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REVIEW

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Exploring the properties of formocresol in dentistry---a comprehensive review

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Abstract

Due to concerns about formocresol's mutagenic and genotoxic potential, its use as a pulpotomy medication is currently debatable. The current paper aimed to review the properties of formocresol and concerns regarding its safety as a pulpotomy medicament for primary teeth. With reference to the context of the recently published literature, the alternatives to formocresol are discussed, together with their benefits and drawbacks. A literature search was conducted using multiple databases comprising of MEDLINE (*via* PubMed), EMBASE, and Web of Science. The terms used for the search were "formocresol", "pulpotomy", and "primary teeth". In total, 364 articles were obtained from the analysis of the databases. Unrelated articles from the available full text of 174 articles were excluded. The main reasons for excluding the articles were: they were usage and precautionary guidelines. A total of 68 studies were finally included in the review. The literature review in this paper supports the notion that formocresol continues to be the most often utilized pulp dressing agent in primary teeth pulpotomies despite offering no advantages over other pulp dressing chemicals that are currently on the market.

Keywords

Chemical; Dental; Formaldehyde; Primary teeth; Pulpotomy

1. Introduction

Numerous physical appliances (such as partial dentures and orthodontic appliances), chemical substances (such as medications, restorative materials, endodontic materials, and retraction agents), and instruments (such as hand pieces, lasers and electrosurgical units) are frequently employed during dental procedures [1]. One such chemical that is widely used for deciduous teeth pulpotomy is formocresol, although due to safety concerns, its use in dentistry is in question.

Due to its anti-bacterial and fixative characteristics, formocresol soon gained popularity for dental procedures such root canal treatment and deciduous teeth pulpotomy [2, 3]. Nitzel's use of tricresol-formalin in 1874 is credited with being the first to describe the use of pulp medication containing formaldehyde as a tanning agent [4]. In order to treat non-vital permanent teeth, Buckley (1904) introduced formocresol [5]. Sweet (1936) then developed a particular treatment technique for use on exposed primary teeth and had outstanding clinical outcomes [6]. Since then, it has been accepted as the preferred intracanal/intrapupal medication for primary teeth receiving pulpotomy [2]. With clinical success rates ranging from 70 to 100% and significant research on its efficacy, it has become the benchmark against which all other emerging modalities are measured [7].

Due to its potential for sensitization, toxicity, mutagenic, or carcinogenic effects as well as the fact that, when used carelessly, it can cause an iatrogenic error and potentially harm the surrounding oral and para-oral tissues, its use as a pulpotomy agent is still controversial despite its widespread use [8, 9]. Contrarily, a small number of researchers have suggested that the negative consequences related to its use in primary teeth are negligible [7]. Thus, with proven alternatives with equal efficacy available, its use in dentistry is still debatable and controversial [9, 10].

In this paper, with literature review, an attempt is being made to update the existing knowledge regarding the properties and safety of the use of formocresol as a pulpotomy medicament for

deciduous teeth. In addition, the available alternative materials for formocresol have been detailed.

2. Materials and methods

This review is in accordance with the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) 2020 Statement in order to maintain a codified organization of the study [11]. The search databases included MEDLINE (*via* PubMed), EMBASE and Web of Science. The terms used for the search were "formocresol", "pulpotomy", and "primary teeth". Further searches were performed in the reference lists of relevant studies and in literature reviews dealing with the topic of interest.

Considering the eligibility criteria, articles relevant to the topic of formocresol, pulpotomy and primary teeth were evaluated as suitable for inclusion in this review. There was no specific duration chosen for selection of studies and articles written in English language were only considered. Interim reports, abstracts, letters, and guidelines were excluded.

All the studies resulting from the search strategies were imported into an Endnote library and duplicates were removed. Two reviewers (1st and 2nd authors) independently assessed the records (title and abstract), selecting the articles that met the eligibility criteria. Any type of disagreement was resolved by consulting a third independent reviewer (3rd author). After this screening, the records selected were analyzed in their full-text version, and two other reviewers (1st and 2nd authors) independently assessed whether they should be included in the review. In case of disagreement, a third author was consulted (3rd author). The same two reviewers carried out the extraction of the data in a standardized data form.

