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REVIEW

Evaluation of formocresol versus ferric sulphate primary molar pulpotomy: a systematic review and meta-analysis

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Abstract

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Aim To present a systematic review of the effects of formocresol and ferric sulphate when used as medicaments in pulpotomized primary molar teeth.

Methodology The study list was obtained by using MEDLINE, the Cochrane Library, EMBASE and SCI search. Only those papers which met the inclusion criteria were accepted. The quality of studies used for meta-analysis was assessed by a series of validity criteria according to Jadad's scale. A systematic review and meta-analysis were performed.

Results Eleven clinical studies comprising four randomized-clinical trials (RCTs), four controlled clinical trials (CCTs) and three retrospective studies were included. The results of the meta-analysis of six prospective clinical trials suggested that the two popular pulpotomy medicaments were not significantly different in terms of clinical outcomes, radiographic findings, prevalence of apical and furcal destruction, internal root resorption or pulp canal obliteration. The relative risk (RR) value and 95% CI for those parameters were 0.72 (0.43–1.23), 0.87 (0.59–1.30), 0.67 (0.27–1.66), 1.77 (0.56–5.58) and 1.41 (0.63–3.15), respectively. The overall clinical and radiographic success rates based on the data of treatments with ferric sulphate from the 11 studies included ranged from 78% to 100% (mean 91.6 ± 8.15%) and from 42% to 97% (mean 73.5 ± 18.40%), respectively.

Conclusions In primary molar teeth with exposure of vital pulps by caries or trauma, pulpotomies performed with either formocresol or ferric sulphate have similar clinical and radiographic success. Ferric sulphate may be recommended as a suitable replacement for formocresol.

Keywords: ferric sulphate, formocresol, meta-analysis, pulpotomy.

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Introduction

Pulpotomy in a primary tooth is a procedure performed when the coronal pulp tissue is exposed by caries, during caries removal or trauma (Fuks 2002). The infected and inflamed coronal pulp is amputated, leaving vital and uninfected radicular pulp tissue. The pulp stump could be treated by electrosurgery (Dean *et al.* 2002), Er:YAG laser (Jeng-fen *et al.* 1999) or with a dressing such as formocresol (Eidelman *et al.* 2001), calcium hydroxide (Rodd *et al.* 2006), glutaraldehyde (Su *et al.* 1990), enriched collagen solution (Llewelyn 2000), ferric sulphate (Fei *et al.* 1991) or mineral trioxide aggregate (MTA; Eidelman *et al.* 2001) to protect it and promote healing. Although many techniques have been suggested (Ranly & García-Godoy 2000), there is no evidence to determine which is the most appropriate technique according to a recent Cochrane Review (Nadin *et al.* 2003).

Formocresol is regarded as the 'gold standard' (King *et al.* 2002) and was first used for pulpotomy by Sweet

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(1930) with a 97% success rate. Formocresol produces an area of necrosis in the adjacent pulp tissue with the fixative effect diminishing as it progresses apically. The apical third of the pulp is unaffected, and retains its vitality for an extended time (Heys *et al.* 1981). Formocresol has been the most popular pulp-dressing material for pulpotomized primary molars for the past 60 years. However, the use of formocresol has been challenged because of its deleterious effects, potential carcinogen in action, immune sensitization, mutagenicity and cytotoxicity. This has led to investigations of alternative techniques and materials for more than 20 years (Block *et al.* 1978, Lewis & Chestner 1981, Yodaiken 1981, Perera & Petito 1982, Lewis 1998). The major concern has been with the formaldehyde component of formocresol (Fujita *et al.* 1981, Yamasaki *et al.* 1994). Formaldehyde has been shown to be distributed systemically after pulpotomy. Cresol is also locally destructive to vital tissue (Ranly & Fulton 1976, Pashley *et al.* 1980).

Ferric sulphate ($Fe_2[SO_4]_3$) has been used as a coagulative and a haemostatic agent for crown and bridge impressions (Fischer 1987). The agglutination of blood proteins results from the reaction of blood with ferric and sulphate ions and with the acidic pH of the solution. The agglutinated proteins form plugs that occlude the capillary orifices (Lemon *et al.* 1993). Fei *et al.* (1991) reported the application of ferric sulphate in pulpotomized human primary molars with clinical and radiographic success rates of 100% and 97%, respectively. Cotes *et al.* (1997) and Fuks *et al.* (1997a) reported on the use of ferric sulphate in rats and baboons, respectively. Ferric sulphate prevented problems arising from clot formation after the removal of the coronal pulp and produced a local, but reversible, inflammatory response in oral soft tissues (Shaw *et al.* 1983). No concerns about toxic or harmful effects of ferric sulphate have been recorded in the dental or medical literature.

