MTA and Ferric Sulfate in Pulpotomy Outcomes of Primary Molars: A Systematic Review and Meta-Analysis

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Objective: *Methods of systematic review and meta analysis were employed to compare the success rate of pulpotomy of primary molars using mineral trioxide aggregate (MTA) and ferric sulfate (FS) as two regenerative and preservative agents, respectively.* ***Study design:*** *After raising a PICO question (In pulpotomy of vital carious-exposed primary molars, how does MTA compare to FS in terms of clinical and radiographic outcomes?) and determining the search strategy, MeSH-matching keywords were searched in four electronic databases and retrieved papers were examined in titles, and if necessary abstracts and full texts, to be relevant. Randomized clinical trials (RCTs) evaluating pulpotomy of vital primary molars after carious/traumatic exposure conducted with either FS or MTA, with at least a 6-month recall, tooth restorability, and those considering clinical and radiographic signs/symptoms, were included. The non-randomized allocation and absence of comparison between the treatment groups caused the exclusion of the article. The quality of the RCTs and also their risk of bias (low, moderate, high), were assessed using a modification of van Tulder list; for meta-analysis of the matching studies, the extracted data were analyzed by Mantel Hanszel analysis.* ***Results:*** *A total number of 620 articles were found. After exclusion of the common titles and application of the eligibility criteria, 4 RCTs [12-month follow-up: n=3, 24-month follow-up: n=4, in total: 264 teeth) comparing MTA and FS, were selected. It was showed that the 12-month outcome of both materials were similar [RR= 0.642 (CI 95%: 0.225-1.833, P=0.407)], while the two-year follow-up results revealed significant differences in treatment outcome, in favor of MTA [RR was 0.300 (CI 95%: 0.132-0.683, P=0.004)].* ***Conclusion:*** *MTA demonstrated superior long-term treatment outcomes in pulpotomy of primary molars than FS.* ***Clinical Significance:*** *Considering the advantages of MTA compared to FS and its better clinical results, use of this bioregenerative material in primary molar pulpotomy is recommended.*

Key words: *ferric sulfate/sulphate, mineral trioxide aggregate, MTA, primary molar, meta-analysis, pulpotomy, vital pulp therapy*

INTRODUCTION

The removal of the coronal pulp tissue, or pulpotomy, is the treatment method for vital primary teeth with deep carious lesions[1]. The ideal pulp dressing material/method should be able to provide hermetic seal, be antibacterial and non-toxic, promote healing of the radicular pulp, and not interfere with the physiological process of exfoliation [2]. Current agents include formocresol, glutaraldehyde, ferric sulfate, zinc oxide eugenol, polycarboxylate cement, and calcium hydroxide [1]. Recently mineral trioxide aggregate (MTA) [1,3,4] and calcium enriched matrix (CEM) cement [5] have been added to the list. The protocol vary according to the type of material and treatment objectives; pulp devitalization and mummification in case of using formocresol, pulp non-inductive preservation with minimal devitalization if Ferric sulfate is used[2], and pulp regeneration if MTA and CEM [5] are used.

Several reports have questioned the safety and efficacy of formocresol (FC) [2,6]. It is stated that FC can lead to premature exfoliation of primary teeth [1-3] and according to the International Agency for Research on Cancer (IARC), there is sufficient evidence for formaldehyde (included in FC) to be classed as carcinogenic which necessitated its substitution with other biomaterials[1-3,6].

Ferric sulfate (FS) has been reported to show promising results

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with reported success rate to range from 81% to 97% [2]. On contact with blood, a ferric ion-protein complex forms that mechanically seals the cut vessels and also prevents the formation of blood clot [7], and thereby minimizes the chance for inflammation and internal resorption[2]. Another study, reported high success rates (97.2%) for FS pulpotomy after 20 months of follow-up and recommended that FC be replaced as a pulpotomy agent by FS, which is nontoxic and easy to manipulate [8].

