Randomized Controlled Trial of Pulpotomy in Primary Molars using MTA and Formocresol Compared to 3Mixtatin: A Novel Biomaterial

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Objective: *This study was conducted to compare the efficacy of 3Mixtatin (a combination of simvastatin and 3Mix antibiotic) with MTA and Formocresol for the pulpotomy of primary molars.* ***Study design:*** *114 children aged 3-6 years old with 150 primary molars were randomly allocated to three groups. MTA, Formocresol or 3Mixtatin were used for Pulpotomies. Hard setting zinc oxide eugenol was used to cover these materials. The teeth were restored with amalgam. Blinded radiographic and clinical examinations were conducted at 6, 12 and 24 months after treatment for the presence of pain, tenderness to palpation and percussion, sinus tract, swelling, presence of internal or external root resorption, inter-radicular radiolucency, and periapical lesion.* ***Results****: 122 teeth were available for 24-month follow-up study. The overall success rate was 78.9% for FC, 90.5% for 3Mixtatin and 88.1% for MTA group. There was no significant difference in overall success rate among the groups after 24-month follow-up (X^2=2.43, df = 2, P =0.27).* ***Conclusion****: Our findings demonstrated remarkable results of 3Mixtatin in pulpotomy of primary teeth at the 24-month follow-up. Therefore, 3Mixtatin may be considered as an effective material in pulpotomy of primary teeth because of its successful results.*

Key words: *Pulpotomy, Primary teeth, mineral trioxide aggregate*

INTRODUCTION

Pulpotomy is widely used for treatment of primary tooth to maintain its integrity until normal exfoliation. Several pulpotomy materials have been investigated through clinical and radiographic studies to clarify their mechanism of action, clinical indication, and advantages. However, a consensus on the ideal pulpotomy material has not yet been reached [1-3].

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An ideal pulpotomy material should have appropriate sealing ability, bio-inductivity, biocompatibility, and have the ability to eliminate bacteria and preserve healthy radicular pulp and promote its healing [2, 4, 5]. However, none of the available and recommended medicaments for pulp therapy present all these properties. Although Formocresol (FC) has long been considered to be the gold standard, researchers are questioning its use in pulpotomy because of possible mutagenic and toxic effects [6, 7]. Different materials such as calcium hydroxide, ferric sulfate, and glutaraldehyde have been suggested as an alternative for FC [1, 2, 8, 9].

In recent years, the introduction of new bio-inductive dental materials like mineral trioxide aggregate (MTA) has improved regenerative dentistry. MTA has been successfully used for vital pulp therapy, apexification and repair of root perforations [10, 11]. It stimulates significantly effective dentinal bridging in a short period of time with significantly lower inflammation and pulpal necrosis [12]. However, MTA has some disadvantages including poor handling characteristics, long setting time, discoloration and being expensive [13-15].

Recently, 3Mixtatin has been used as a direct pulp capping and root canal filling material in primary teeth [14, 16]. It is composed of 3Mix (a combination of metronidazole, minocycline, and ciprofloxacin) and statin, and has yielded promising results in 12- and 24-month follow-up studies [14, 16]. In a study of direct pulp capping in primary molars using 3Mixtatin compared to MTA, no significant

difference was observed between the outcomes of 3Mixtatin and MTA [14]. In addition, more successful radiographic and clinical healing was reported following root canal treatment with 3Mixtatin compared to MTA in primary molars with inflammatory root resorption [16].

Considering the successful results reported for 3Mixtatin in previous investigations, this study was carried out to examine whether 3Mixtatin can be successful in pulpotomy of primary molars compared with MTA and FC after 24-month follow-up. We hypothesized that 3Mixtatin would yield superior outcomes compared to MTA and FC after 24-month follow-up.