Randomized-clinical trials (RCTs), in which participants are randomly assigned to treatment and control groups, are considered the gold standard of experimental design (Coward 2002). Archie Cochrane, a British epidemiologist and therapist, recommended aggregating these individual results and performing a strict systematic review so as to acquire of a true and reliable conclusion (Kavale & Glass 1981). The Centre for Evidence-based Medicine (Torabinejad & Bahjri 2005) identifies RCTs and systematic reviews of RCTs as Level 1 according to the levels of evidence (LOE) corresponding to study design (http://www.cebm.net/levels_of_evidence.asp).

The purpose of this meta-analysis of the literature was to evaluate the effects of formocresol versus ferric sulphate primary molar pulpotomy in terms of clinical and radiographical outcomes.

Materials and methods

Literature search

A computerized literature search was performed using MEDLINE (1966–2006) (Table 1), the Cochrane Library (Issue 4, 2005), EMBASE (1984–2006), SCI (1995–2006), CNKI (1994–2006). RCTs, quasi-RCTs, controlled clinical trials (CCTs) comparing formocresol versus ferric sulphate used in pulpotomized primary molar teeth conducted in humans were identified for meta-analysis. Other papers that involved clinical and radiographic data of pulpotomy treatment with ferric sulphate were also checked for the overall statistical analysis. Many useful references and optimum search strategies were obtained from the Cochrane Handbook for Systematic Reviews of Interventions (Higgins & Green 2005). The title and abstract of all potentially relevant studies were identified for their contents before the retrieval of full articles. Full articles were scrutinized for relevance if the title and abstract were ambiguous. The search ended in Week 4 May 2006.

Inclusion criteria

All searches were conducted independently by at least two reviewers. The inclusion criteria included: (i) all selected teeth were primary molars with symptomless

Table 1 MEDLINE (Ovid) and EBMR search strategy

	Search history	Results
1	Dental pulp capping	1523
2	Pulpotomy	1063
3	Dental pulp devitalization	382
4	Dental pulp exposure	553
5	Pulp therapy	155
6	Primary molar$	962
7	Formocresol$	404
8	FC	24 826
9	Ferric sulphate$	235
10	Ferric sulphate$	30
11	FS	4728
12	7 or 8	25 210
13	9 or 10 or 11	4959
14	1 or 2 or 3 or 4 or 5 or 6	3713
15	12 and 13 and 14	29
16	Limit 15 to human	26

Use '$' for truncation.

exposure of vital pulp tissue by caries or trauma; (ii) all selected teeth had a 6-month follow-up time at least; (iii) all selected teeth had no internal root resorption, periapical bone destruction, periodontium involvement, swelling or sinus tract; (iv) all selected teeth were restorable with posterior stainless steel crowns; (v) the outcome was evaluated by clinical symptoms and/or radiographic evidence; (vi) the outcome comparison followed a standard definition of success/failure and was indicated by the number of teeth and (vii) the studies were not carried out *ex vivo* or on retreatment cases.

The inclusion criteria solely for meta-analysis included: (i) studies are RCTs, quasi-RCTs or CCTs; (ii) the selected teeth were treated by formocresol or ferric sulphate without other additional methods and (iii) comparison between formocresol and ferric sulphate in terms of clinical and/or radiographic success rates appeared within the same study.

Data analysis and quality assessment

Data were extracted from each study independently and entered into a computerized database. The information extracted included the name of the first author, year of publication, mean age of all cases and controls, the number of cases, the number of controls, the follow-up years and the loss of follow up. Differences were resolved by discussion amongst the reviewers to reach consensus. The quality of studies used for meta-analysis was assessed, using a series of validity criteria according to Jadad's scale (Jadad *et al.* 1996). Two independent readers who were blinded to the names of the authors, their institutions and names of the journals were required to evaluate the quality of the studies. The criteria for quality were based on the following: (i) Was the study described as randomized? (ii) Was the study described as double-blind? and (iii) Was there a description of withdrawals and dropouts? The scores for first two questions ranged from 0 to 2 and for last question 0 to 1. The studies with the higher scores were weighed more when the meta-analysis was performed.