Mineral trioxide aggregate (MTA), was first introduced for the repair of lateral root perforations [6]. In 1998, the Food and Drug Administration of the United States (FDA) approved MTA as a therapeutic endodontic material for human use[3]. MTA is a powder consisting of tricalcium silicate, dicalcium silicate, bismuth oxide, tetracalcium aluminate, tetracalcium aluminate ferrate and dehydrated calcium sulfate, that sets in the presence of moisture [3,6]. It is showed that MTA performed ideally as a pulpotomy agent with highest success rate [2,9,10]. It has a pH of 12.5 [6] and induces dentin bridge formation while maintaining normal pulpal histology [11,12]. MTA does not cause internal root resorption, a frequent finding in teeth treated with FC, FS, and calcium hydroxide [13] and has no side effects on the developing dentition [6], but tooth discoloration and rather high cost are stated to be its main drawbacks [9,14,15].

Although a considerable number of clinical trials on the subject of primary tooth pulpotomy medicaments have been published, a Cochrane systematic review (SR) published in 2003 concluded that evidence is lacking to indicate which is the most appropriate technique for pulpotomy in primary teeth[16]. In 2008, the results of (non)/randomized clinical trials (RCTs) comparing primary molar pulpotomy with either MTA or FS, that were conducted from 1966 to October 2005, were assessed in a systematic review[17]; the results showed that compared to FS, MTA was more likely to produce clinical success despite being non-significant, but in terms of radiographic success, the difference was significant in favor of MTA[17].

After excluding the irrelevant papers, the SR in 2008 has included not only 14 RCTs but also 4 non-randomized trials [17] and it can be assumed that it does not provide the highest level of evidence (LoE) in evidence-based practice, which belongs to SRs of high-quality RCTs[18]. It is noteworthy that lack of randomization can negatively influence the reported results of a study[18,19]. Considering the rather high number of clinical trials reporting the results of FS pulpotomy to be at least comparable to MTA, and noting the only systematic review in this regard being published in 2008 that had evaluated the articles before 2005[17], the aim of the current systematic review and meta-analysis is to compare the treatment outcomes of MTA or FS in primary teeth pulpotomy merely based on RCTs.

MATERIALS AND METHOD

1- Raising a focused question

The focused question was structured according to the PICO format (Population, Intervention, Comparison, and Outcome): In pulpotomy of vital carious-exposed primary molars, how does MTA compare to FS in terms of clinical and radiographic outcomes?

2- Determination of inclusion and exclusion criteria

The inclusion criteria for the studies were: English studies with original data that had evaluated pulpotomy treatment of primary human molars with vital pulp exposure due to caries or trauma which included either FS or MTA, follow-up period of at least 6 months restorable teeth, and evaluation by clinical symptoms and radiographic methods. The exclusion criteria were articles published in languages other than English, with non-randomized allocation, follow-up shorter than 6 months, non-restorable teeth, articles in which omitted either clinical or radiographic evaluation, and absence of comparison between the treatment groups.

3- Search Strategy

A comprehensive computerized search (since 1967 to June 2013) was conducted in Medline, the Cochrane database of systematic reviews, Science Citation Index (SCI), Embase and Google Scholar. In PubMed the Clinical Queries filter, facilitated finding the controlled clinical trials (RCTs) for comparing FS and MTA as primary pulpotomy agents. The following MeSH terms and keywords were used with different combinations for trial searching [20]: ferric sulfate/sulfate, mineral trioxide aggregate, MTA, pulpotomy, pulp therapy, primary, and deciduous. The titles and abstracts of the identified studies were reviewed for relevance. Also the existing systematic reviews in this regard [16,17] were included for preliminary searching. Not entered to our search were grey literature and experts' opinion. Also hand searching was performed which did not add more data to the digital search results.

4- Data extraction and quality assessment

Data were extracted from the full texts (Table-1) and two independent reviewers evaluated them. Each article was evaluated according to the modified van Tulder list (Apendix-1) [21] and one score was given to each criteria. If the article did not mention any of the aforementioned criteria, it would gain no score for that criterion. In case of probable disagreement(s), the text and discussion were re-checked to reach a common consensus (Then the total score of each article was calculated. The range of scores$\leq$ 7 was assigned for "high risk of bias" whiles the scores in the range of 8-11 and scores$\geq$ 12 were interpreted as "moderate-" and "low-risk of bias", respectively.