The PRISMA flow diagram (Fig. 1) was used to report the included articles according to the eligibility criteria and those excluded during the study selection process.

3. Results

In total, 364 articles were obtained from the analysis of the databases. Unrelated articles from the available full text of 174 articles were excluded. The main reasons for excluding the articles were: they were usage and precautionary guidelines. A total of 68 studies were finally included in the review.

4. Discussion

4.1 Formocresol

Despite being the subject of much debate, formocresol is still the most often utilized intracanal and pulpotomy medication for primary teeth [8].

4.1.1 Composition

Chemically, the Buckley's formocresol is composed of 31% water base, 15% glycerin to prevent formaldehyde from polymerizing to para formaldehyde, 19% formaldehyde as an alkylating agent, and 35% tricresol as a protein-coagulating phenolic substance [12]. Although studies have indicated that many dentists continue to use formocresol at full dosage, it has been advised that it be administered either in a 1:5 or 1:25 dilution [12–14]. It is understood that it is due to non-availability of dilution solution and that recommendations have been made to the manufacturer to develop 1:5 dilution of formocresol replacing the full strength formulation and that which is as effective as full strength medicament [2].

4.1.2 Mode of action

The emission of formaldehyde vapors, which act as a germicidal agent and reversibly inhibit many enzymes involved in the inflammatory process, is thought to be the mode of action of formocresol [12]. The pulp tissue is fixed as a result, and further enzymatic decay is prevented [15]. It was initially employed to render all non-viable tissues within the root canal inert. Recently, techniques have been developed to preserve the integrity of radicular pulp while just fixing the superficial layers of pulp [7]. Cresol is very lipophilic and has been shown to completely destroy cellular integrity, which presumably would allow the formaldehyde component of formocresol for deeper tissue fixation [16].

4.1.3 Clinical procedure

Using sterile cotton pellets, the pulp chamber is dried, and then the cotton pellets are moistened with formocresol. The surplus formocresol is then blotted over sterile gauze before being applied to the pulp stumps. After removing the cotton pellets and drying the pulp chamber, zinc oxide-eugenol is applied over the pulp stumps. The procedure is finished by cementing the stainless-steel crowns. The aforementioned method was initially done in 5 visits and the recommended application time was 5 minutes [2, 7]. Recent research, however, suggest that contact for few seconds may be sufficient and may even be preferable to the previous method [12]. Since 1960, it has been done as a single visit technique due to economic and behavior management factors [6].

4.2 Concerns about formocresol

The safety of formocresol has occasionally been questioned for more than the last 20 years [2]. Here, the main issues surrounding formocresol are highlighted.

4.2.1 Systemic effects

Recent assessments have revealed that modern dentists still employ formocresol despite the widespread systemic dissemination of formaldehyde during formocresol pulpotomy [8]. High dosages of intravenously injected formocresol can cause a systemic toxic response that is defined by changes in blood and urine enzymes as well as histological evidence of kidney, liver, heart, and lung damage [8]. The distribution of radioactively labeled formaldehyde in the viscera, urine, bone, dentine, and periodontal ligament was shown in a study by Ranly DM (1985) on formocresol pulpotomy in a single molar in rats [17]. After receiving thorough dental care with at least one pulpotomy, 30 children were examined by gas chromatography and mass spectrometry in another study by Kahl J *et al.* [18] (2008). It was discovered that neither formaldehyde nor cresol were present in the blood samples. Instead, their research showed that after the placement of formocresol pellets, benzyl alcohol could be found in traces in their blood samples. Since