Meta-analysis

The meta-analysis was performed by software REVMAN 4.2.8 provided by The Cochrane Collaboration (http://www.cc-ims.net/RevMan). Relative risk (RR) and 95% confidence interval (CI) were calculated using raw dichotomous data of the selected studies. The heterogeneity between studies was assessed using the standard chi-squared test. If homogeneity existed amongst the studies ($P \geq 0.1$, $I^2 \leq 50\%$), the fixed effect model (Peto method) was applied to aggregate the data. If the presence of homogeneity was rejected ($P < 0.1$, $I^2 > 50\%$), sensitivity analyses were performed to evaluate whether the exclusion of one or more studies substantially reduced the heterogeneity, alternatively, a random effect model (D-L method) was the option selected. Descriptive statistics were developed when heterogeneity was evident.

Results

Study selection and data summary

Six studies included four RCTs (Fei *et al.* 1991, Markovic *et al.* 2005, Hu & Qian 2005, Huth *et al.* 2005) and two CCTs (Fuks *et al.* 1997b, Ibricevic & Al-Jame 2003) were included in the meta-analysis. Comparison of the six studies that were used in the meta-analysis is shown in Table 2. There were other two CCTs: one CCT (Casas *et al.* 2004) reported on the long-term outcomes of the primary molar ferric sulphate pulpotomy and the root canal treatment, whilst the other (Papagiannoulis-Alexandridis & Kouvelas 1985) could not be obtained. In addition, 11 studies, including three retrospective studies (Smith *et al.* 2000, Burnett & Walker 2002, Vargas & Packham 2005), four RCTs (Fei *et al.* 1991, Hu & Qian 2005, Huth *et al.* 2005, Markovic *et al.* 2005) and four CCTs (Papagiannoulis-Alexandridis & Kouvelas 1985, Fuks *et al.* 1997a, Ibricevic & Al-Jame 2003, Casas *et al.* 2004) were used for the statistical analysis of clinical and radiographic success of treatment with ferric sulphate.

Meta-analysis

The outcome of clinical assessment, radiographic findings, apical and furcal destruction, internal root resorption and pulp canal obliteration with formocresol versus ferric sulphate in pulpotomized primary molars are shown in Table 3. Heterogeneity was nonexistent in all assessment items. All the five assessment items did not reveal statistical differences between the two medicaments in pulpotomized primary molars.

Overall clinical and radiographic outcome

Data summary of the 11 studies used in the overall statistical analysis is presented in Table 4. The overall clinical and radiographic success rates of treatment with ferric sulphate ranged from 78% to 100% (mean

Table 2 Comparison of the outcome of clinical assessment, radiographic findings, apical and furcal destruction, internal root resorption and pulp canal obliteration with formocresol versus ferric sulphate in pulpotomized primary molars in six studies that were used in the meta-analysis

Study	Fei	Fuks	Ibricevic	Hu	Markovic	Huth
Number of primary molars	56	92	164	80	70	97
Follow-up time (months)	3–12	6–34	42–48	6–12	18	6–24
FC-treated teeth						
Clinical failure/total	1/27	6/37	2/80	11/40	3/33	2/48
Radiographic failure/total	5/27	6/37	4/80	15/40	5/33	5/48
Apical and furcal destruction	–/–	5/37	–/–	–/–	3/33	3/48
Internal root resorption	–/–	2/37	–/–	–/–	0/33	2/48
Pulp canal obliteration	12/27	4/37	–/–	–/–	–/–	–/–
FS-treated teeth						
Clinical failure/total	0/29	4/55	3/84	9/40	4/37	0/49
Radiographic failure/total	1/29	4/55	7/84	12/40	7/37	7/49
Apical and furcal destruction	–/–	2/55	–/–	–/–	2/37	5/49
Internal root resorption	–/–	4/55	–/–	–/–	3/37	2/49
Pulp canal obliteration	14/29	10/55	–/–	–/–	–/–	–/–
Jadad's scale	5	1	1	2	2	5