5- Summary measures and synthesis of results

The main outcome for meta-analysis was clinical or radiologic failure. When data are sparse, both in terms of event rates being low and trials being small, the estimates of the standard errors of the treatment effects that are used in the inverse variance methods may be poor. Mantel–Hanszel methods, use an alternative weighting scheme, and have been shown to be more robust when data are sparse, and may therefore be preferable to the inverse variance method. Thus the Mantel Hanszel analysis was used to estimate pooled Relative Risk (RR) As a result, the extracted data from each study was the number of successes and failures (Tables 2- 4). The results of 6-, 12- and 24-month follow-ups were compared to calculate pooled RR for each interval. For one of the studies in which the results were reported based on "time to event" analysis instead of binary outcome [20], the probability of 24-month survival was considered as the basis of data extraction from the study..

Statistical analyses were performed using STATA software (version 12), (STATA Corporation, College Station, Texas, USA). The level of statistical significance was set at 0.05. The heterogeneity among studies and estimation between study variance was assessed using Q statistic test.

Table-1: data extraction from the included studies

		Erdem *et al* (2011)	**Sonmez *et al* (2008)**	**Doyle *et al* (2009)**	**Odabash *et al* (2012)**
General information	Type of publication	Article, Randomized clinical trial	Article, Randomized clinical trial	Article, Randomized clinical trial	Article, Randomized clinical trial
	Country of origin	Turkey	Turkey	Canada	Turkey
Study characteristics	Aim	to evaluate the total success rates of mineral trioxide aggregate (MTA), ferric sulfate (FS), and formocresol (FC) as pulpotomy agents in primary molars	to evaluate the effects of formocresol (FC), ferric sulphate (FS), calcium hydroxide (Ca[OH]2), and mineral trioxide aggregate (MTA) as pulp dressing agents in pulpotomized primary molars	to investigate the outcomes of vital pulpotomies using eugenol and eugenol-free materials To compare clinical and radiographic outcomes of ferric sulfate (FS), eugenol free ferric sulfate, MTA and FS/ MTA pulpotomy in primary molars	The purpose of this study was to evaluate and compare the clinical and radiographic findings of ferric sulphate (FS) and mineral trioxide aggregate (MTA) as vital pulpotomy materials in primary molars
	Design	Randomized controlled trial	Randomized controlled trial	Randomized controlled trial	Randomized controlled trial
	Recruitment procedure	A total of 128 primary molars in 32 patients were selected (1 tooth from each quadrant) based on clinical and radiographic Criteria	A total of 16 children (10 boys and 6 girls) were selected from among the patients attending the clinic of the Pediatric Dentistry Department at the Ankara University (Ankara, Turkey)	subjects were selected from children who were treated at The hospital for Sick Children , Toronto, Canada, under general anesthesia between January 2005 and October 2007	Participants, including 40 boys and 53 girls ranging between 5 and 10 years of age (mean age 7.7 years) were selected from the patient population at the University of Gazi Department of Pediatric Dentistry
	Details of randomization, allocation and blindness	No details	No details	No details	No details
	Number per groups	25 teeth	15 teeth	46 and 47 teeth	51 and 42 teeth
Participants and comparisons	Age, Gender, Ethnicity	5- to 7-yearold children (18 females and 14 males)	1-The age of the children ranged from 4 to 9 years, with a mean age of 6.6 years 2-there were 10 boys and 6 girls		Participants, including 40 boys and 53 girls ranging between 5 and 10 years of age (mean age 7.7 years) were selected from the patient population at the University of Gazi Department of Pediatric Dentistry
	disease	Each child had at least 4 primary molars (first or second), each of which was in a different quadrant and similarly cariously involved so as to require a pulpotomy	Each child had at least four primary molars with nearly equal carious involvement requiring pulpotomy.	Healthy children with 1 or more carious primary molars where removal o dental caries was likely to produce a vital pulp exposure were invited to participate in this investigation	The children were healthy and cooperative, with at least 1 symptom free restorable and vital primary molar with deep carious lesions.
	Co-morbities	Non	Non	Non	Non

