeluri R. Comparative Evaluation of Fresh Aloe barbadensis Plant Extract and Mineral Trioxide Aggregate as Pulpotomy Agents in Primary Molars: A 12-month Follow-up Study. *Contemp Clin Dent*. 2017;8:106-111.
24. Asgary S, Ahmadyar M. Vital pulp therapy using calcium-enriched mixture: An evidence-based review. *J Conserv Dent*. 2013;16:92-98.
25. Malekafzali B, Shekarchi F, Asgary S. Treatment outcomes of pulpotomy in primary molars using two endodontic biomaterials. A 2-year randomised clinical trial. *Eur J Paediatr Dent*. 2011;12:189-193.
26. Musale PK, Soni AS. Clinical Pulpotomy Trial of Copaifera Langsdorffii Oil Resin Versus Formocresol and White Mineral Trioxide Aggregate in Primary Teeth. *Pediatr Dent*. 2016;38:5-12.
27. Alolofi H, El-Sayed M, Taha S. Clinical and radiographical evaluation of propolis and thymus vulgaris extracts compared with formocresol pulpotomy in human primary molars. *BDJ Open*. 2016;2:16005.

28. Patidar S, Kalra N, Khatri A, Tyagi R. Clinical and radiographic comparison of platelet-rich fibrin and mineral trioxide aggregate as pulpotomy agents in primary molars. *J Indian Soc Pedod Prev Dent*. 2017;35:367-373.
29. Subramanyam D, Somasundaram S. Clinical and Radiographic Outcome of Herbal Medicine Versus Standard Pulpotomy Medicaments in Primary Molars: A Systematic Review. *J Clin Diagn Res*. 2017;11:ZE12-ZE16.
30. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Ann Intern Med*. 2009;151:264-269.
31. Mohammad SG, Raheel SA, Baroudi K. Clinical and Radiographic Evaluation of Allium sativum Oil as a New Medicament for Vital Pulp Treatment of Primary Teeth. *J Int Oral Health*. 2014;6:32-36.
32. Kalaskar RR, Damle SG. Comparative evaluation of lyophilized freeze dried platelet derived preparation with calcium hydroxide as pulpotomy agents in primary molars. *J Indian Soc Pedod Prev Dent*. 2004;22:24-29.
33. Elbourne DR, Altman DG, Higgins JP, Curtin F, Worthington HV, Vail A. Meta-analyses involving cross-over trials: methodological issues. *Int J Epidemiol*. 2002;31:140-149.
34. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ*. 2003;327:557-560.
35. Higgins JP, Altman DG, Gotzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ*. 2011;343:d5928.
36. Richards D. GRADING--levels of evidence. *Evid Based Dent*. 2009;10:24-25.
37. McHugh ML. Interrater reliability: the kappa statistic. *Biochem Med (Zagreb)*. 2012;22:276-282.

38. Cantekin K, Gümüş H. Success Rates of Ankaferd Blood Stopper and Ferric Sulfate as Pulpotomy Agents in Primary Molars. *Int Sch Res Notices*. 2014;2014:819605.
39. Hugar SM, Kukreja P, Hugar SS, Gokhale N, Assudani H. Comparative Evaluation of Clinical and Radiographic Success of Formocresol, Propolis, Turmeric Gel, and Calcium Hydroxide on Pulpotomized Primary Molars: A Preliminary Study. *Int J Clin Pediatr Dent*. 2017;10:18-23.
40. Khorakian F, Mazhari F, Asgary S, et al. Two-year outcomes of electrosurgery and calcium-enriched mixture pulpotomy in primary teeth: a randomised clinical trial. *Eur Arch Paediatr Dent*. 2014;15:223-228.
41. Kusum B, Rakesh K, Richa K. Clinical and radiographical evaluation of mineral trioxide aggregate, biodentine and propolis as pulpotomy medicaments in primary teeth. *Restor Dent Endod*. 2015;40:276-285.
42. Ozmen B, Bayrak S. Comparative evaluation of ankaferd blood stopper, ferric sulfate, and formocresol as pulpotomy agent in primary teeth: A clinical study. *Niger J Clin Pract*. 2017;20:832-838.
43. Yaman E, Görken F, Pinar Erdem A, Sepet E, Aytepe Z. Effects of folk medicinal plant extract Ankaferd Blood Stopper® in vital primary molar pulpotomy. *Eur Arch Paediatr Dent*. 2012;13:197-202.
44. Rennie D. CONSORT Revised - Improving the Reporting of Randomized Trials. *JAMA*. 2001;285:2006-2007.
45. Kassebaum NJ, Bernabe E, Dahiya M, Bhandari B, Murray CJ, Marcenes W. Global burden of untreated caries: a systematic review and metaregression. *J Dent Res*. 2015;94:650-658.