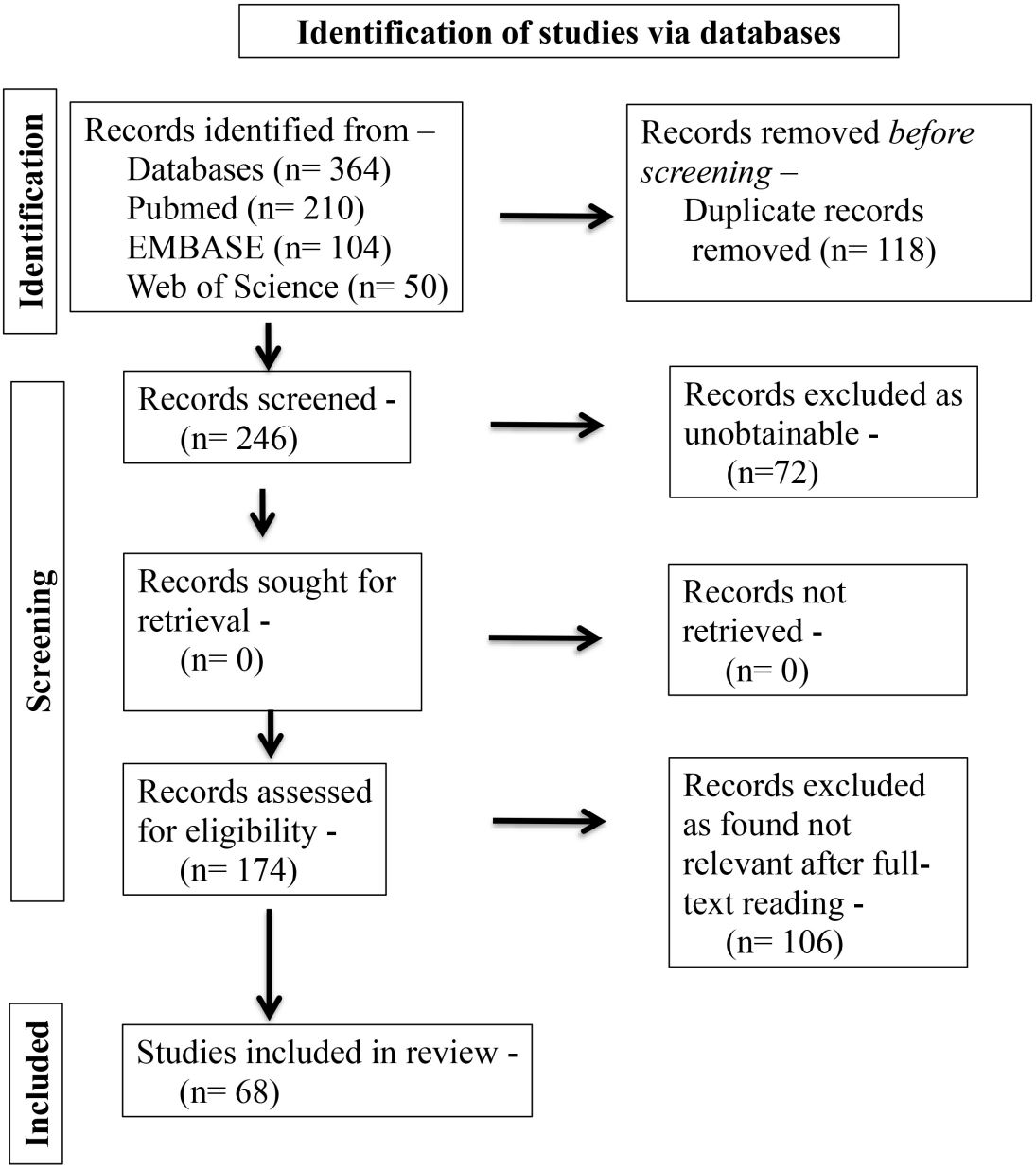

FIGURE 1. PRISMA flowchart of study selection process.

these compounds are neither carcinogenic nor mutagenic, it is believed that their presence is insignificant. The half-life of formocresol, on the other hand, is well known to be 1–2 minutes, and studies have shown that formaldehyde is rapidly converted into formic acid and carbon dioxide after its application. As a result, it is assumed that formocresol exposure is within the allowed exposure limits [7]. Also the studies where more number of formocresol pulpotomies were done on a small animal like dog represents a considerably higher exposure to systemic formocresol than would occur when performing one or two pulpotomies on a child [8].