setting	Confounding factors	Non	Non	Non	Non
	Follow-up period	6, 12, 24 months	6,12,18,24 months	12, 24, 36 months	3, 6, 12 months
	Unity of assessment analysis	The children were examined clinically and radiographically by 3 experienced pediatric dentists (not the operators) blinded to the technique, and in cases of disagreement, consensus was forced The inter- and intraexaminer reproducibility were calculated by Cohen's unweighted kappa statistic (Cohen's κ=0.80, κ=1).	There were objective criteria for assessing outcomes Blinding of assessors was not mentioned	Radiographs of pulpotomy-treated molars were evaluated by 2 disinterested pediatric dentists who were not involved in any other aspect of the investigation The raters were previously calibrated and participated in the rating of radiographs in a previous pulp therapy investigation	Clinical outcome assessments were made by the primary investigator at each follow-up visit, whereas the radiographic outcome assessments were made by the primary investigator and one independent experienced clinician who were blind to the treatment. The inter- and intra-examiner reproducibility was calculated by Cohen unweighted kappa statistic.
Outcomes and results	Measurement methods	Pulpotomy was considered a failure clinically and/or radiographically if 1 or more of the following signs was present: pain; swelling; mobility; percussion pain; internal root resorption; and furcation and/or periapical bone destruction. Pulp canal obliteration (PCO) was not regarded as a failure	Teeth that exhibited no symptoms of pain, tenderness to percussion, swelling, fistulization, or pathological mobility were judged clinically successful. Teeth that showed no evidence of periradicular or interradicular radiolucency, internal or external root resorption, or periodontal ligament space widening were judged radiographically successful. Radiographic evidence of pulp canal obliteration was noted, but it was not regarded as failure	The raters classified each treated molar into 1 of 3 outcomes: 1. N =normal molar without evidence of pathologic radiographic change; 2. P0 =pathologic radiographic change not requiring immediate extraction and re-assessment recommended in 6 months 3. Rx= pathologic radiographic change requiring immediate extraction	The outcome in terms of success or failure was determined by the following clinical and radiographic criteria. 1. No tenderness to percussion; teeth remained asymptomatic. 2. Absence of a sinus tract. 3. Absence of furcal or periapical radiolucency. 4. Absence of external or internal root resorption. 5. Widened periodontal ligament spaces. 6. Premature tooth loss.
	Statistical techniques	Difference between failure percentage using chi- square test	Difference between failure percentage using chi- square test	Difference between failure percentage using chi- square test	Difference between failure percentage using chi-square test
	Results	Table 3	Table 3	Table 3	Table 3

RESULTS

Computerized searches in Medline, the Cochrane database of systematic reviews, SCI, Embase and Google Scholar, yielded 619 published English studies matching the aforementioned keywords in alternating combinations. The common titles that were found in more than one keyword combination search were excluded and finally, four RCTs comparing FS and MTA for primary molar pulpotomy matched the inclusion and exclusion criteria [2,22-24], the data and characteristics of which are included in Tables 1-3.. For one of the studies in which the results were reported based on "time to event" analysis instead of binary outcome [22], the probability of 24-month survival was considered as the basis of data extraction from the study.

The extracted data from included studies and their follow-up periods are summarized in Tables 1-3; from 4 included studies 3 had 12-month follow-up. The result of one study was excluded from meta analysis due to zero weight calculated by the software. Results of the inverse-variance weighting using Q-test (Table 4), revealed non-significant differences (P= 0.230) and this means that the results of fixed and random effects are not significantly different. According to meta-analysis using Mantel-Hanszel method, pooled RR for 12-month follow-up for the two remaining studies was estimated as RR= 0.642 (CI 95%: 0.225-1.833, p=0.407), which showed a non-significant difference. Forest plots of the results are presented in Figure 1 and the result of 12-month recall shows that the diamond crosses the vertical line, indicating no significant difference in clinical failures for FS and MTA after 12 months of follow-up. Pooled RR for 24-month follow-up observations using Inverse Variance-weighted method including three study results is also tabulated in Table 4. The pooled RR was 0.300 (CI 95%: 0.132-0.683, p=0.004) which indicates a significant difference between the two materials in favor of MTA. Figure 1 also demonstrates the forest plot for 24-month follow-up with the diamond not reaching the vertical line, as an indicator of significance.