46. Abanto J, Carvalho TS, Mendes FM, Wanderley MT, Bonecker M, Raggio DP. Impact of oral diseases and disorders on oral health-related quality of life of preschool children. *Community Dent Oral Epidemiol*. 2011;39:105-114.
47. Wong HM, McGrath CP, King NM, Lo EC. Oral health-related quality of life in Hong Kong preschool children. *Caries Res*. 2011;45:370-376.
48. John MT. Health Outcomes Reported by Dental Patients. *J Evid Based Dent Pract*. 2018;18:332-335.
49. Park JS, Anthonappa RP, King NM, McGrath CP. The family impact of dental general anaesthesia in children: A meta-analysis. *Int J Paediatr Dent*. 2018. <https://doi.org/10.1111/ipd.12452>
50. Park JS, Anthonappa RP, Yawary R, King NM, Martens LC. Oral health-related quality of life changes in children following dental treatment under general anaesthesia: a meta-analysis. *Clin Oral Investig*. 2018;22:2809-2818.
51. BaniHani A, Deery C, Toumba J, Munyombwe T, Duggal M. The impact of dental caries and its treatment by conventional or biological approaches on the oral health-related quality of life of children and carers. *Int J Paediatr Dent*. 2018;28:266-276.

Legends:

Figure 1. Process of data collection in accordance with the PRISMA statement for systematic reviews.

Figure 2. Assessment of risk of bias of the studies included in the meta-analysis.

Figure 3. Forest plot of overall success based on prospective clinical trials.

Figure 4. Forest plot of clinical success based on prospective clinical trials.

Figure 5. Forest plot of radiographic success based on prospective clinical trials.

Table 1 - Overall success based on prospective clinical trials

Study	Country	Age	Tooth	Duration	Intervention	Comparison	Outcome (Success Rate - %)
Kalra et al. 2017	India	4 - 10 years	60	12 months	AV	MTA	6.9% vs 71.4% (P < 0.001)
Malekafzali et al. 2011	Iran	4 - 8 years	80	24 months	CEM	MTA	85.0% vs 80%
Mohammad et al. 2014	Egypt	4 - 8 years	40	6 months	AS	FC	90% vs 85% (P > 0.05)
Patidar et al. 2017	India	5 - 9 years	50	6 months	PC	MTA	90% vs 92% (P < 0.0005)
Yaman et al. 2012	Turkey	6 - 9 years	60	12 months	ABS	FC	85.7% vs 89.3%

AS - *Allium sativum* oil; ABS - Ankaferd blood stopper; AV - *Aloe vera*; CEM - Calcium enriched mixture; FC - Formocresol; MTA - Mineral trioxide aggregate; PC - Platelet concentrates

Table 2 - Clinical success based on prospective clinical trials

Study	Country	Age	Tooth	Duration	Sub-Groups	Intervention	Comparator	Outcome (Success Rate - %)
Alolofi et al. 2016	Egypt	4 - 6 years	60	12 months	Group 1	P	TV	88.2% vs 94.4% (P = 0.37)
					Group 2	P	FC	88.2% vs 88.2% (P = 0.37)
Cantekin and Gümüş, 2014	Turkey	4 - 6 years	66	12 months		ABS	FS	84.8% vs 90.9% (P > 0.05)
Hugar et al. 2017	India	4 - 9 years	90	3 months	Group 1	P	T	100% vs 100%
					Group 2	P	CH	100% vs 80% (P = 0.22)
					Group 3	TV	CH	100% vs 80% (P = 0.22)
Kalaskar and Damle, 2004	India	4 - 7 years	56	6 months		PC	CH	100% vs 96.4%
Kalra et al. 2017	India	4 - 10 years	60	12 months		AV	MTA	100% vs 100%
Kathal et al. 2017	India	6 - 9 years	40	12 months		AM	MTA	94.7% vs 88.9% (P = 0.604)
Khorakian et al. 2014	Iran	4 - 6 years	102	24 months		CEM	ES+ZOE	100% vs 100%
Kusum et al. 2015	India	3 - 10 years	75	9 months	Group 1	P	BD	84% vs 100% (P = 0.03)
					Group 2	P	MTA	84% vs 100% (P = 0.03)
Malekafzali et al. 2011	Iran	4 - 8 years	80	24 months		CEM	MTA	100% vs 100%
Mohammad et al. 2014	Egypt	4 - 8 years	40	6 months		AS	FC	90% vs 80% (P > 0.05)
Musale and Soni, 2016	India	4 - 8 years	142	12 months	Group 1	CLOR	FC	100% vs 100%
					Group 2	CLOR	WMTA	100% vs 100%
Odabaş et al. 2011	Turkey	4 - 8 years	48	12 months		ABS+CH	CH	95% vs 90% (P > 0.05)
Ozmen and Bayrak, 2017	Turkey	6 - 9 years	45	24 months	Group 1	ABS	FC	87% vs 87% (P > 0.05)
					Group 2	ABS	FS	87% vs 100% (P > 0.05)
Patidar et al. 2017	India	5 - 9 years	50	6 months		PC	MTA	92% vs 92% (P < 0.0005)
Yaman et al. 2012	Turkey	6 - 9 years	56	12 months		ABS	FC	100% vs 100%