Table 3 Meta-analysis data summary of the outcome of clinical assessment, radiographic findings, apical and furcal destruction, internal root resorption and pulp canal obliteration with formocresol versus ferric sulphate in pulpotomized primary molars

		95% CI		Test for heterogeneity			Overall effect
	RR	Lower	Upper	Q	*P*-value	I^2 (%)	(*P*-value)
Clinical failure/total	0.72	0.43	1.23	2.75	0.74	0	0.23
Radiographic failure/total	0.87	0.59	1.30	5.64	0.34	11.4	0.51
Apical and furcal destruction	0.67	0.27	1.66	2.92	0.23	31.6	0.39
Internal root resorption	1.77	0.56	5.58	1.19	0.55	0	0.33
Pulp canal obliteration	1.41	0.63	3.15	0.30	0.59	0	0.40

Table 4 Data summary of the 11 studies used in the overall statistical analysis

Paper	Follow-up time (mean months)	Number of primary molars	Number of clinical success (%)	Number of primary molars	Number of radiographic success (%)
Papagiannoulis-Alexandridis & Kouvelas (1985)	36	73	66 (90)	–	–/–
Fei *et al.* (1991)	12	29	29 (100)	29	28 (97)
Fuks *et al.* (1997a)	20.5	55	51 (93)	55	41 (74)
Smith *et al.* (2000)	19	242	237 (99)	117	87 (74)
Burnett & Walker (2002)	18	357	332 (93)	45	34 (76)
Ibricevic & Al-Jame (2003)	42–48	84	81 (96)	84	77 (92)
Casas *et al.* (2004)	24	41	32 (78)	41	17 (42)
Vargas & Packham (2005)	24	–	–/–	35	15 (43)
Hu *et al.* (2005)	12	40	31 (78)	40	28 (70)
Markovic *et al.* (2005)	18	37	33 (89)	37	30 (81)
Huth *et al.* (2005)	24	49	49 (100)	49	42 (86)

91.6 ± 8.15%) and from 42% to 97% (mean 73.5 ± 18.40%), respectively.

Discussion

Formocresol has become a controversial pulpotomy medicament. The International Agency for Research on Cancer (2004) of the World Health Organization determined that formaldehyde causes nasopharyngeal cancer and reclassified formaldehyde as a known human carcinogen. In addition, people who used formaldehyde are at the high risk of having nasal and paranasal sinus carcinoma and leukaemia (http://www.iarc.fr/ENG/Press_Releases/archives/pr153a.html). The safety of formocresol has also been questioned, as it was known to cause a toxic, immune sensitization, mutagenic and chromosomal aberrations (Fujita *et al.* 1981, Yamasaki *et al.* 1994). Therefore, dentists should not ignore the risks of formocresol, but realize its use in paediatric dentistry is unwarranted (Casas *et al.* 2005).

Although ferric sulphate is not a new pulp medicament for pulpotomized primary molars, the number of clinical studies, especially high quality RCTs, is limited. In the selection of studies, only 11 clinical studies and one meta-analysis (Loh *et al.* 2004) comparing formocresol versus ferric sulphate were identified. Loh *et al.* (2004) reported the same conclusion in their evidence-based assessment, but that study search in their meta-analysis ended 2002. It included only one RCT and one CCT, which provided inadequate information that was less valuable for clinical practice. With the limited number of studies and different or even controversial results, aggregating the results of different studies by meta-analysis is an optional way to provide reliable results and suggestions for clinical practice. Therefore, a further meta-analysis that included four RCTs and two CCTs was necessary. Moreover, the overall clinical and radiographic success rates of ferric sulphate pulpotomized primary molars were statistically analysed with data from 11 studies.