DISCUSSION

Evidence-Based practice (EBP) was first introduced in early 1990s by Guyatt [25] and since then, it has been the base of clinical decision making to provide the best treatment option for patients; dentistry is not an exception in this revolutionary phase.

The aim of the current meta-analysis and systematic review was to provide a general consensus regarding the success rate of primary molar pulpotomy using either ferric sulfate (FS) or mineral trioxide aggregate (MTA), after raising a PICO question. The only systematic review comparing MTA and FS in this regard was published in

Table 2. Characteristics of four randomized clinical trials matching the inclusion and exclusion criteria that were analyzed (N/M; non-mentioned)

Study characteristics	Baseline characteristics of groups	Co-interventions	Patient blinding	Follow-up (month)	Lost to follow up		Outcome measure		
					MTA	FS	Objective	Calibrated investigators	Blinded investigators
Erdem *et al* (2011)	N/M	Calibrated	yes	6, 12, 24	28/128		Yes	N/M	N/M
Sonmez *et al* (2008)	N/M	Calibrated	N/M	6,12,18,24	0/15	10/23	Yes	no	No
Doyle *et al* (2009)	Adjusted	Calibrated	N/M	12, 24, 36	20/112		Yes	yes	N/M
Odabash *et al* (2012)	N/M	Calibrated	N/M	1, 3, 6, 9, 12	4/42	5/51	Yes	N/M	yes

Table 3. Treatment outcomes of included randomized clinical trials at 12- and 24-month follow-ups

	12 months				24 months			
	Failures in MTA group	Successes in MTA group	Failures in FS group	Successes in FS group	Failures in MTA group	Successes in MTA group	Failures in FS group	Successes in FS group
Erdem *et al* (2011)	0	25	0	25	1	24	3	22
Sonmez *et al* (2008)	2	13	1	14	5	10	4	11
Doyle *et al* (2009)	-	-	-	-	0	47	14	32
Odabash *et al* (2012)	3	35	8	38	-	-	-	-

Table 4. Inverse-variance weighting results of the 12- and 24- month follow up using Q-test

Method	Pooled Est	95% CI		*Z*_value	*P*_value	No. of studies
		Lower	Upper			
Fixed	0.524	0.273	1.009	-1.935	0.053	4
Random	0.510	0.223	1.167	-1.595	0.111	

Test for heterogeneity: Q= 6.877 on 5 degrees of freedom (*P*= 0.230)