4.2.2 Mutagenicity and carcinogenicity

Due to the presence of formaldehyde, the International Agency for Research on Cancer has categorized formocresol as a potential carcinogen [19]. Additionally, mutagenic and genotoxic effects of cresol on mammalian cells are now established [13, 20]. We are often exposed to formaldehyde due to the type of food we eat and the environment we live in, which can harm specific body organs and systems [21]. It has been discovered that the degree of such damage is directly proportional to the formaldehyde dose. For instance, formaldehyde has been reported to impact the eyes, neurological system, and upper respiratory system at levels as low as 0.05 parts per million (ppm), while higher dosages of about 5 ppm can harm the lower respiratory tract and, at doses of 20 ppm and above, can cause death [21]. The World Health Organization has determined that the daily average intake of formaldehyde is 7.8 mg, ranging from 1.5 to 14 mg [16]. An adult consumes 10.55 mg of formaldehyde daily, assuming a contribution of 9.4 mg from food, 1 mg from inhalation, and 0.15 mg from water [16]. If formocresol is diluted 1:5 and applied to a no. 4 cotton pellet that has been squeezed dry, the estimated formaldehyde dose related to one pulpotomy treatment is 0.02 to 0.10 mg [16].

Numerous genetic abnormalities have been linked to formaldehyde exposure in cells, including chromosomal

abnormalities, development of micronuclei and sister chromatid exchanges (SCEs), and deletions that result in the production of DNA-protein cross-links (DPX) [22–25]. Formation of DPX has been demonstrated in a study by Heck DA *et al.* [22] (1990) in the upper respiratory tract when rats were exposed to higher doses of formaldehyde. According to a study by Lu Z-S *et al.* [26] (2003) on human buccal mucosal cells, exposure to greater amounts of gaseous formaldehyde increases the risk of cancer development because it causes DNA breaks and the production of DPX. However, a research by Quievryn and Zhitkovitch (2000) revealed that DPX are either spontaneously hydrolyzed or the chromosomal damage is reversed by proteolytic destruction within a few hours of their production [27]. In a research by Zarzar PA *et al.* [28] (2003) on 20 children using Buckley's formula, no chromatid gaps, breaks, or chromosomal abnormalities were noted. They stated that although chromosomal abnormalities were discovered in 1 child (5%) there was no proof that this was specifically caused by either formocresol or other factors that could have caused such a finding [28]. *In vitro* research by Ribeiro and Scolastici (2005) [29] using the single cell gel (comet) assay revealed possible genetic damage caused by formocresol in mammalian cells, and research by Kreiger and Garry (1983) [30] found that no mutations in cultured human lymphocytes were found below a formaldehyde threshold of 5 mg/L in the culture medium. In contrast, genotoxic events have been shown by Hagiwara M *et al.* [31] (2006) and Nishimura H *et al.* [32] (2008) when the dosage of formocresol was much lower than the normal dose used in pulpotomy.

The aforementioned findings have led various researchers to recommend that formocresol no longer be used in dental procedures. Research showing that formaldehyde does not have mutagenic or carcinogenic effects at low exposure levels, on the other hand, has been used by some to promote the use of formocresol [14]. There is no strong scientific evidence against it, therefore clinicians may continue to use it cautiously.

4.2.3 Allergic and immunogenic effects

There are conflicting studies on the allergenicity of formocresol. Studies have shown that after formocresol pulpotomy in dogs, formaldehyde-specific antibodies are formed [33]. A review on immunology of pulpal-periapical infections by Morse DR (1977) indicated that the endodontics "flare-ups" such as pain, swelling and bone resorption following the use of formocresol occur as consequence of immunological reaction [34]. Formocresol may act as a hapten, which binds to host proteins and stimulates an immunological response [34]. According to case reports by Cambruzzi and Greenfield (1983) [35] and Kopczyk RA *et al.* [36] (1986), formocresol caused necrosis of the crestal bone and the surrounding soft tissue, as well as a significant loss of the alveolar bone that served as support.