AM - Antioxidant mix; AS - *Allium sativum* oil; ABS - Ankaferd blood stopper; AV - *Aloe vera*; BD - Biodentine[®]; CEM - Calcium enriched mixture; CH - Calcium hydroxide; CLOR - *Copaifera langdorffii* oil resin; ES - Electrosurgery; FC - Formocresol; FS - Ferric sulphate; MTA - Mineral trioxide aggregate; P - Propolis; PC - Platelet concentrates; TV - *Thymus vulgaris*; ZOE - Zinc oxide Eugenol; WMTA - White mineral trioxide aggregate

Table 3 Radiographic success based on prospective clinical trials

Study	Country	Age	Tooth	Duration	Sub-Groups	Intervention	Comparator	Outcome (Success Rate - %)
Alolofi et al. 2016	Egypt	4 - 6 years	60	12 months	Group 1	P	TV	73.3% vs 88.2% (P = 0.14)
					Group 2	P	FC	73.3% vs 73.3% (P = 0.14)
Cantekin and Gümüş. 2014	Turkey	4 - 6 years	66	12 months		ABS	FS	84.8% vs 87.8% (P > 0.05)
Hugar et al. 2017	India	4 - 9 years	90	3 months	Group 1	P	T	93.3% vs 86.7% (P = 0.61)
					Group 2	P	CH	93.3% vs 73.3% (P = 0.33)
					Group 3	TV	CH	86.7% vs 73.3% (P = 0.65)
Kalaskar and Damle. 2004	India	4 - 7 years	56	6 months		PC	CH	100% vs 96.4%
Kalra et al. 2017	India	4 - 10 years	60	12 months		AV	MTA	0% vs 100%
Kathal et al. 2017	India	6 - 9 years	40	12 months		AM	MTA	94.7% vs 88.9% (P = 0.604)
Khorakian et al. 2014	Iran	4 - 6 years	102	24 months		CEM	ES+ZOE	90.0% vs 95.2% (P = 0.62)
Kusum et al. 2015	India	3 - 10 years	75	9 months	Group 1	P	BD	72% vs 82% (P = 0.001)
					Group 2	P	MTA	72% vs 92% (P = 0.001)
Malekafzali et al. 2011	Iran	4 - 8 years	80	24 months		CEM	MTA	100% vs 100% (P = 0.40)
Mohammad et al. 2014	Egypt	4 - 8 years	40	6 months		AS	FC	80% vs 40% (P > 0.05)
Musale and Soni. 2016	India	4 - 8 years	142	12 months	Group 1	CLOR	FC	76% vs 90.9% (P = 0.1)
					Group 2	CLOR	WMTA	76% vs 88.2% (P = 0.1)
Odabaş et al. 2011	Turkey	4 - 8 years	48	12 months		ABS+CH	CH	95% vs 90% (P > 0.05)
Ozmen and Bayrak. 2017	Turkey	6 - 9 years	45	24 months	Group 1	ABS	FC	87% vs 80% (P > 0.05)
					Group 2	ABS	FS	87% vs 87% (P > 0.05)
Patidar et al. 2017	India	5 - 9 years	50	6 months		PC	MTA	87% vs 92% (P < 0.0005)

Yaman et al. 2012

Turkey

6 - 9 years

56

12 months

ABS

FC

100 vs 100%

AM - Antioxidant mix; AS - *Allium sativum* oil; ABS - Ankaferd blood stopper; AV - *Aloe vera*; BD - Biodentine[®]; CEM - Calcium enriched mixture; CH - Calcium hydroxide; CLOR - *Copaifera langdorffii* oil resin ; ES - Electrosurgery; FC - Formocresol; FS - Ferric sulphate; MTA - Mineral trioxide aggregate; P - Propolis; PC - Platelet concentrates; TV - *Thymus vulgaris*; ZOE - Zinc oxide Eugenol; WMTA - White mineral trioxide aggregate

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Five studies reported overall success
Four studies had two subgroups for comparison
One study had three subgroups for comparison

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and researchers (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other biases	Hierarchy of evidence
Alolofi et al. 2016								2B
Cantekin and Gümüş. 2014								2B
Hugar et al. 2017								2B
Kalaskar and Damle. 2004								2B
Kalra et al. 2017								2B
Kathal et al. 2017								2B
Khorakian et al. 2014								2B
Kusum et al. 2015								2B
Malekafzali et al. 2011								2B
Mohammad et al. 2014								2B
Musale and Soni. 2016								2B
Odabaş et al. 2011								2B
Ozmen and Bayrak. 2017								2B
Patidar et al. 2017								2B
Yaman et al. 2012								2B

Green: Low risk of bias / Red: High risk of bias / Yellow: Unclear risk of bias