Moment-based estimate of between studies variance = 0.280

Figure 1: The PRISMA flow chart

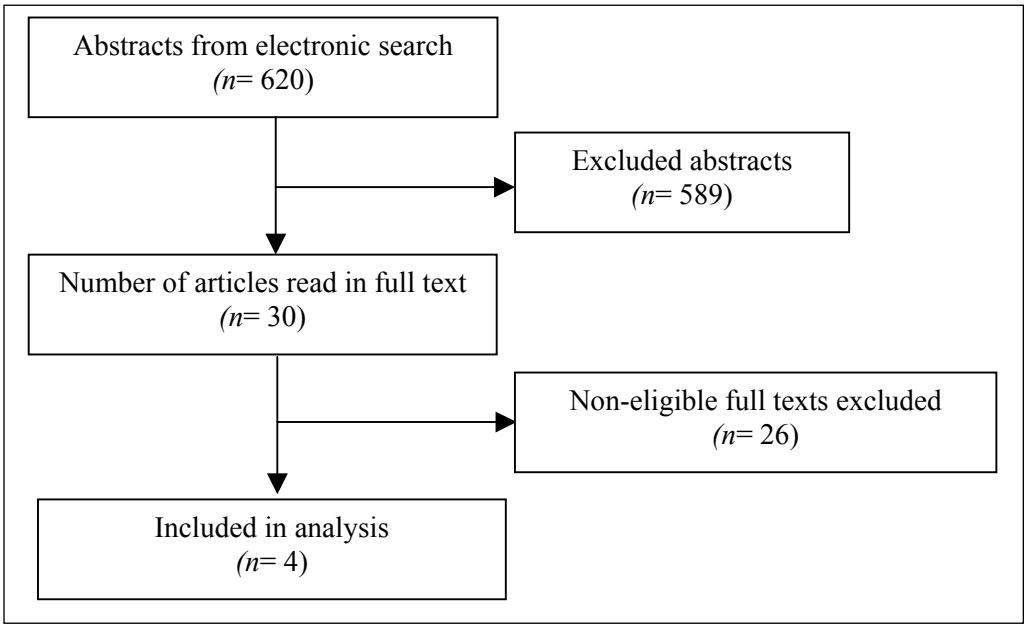
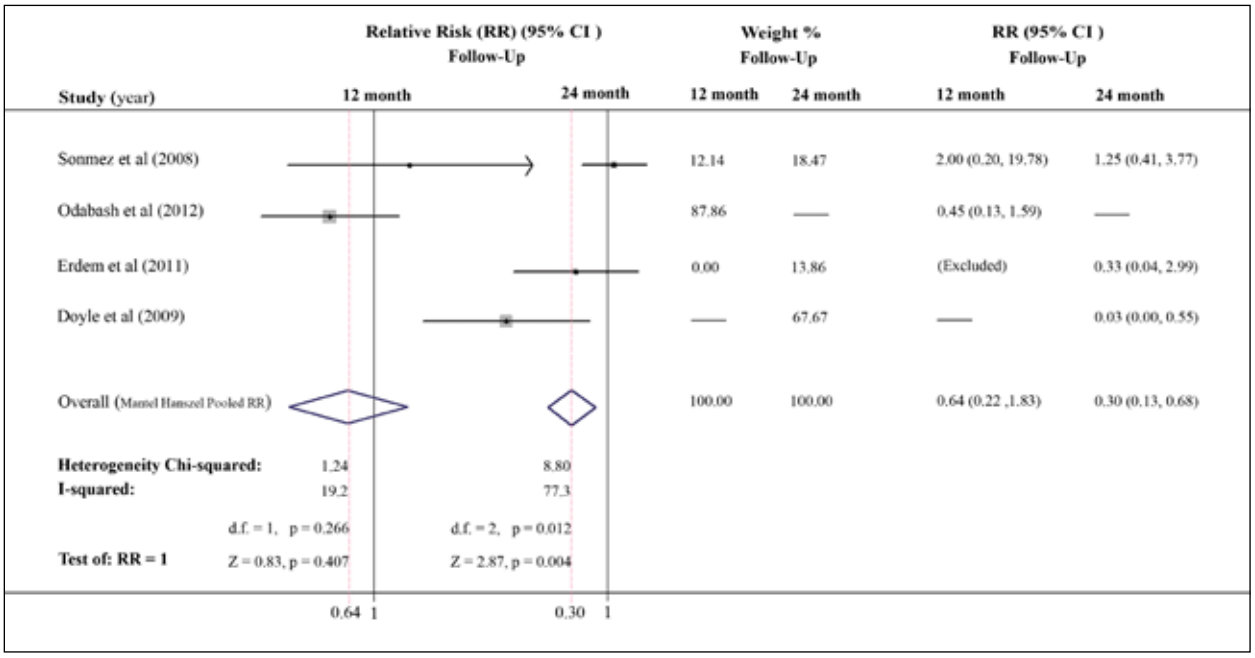


Figure 2. Forest Plots. Horizontal line for trials in each follow-up period illustrates the 95% CI; shorter line indicating higher precision of the trial. Blue line diamonds are the pooled result, with horizontal tips signifying 95% CI, and the vertical tips indicating pooled RR. The vertical line at 1 indicates no treatment outcome difference between the two experimental groups.