Female patients are more immunologically reactive to formaldehyde, according to a recent systematic analysis by Syed M *et al.* [37] (2015). In a case report by Ding YJ *et al.* [38] (2013), the patient initially had nausea and vomiting after using formocresol as a pulp medication, but within 10 minutes of application on the second visit, the patient experienced anaphylactic shock. Formocresol can cause a type-I allergic reaction as seen in magnetic resonance imaging, which revealed brain injury and swollen gyri in the cerebral watershed territory of the left parietal-occipital lobe [38].

However, Dilley and Courts (1981) found no evidence of similar effects in their experimental investigation using rabbits [39]. None of the 128 schoolchildren who were patch tested in a different study by Rölling I *et al.* [40] (1976) showed any positive reaction following formocresol pulpotomy. The absence of therapeutic relevance of formaldehyde-specific immunoglobulin E was reported by Doi S *et al.* [41] (2003). Therefore, it has not been proven that formocresol "sensitizes" children.

4.2.4 Formocresol injuries localized to oral and para-oral tissues

When employing formocresol, proper precautions must be taken, especially to prevent contact with any nearby soft tissues; otherwise, there is a risk of the tissue damage [12]. Inappropriate usage of formocresol often results in localized gingival recession, ulcerations, and mucosal burns along with extensive mucosal sloughing throughout the entire affected area [42]. The ulcerative lesion could be severe, and there could be sloughing that resembles coagulative necrosis [43]. The lesions may seem erythematous, edematous, or whitish [43]. Injuries to salivary gland ducts may first result in transient obstructive sialadenitis and ductal opening scarring before becoming permanently obstructed and resulting in chronic sialadenitis. Reduced food intake and a reduced mouth opening may be observed, in addition to pain and edema in the exposed area. In severe situations, the alveolar bone and teeth may also be affected [1].

Burns to the oral mucosa account for the majority of case reports of formocresol injuries in dental offices. However, there is paucity of reports of the effects of formocresol on facial skin. In a case of formocresol exposure, Issrani R *et al.* [44] (2020) described a patch of darkly stained skin with mild to severe pain and a burning sensation. Conjunctiva injury caused by the unintentional use of formocresol as eye drops has been documented in another instance [45].

4.3 Formocresol alternatives

Dental experts have searched for substitute pulpotomy medications that indicate comparable (or better) efficacy with fewer safety issues due to the topical and systemic toxicity of formocresol [6, 9]. The following are some substitutes for formocresol:

4.3.1 Glutaraldehyde

The clinical success rate of glutaraldehyde was reported to be 100% in the study by Havale R *et al.* [6] (2013), which was better than the clinical success rate of formocresol (86.7%). Glutaraldehyde has a radiographic success rate that ranges from 75.8% to 83.3% [6, 46]. On the contrary, a study by Fuks AB *et al.* [47] (1991) with 2% glutaraldehyde, showed 18% failure in deciduous molars 25 months after pulpotomy and 45% of teeth showed faster resorption than their controls in 42-month follow-up.

4.3.2 Mineral trioxide aggregate (MTA)

According to recent study, MTA is the most popular choice because of its excellent characteristics, which include preserving pulpal health and promoting healing and pulp regeneration [13, 48]. In five of the six clinical tests comparing formocresol and MTA that Fuks AB (2008) reported, MTA was more successful than formocresol [49]. In studies by Holan G *et al.* [50] (2005) and Farsi N *et al.* [51] (2005), success rates in pulpotomized molars with formocresol were 97% and 100%, respectively, after follow-up periods of 38.2 months and 2 years. However, formocresol, MTA, sodium hypochlorite, and ferric sulfate did not significantly vary from one another in a randomized clinical trial conducted by Fernández CC *et al.* [52] (2013).