To comprehend the results of an RCT, readers must understand its design, conduct, analysis and interpretation. Investigators and editors developed the original Consolidated Standards of Reporting Trials (CONSORT) statement to help authors improve reporting by following the CONSORT guidelines (Moher *et al.* 2001). Most of the included RCTs failed to follow the guidelines. First, the randomization method (i.e. computer, envelope, random sequence, etc.) will exclude subjective interference in case selection and distribution. Fei *et al.* (1991) and Huth *et al.* (2005) used the table of random numbers and block randomization, respectively. Other studies failed to describe their ways of randomization clearly. Secondly, allocation concealing, which means the estimator, the patient himself and outcome reporter were blinded to the treatments allocation, will guarantee an objective and accurate assessment. This was reported only in the studies of Fei *et al.* (1991) and Huth *et al.* (2005). Thirdly, a small sample size will lead to a lower power of test and lack of adequate evidence, whereas a large one will cause the difficulties of trial control and obtaining long-term data, waste of labour, money and time. Only Huth *et al.* (2005) reported a rational calculation for the sample size. In addition, withdrawal rates that are caused by emigration, death, etc. during a long-term follow-up should be <10% of the total number of the included cases. For children, the reason for dropout from studies is mainly caused by naturally exfoliated teeth. To classify the different qualities of the included studies for meta-analysis, the weight of an individual study is evaluated by a series of validity criteria according to Jadad's scale (Jadad *et al.* 1996). As a result, the well-designed studies, with higher weight, will exert a more important role in the meta-analysis.

The heterogeneity test revealed that there was no heterogeneity in all the five assessment items of the meta-analysis. Many consistencies were observed in the six included studies for meta-analysis, which guaranteed the character of homogeneity and comparability. For example, ferric sulphate used in these studies was a 15.5% solution; the criteria for selection of teeth and the pulpotomy procedures were identical.

In this meta-analysis, the prognosis of pulpotomy in primary molars with formocresol versus ferric sulphate was evaluated clinically and radiographically. As there is little consensus on how internal root resorption and pulp canal obliteration affect the outcome, the findings are listed in Table 2. As to the definition of success and failure, all the six studies demonstrated that the case was regarded as failure when one or more of the following signs was or were present: furcation radiolucency, periapical bone destruction, internal root resorption, pain, swelling or sinus tract. However, Holan *et al.* (2005) claimed that the internal root resorption should be regarded as failure only if the process reached the outer surface of the root, thereby inducing an inflammatory process in the periodontal ligament and the surrounding bone. The arrest of internal resorption and calcifying metamorphosis of the pulp were not regarded as failure. Eidelman *et al.* (2001) disagreed with this theory, and argued that pulpotomy cannot be regarded as successful if it presents internal resorption or any other pathological consequence of the treatment, even if the permanent successor erupts into its proper location and presents no enamel defect. Not every pathological finding in a primary tooth requires intervention, as the primary tooth survival or the permanent successor may not necessarily be affected. In this meta-analysis, the internal root resorption was regarded as a sign of failure. Pulp canal obliteration was the most common radiographical finding in both groups. Pulp canal obliteration is the result of extensive activity of odontoblast-like cells, demonstrating that the tooth has retained some degree of vitality. Therefore, it was not regarded as failure (Willard 1976, Tziafas *et al.* 2000). Besides the rate of radiographic outcome, the rate of internal root resorption and pulp canal obliteration were analysed, respectively, in order to provide a detailed radiographic assessment.

Compared with permanent teeth, deciduous teeth have a shorter life span. As a result, studies with longer follow-up time will be at the risk of losing case information. In addition, the increasing rate of loss to follow up and some uncertainty factors, such as emigration or death, will affect the accurate estimation of success/failure rates. Therefore, longer observation periods may lead to observed lower success rates than at shorter time periods. Huth *et al.* (2005) verified in their study that the rate of success or failure was stable in the 18- to 24-month period. Due to the different observation periods of the cases in the six studies, the follow-up time in this meta-analysis was not unified. As the proper follow-up time for primary teeth has not been identified, 1 year at least was regarded as one of the inclusion criteria in this meta-analysis. There was no difference in the mean follow up between the formocresol- and ferric sulphate-treated groups.

In addition, the overall success rates based on the clinical and radiographical data for treatment with ferric sulphate in all the 11 trials were also statistically analysed. As the mean clinical and radiographic success rates were the result of aggregating the outcomes of four RCTs, four CCTs and three retrospective studies, it can only be a general reference for clinical practice.

Conclusions

The results of this meta-analysis demonstrated that in the human primary molar with exposure of vital pulp by caries or trauma, pulpotomies performed with either formocresol or ferric sulphate are likely to have similar clinical and radiographic successes. The mean clinical and radiographic success rates of treatment with ferric sulphate were 91.6% and 73.5%, respectively. Due to the deleterious effect of formocresol, it is suggested that ferric sulphate be recommended as a replacement.

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