2008 [17] that had evaluated both randomized and non-randomized clinical trials and thus may not provide the best evidence [17]. This is while the second highest LoE belongs to *randomized* clinical trials and rather high number of clinical trials with the same subject were conducted afterwards, thus the aforementioned SR may provide the evidence but not the best current one. The present meta-analysis can provide the best current evidence with a high LoE in evidence-based practice. A computerized database search was performed to identify relevant articles and this evidence-based strategy revealed four RCTs matching the inclusion criteria [2,22-24].

The Level of Evidence (LoE) pyramid, assigns the highest grade (LoE 1) to high-quality randomized clinical trials (RCTs) as well as systematic review of such RCTs [26]. One important issue is the trials that have not included features such as blinding and allocation concealment, and this fact has a negative impact on the reported treatment outcome(s) compared with those studies that did include these features[18]. Considering the variations in the *methodological* and *reporting* quality of RCTs which can affect their conclusion(s) about the existing evidence, the quality assessment of RCTs is of utmost importance[19]. Assessing the methodology of studies by means of scales and checklists is useful to evaluate the quality of RCTs[19]. As a modification of Delphi List, van Tulder list have been used for quality assessment of RCTs[19]. The articles in the present review were assessed by means of a modified version of van Tulder scale (Apendix-1), in which many important particles of a study are taken into consideration. As they tent to eliminate biases[19], randomization and allocation concealment should be evaluated for assessing methodological quality of a RCT. Randomization is one of the most common items in measuring methodological quality, without which the treatment effect(s) can change [18]. Also inadequate allocation concealment can produce an exaggeration of treatment effects in clinical trials [27]. Moreover many other important issues of a RCT are evaluated with this list: double-blinding (its absence can exaggerate the results) [28], samples size (trials with small sample sizes have more of a risk for a type *II* error) [19], appropriate statistical analysis, description of withdrawals and dropouts, baseline similarity and objectivity of outcome measures. The lack of these items can have a negative impact on the quality of the trial[18,18,29]. According to the list, one score was given to each assessment item and the total score was gained after summing up the values. All the articles evaluated in this systematic review scored within the acceptable range (≥ score 8), which indicates that the current best evidence belongs to RCTs with "moderate risk of bias"

All of the matching trials were checked, scored and then the result of the total scores were analyzed. The meta-analysis showed that although the difference in outcome after 12 months of follow-up was not significant but the two-year evaluation presented significant differences in favor of MTA. Contrary to FS, MTA's success rate remained stable with almost no failures observed after 24 months. Considering the main objectives of pulp treatment being regeneration of the radicular pulp and maintaining the tooth and thus the integrity and health of oral tissues [3], it is sensible to provide the best treatment for the patients. The high success rate of pulpotomy with MTA is impressive, especially regarding the long-term follow-up period. Histologically, MTA can induce a thick dentine bridge at the amputation site and this can prove the bioregenerative characteristic of MTA [2,11,12,29], which is not applicable to FS[2]. On the other hand, pulp canal obliteration (PCO) is a common radiographic finding at widely varying frequencies in FS pulpotomized teeth[2]. Also instances of internal resorption have been previously reported in FS pulpotomies[2,30]. Considering the long-time success rate and lack of side effects associated with FS in MTA pulpotomy of primary molars, MTA can be a good alternative to FS for pulpotomy of primary molars and its use is recommended.

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Apendix-1. Modified van Tulder List, items in *italic* are added to the original van Tulder list (21)

	Yes/No/Don't Know
Was an appropriate method of randomization performed?	
Treatment allocation: Was the treatment allocation concealed?	
Were the groups similar at baseline regarding the most important prognostic indicators?	
Was the outcome assessor(s) blinded?	
Was the care provider(s) blinded?	
Was the patient(s) blinded?	
Were the outcome assessor(s) calibrated?	
Was the co-interventions avoided?	
Was the follow-up period adequate?	
Was the compliance acceptable in all groups?	
Were withdrawal and dropout rates described and acceptable? (>85%)WCA	
Was the timing of the outcome assessment comparable in all groups?	
Were relevant outcomes used?	
Was the sample size adequate?	
Were the outcome measures objective?	
Did the analysis include an intention-to-treat analysis?	