4.3.3 Ferric sulphate

Studies by Havale R *et al.* [6] (2013), Fuks AB *et al.* [53] (1997) and Fei AL *et al*. [54] (1991) on pulpotomy of primary teeth have demonstrated that ferric sulfate is more effective than formocresol. Prabhu and Munshi (1997) have reported a 100% clinical and radiographic success rate with ferric sulfate [55]. According to a recent systematic review and meta-analysis, ferric sulfate could serve as an acceptable substitute for formocresol because there is no difference between the two in terms of the clinical and radiographic success rates in primary molar pulpotomies [8].

4.3.4 Calcium hydroxide

According to Markovic D *et al.* [56] (2005), 47.0% of pulpotomized teeth treated with calcium hydroxide had a dentin bridge above the site of the pulp amputation. Using an alternate hemorrhage control technique, aluminum chloride, Heilig J *et al.* [57] (1984) performed calcium hydroxide pulpotomies in 17 carious primary molars and suggested that this procedure might be preferable to formocresol pulpotomies. Similarly, Waterhouse PJ *et al.* [58] (2000) conducted a study to compare the clinical and radiological outcomes following single visit vital pulp therapy techniques, using formocresol and calcium hydroxide and confirmed that calcium hydroxide in its pure, powder form is a clinically acceptable alternative when combined with strict selection criteria for this method of restorative care. In a recent study, Kaya C *et al.* [59] (2022) compared calcium hydroxide pulpotomies with biostimulation to calcium hydroxide, formocresol, and MTA pulpotomies without biostimulation in primary molars. They found that, clinically, the calcium hydroxide pulpotomies with biostimulation had a similar success rate to the formocresol and MTA group, whereas radiographically, calcium hydroxide pulpotomy with biostimulation showed higher success rate compared to calcium hydroxide but this success was not high as compared to formocresol and MTA. Also, Yildiz E *et al.* [60] (2014) had found a lower clinical and radiographic success rate of calcium hydroxide as compared to formocresol when used as the pulpotomy material.

4.3.5 Sodium hypochlorite (NaOCl)

According to a study by Vargas KG *et al.* [61] (2006), the clinical and radiological success rates of pulpotomies with NaOCl were comparable to those of ferric sulfate and formocresol. Kola SR *et al.* [62] reported similar results (2019). To validate and establish such a conclusion, however, more research with longer follow-up times might be needed before it can be recommended as a suitable alternative to formocresol.

4.3.6 Electrosurgical pulpotomy

Infected radicular pulp tissue has been treated with electrocautery and lasers in addition to the standard formocresol and other pharmaceutical treatments [7]. The use of such techniques was found to be highly successful, as shown by Mack and Dean (1993) [63]. El-Meligy O *et al.* [64] (2001) showed that electrosurgery pulpotomy causes less tissue reaction histopathologically than formocresol treated teeth. But Oztas N *et al.* [65] showed that formocresol pulpotomies were histologically superior to electrosurgery (1994). A recent study by Bahrololoomi Z *et al.* [66] (2008) compared the failure rates of formocresol pulpotomy and electrosurgery on 70 primary molars in children aged 5 to 10 years found no statistically significant difference between the two procedures. Before considering these treatments as alternatives to formocresol pulpotomies, more research is needed due to the conflicting findings from numerous studies.

4.3.7 Laser surgery

Elliott RD (1999) [67] evaluated and compared human primary pulp responses to carbon dioxide laser and formocresol and found no significant differences between the two procedures in their clinical or radiographic findings suggesting that the use of lasers may be beneficial in vital pulpotomy.

4.3.8 Miscellaneous

It has been demonstrated that Biodentine, a calcium-based bioactive cement, exhibited some promising outcomes in the search for newer alternatives for pulp dressing in primary teeth [7, 68–70]. Additionally, it was determined that White Portland Cement and beta-tricalcium phosphate were superior to formocresol and ferric sulfate [13]. Formocresol or other chemicals commonly used as dressings in deciduous teeth pulpotomies could potentially be replaced by a variety of other materials, including calcium phosphate cement, freeze-dried bone, allogenic bone morphogenetic protein, supersaturated collagen solutions, and allogenic dentin matrix [71–73]. Although many alternatives to formocresol are available, an ideal agent for pulp dressing in pulpotomies of deciduous teeth has not been established thus far. Until such an agent is found, formocresol, ferric sulphate or MTA may be continued to be used as pulp capping agents in primary tooth pulpotomies [7].

The advantages and disadvantages of alternative materials to formocresol are highlighted in Table 1 [2, 6–8, 43, 72, 74].

4.4 Future recommendations

It is difficult to predict future choices, but as new materials and techniques are introduced they must be thoroughly assessed for their potential for both immediate and long-term success using longitudinal research and randomized controlled trials.

TABLE 1. Potential substitutes for formocresol.

Type and features	Substitute	Recommended concentration	Advantages	Disadvantages
Preservation (maintains vital tissue with no induction of reparative dentine)	Glutaraldehyde	2%	● Better bacteriocidal activity ● Potentially less toxic ● No external root resorption	● Hypersensitivity reactions ● Short shelf life ● Need to be freshly prepared
	Ferric sulphate	20%	● Comparable clinical and radiographic success rates ● Inexpensive	● Internal root resorption ● Calcification of root canals ● Classified as a hazardous, corrosive liquid and decomposes to form sulphuric acid that can cause superficial tissue burns if it is not confined to the pulpotomy site
	Calcium hydroxide	-	● Inexpensive ● Ability to induce the formation of dentin bridge	● Internal root resorption ● More technique sensitive ● Extremely cytotoxic ● Calcification of root canals
Regeneration (causes formation of dentin bridge)	Mineral Trioxide Aggregate (MTA)	MTA powder with sterile saline at a ratio of 3:1	● Excellent biocompatibility ● High sealing capacity ● Ability to induce the formation of dentin, cement, and bone ● No internal root resorption ● Less cytotoxic ● Less time for procedures	● Expensive ● Not easily available ● Difficult to use and requires a learning curve ● Exposure to MTA dust and crystalline silica can cause respiratory irritation, ocular damage and skin irritation ● Since the material cannot be kept once the envelope is opened, its clinical use becomes almost prohibitive

TABLE 1. Continued.

Type and features	Substitute	Recommended concentration	Advantages	Disadvantages
Root canal irrigant and regeneration	Sodium hypochlorite (NaOCl)	5%	● Good biocompatibility ● Excellent bacteriocidal activity	● Causes soft-tissue inflammation and necrosis if it is expressed outside the confines of root canal ● Secondary infections ● Leads to acute sinusitis, if extruded into maxillary sinus
Devitalization (intended to mummify the vital tissue)	Electrosurgical pulpotomy	-	● Good visualization and homeostasis ● No systemic involvement ● Less time-consuming	● Internal root resorption ● Not be suitable if apical root resorption has occurred ● High intensity current can lead to peri-apical or furcal involvement ● Lead to earth leakage burns
	Laser surgery	CO_2, neodymium-doped yttrium aluminum garnet (Nd:YAG), and erbium: yttrium-aluminum-garnet (Er:YAG) lasers	● Less time-consuming ● Photobiomodulation ● Better patient cooperation ● Effective in minimizing post-treatment inflammation	● Expensive and large-sized device ● Major thermal change (carbonization and strong coagulation)

5. Conclusion

The literature review in this paper supports the notion that formocresol remains the most widely used pulp dressing agent in primary tooth pulpotomies despite having no additional benefits over other currently available chemicals used for pulp dressing in primary teeth pulpotomies or other non-pharmacotherapeutic techniques. Evidence also suggests that when used in primary tooth pulpotomies with proper precaution and the lowest dose and shortest exposure time possible, it is less likely to have any adverse effects on children and still produce the intended results. Presently, there is no scientific evidence against the use of formocresol as a pulp dressing agent in primary teeth and its use can be continued till a biologically superior alternative is identified.

AVAILABILITY OF DATA AND MATERIALS

The data are contained within this article.

AUTHOR CONTRIBUTIONS

RI and NP—designed the research study. RI—performed the research. AKB, AYA and KKA—analyzed the data. RI, SHA, KKG and MKA—wrote the manuscript. All authors read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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