MATERIAL AND METHOD

This study was registered at the database for clinical trials (Ref no. IRCT138902203893N2), and guidelines of the Consort Statement was followed. This randomized controlled clinical trial was performed between January 2013 and September 2014. A total of 390 children were screened and selected considering the following inclusion criteria: complete physical health with no confounding history of systemic diseases, allergic reactions, and special use of local or systemic drugs; having at least one vital primary molar indicated for pulpotomy with pulpal exposure after caries removal which had appropriate intact tissue to be restored by amalgam, with no history of spontaneous pain, pathologic mobility, redness and swelling of the vestibule, sensitivity to vestibular palpation, furcal/periapical radiolucencies, pathologic root resorption; no pathology of the succedaneous permanent tooth follicle; parents willing to participate in the study and availability during the 24-month follow-up. In cases that more than two eligible teeth were available in the same patient, the teeth were assigned randomly to the study groups.

All procedures performed in this study were in accordance with the ethical standards of the institutional research committee (registered with number 1395.47) and with the Helsinki declaration. The study procedure as well as probable risks and benefits of the treatments were explained to the parents and written informed consents were obtained.

Sample size

To calculate the appropriate sample size, 24 teeth were treated with MTA or 3Mixtatin and were followed up for three months. Considering pain as the primary outcome, there was 30% outcome difference between the two materials. Considering $\alpha = 0.05$, power = 80%, and 30% outcome difference, a sample size of 37 teeth for each group was required which was increased to 50 to improve the validity of the study and compensate for probable lost to follow-ups. The outcome of pilot study was used to calculate sample size and the pilot cases were not included in the main study.

Preparation of 3Mixtatin

3Mixtatin was prepared according to the technique described by Aminabadi *et al* [14]. A total of 100 mg ciprofloxacin (Farabi, Tehran, Iran), 100 mg metronidazole (Abidi, Tehran, Iran), and 100 mg cefixime (Farabi, Tehran, Iran) were mixed in a ratio of 1 : 1 : 1. The drugs were pulverized by porcelain mortars and pestles to achieve fine powders. Two milligrams of simvastatin were added to the drugs blend to form 3Mixtatin. Preparation of 3Mixtatin was under supervision of an expert pharmacist [14, 16].

Clinical procedures

One hundred and fifty teeth with indication of pulpotomy in 114 children were randomly allocated to three groups. Randomization software (RandList, version 1.2; DatInf GmbH, Tubingen, Germany) was used to generate random allocation list [17]. The study comprised of two consecutive sessions.

In the first session, the Tell Show Do method was employed to allow the children to be more familiar with the dental environment, instruments and procedures. Thereafter, the children received prophylaxis followed by a professional topical fluoride therapy [18].

In the second session, pulpotomy procedures were performed by an expert pediatric dentist according to the guidelines of the American Academy of Pediatric Dentistry [19]. The operator was not blinded to the treatment because of different manipulation techniques needed for the study materials. All other contributors to the study were blinded to the groups and procedures. In all groups, the teeth were anesthetized using lidocaine 2% with epinephrine 1/80000 and isolated with rubber dam. Access to the pulp chamber was obtained after the removal of caries and exposure of the vital pulp, using a #330 high-speed bur with a water spray. Subsequently, the coronal pulp tissue was removed down to the canal orifices using a sterile slow-speed round bur (#6 or #8). The pulp chamber was then irrigated with a light flow of water from the water syringe and evacuated. A sterile cotton pellet soaked in sterile saline was then placed against the stumps of the pulp at the openings of the root canals for 5 minutes [19, 20]. After hemostasis, the materials were applied based on the study group as specified bellow. The cases that bleeding was not controlled after 5 minutes of pressure with moisten cotton pallet in normal saline were excluded. All procedures were performed in one session and periapical radiographs were obtained immediately after treatment.

Formocresol group

A cotton pellet moistened with FC (Sultan Chemists, Englewood, USA) was placed on the remaining pulp tissue and removed after 5 minutes. Thereafter, the cotton pellet was removed from the cavity and it was confirmed that the bleeding was stopped and the pulp tissue was turned brown. Then, a layer of hard-setting zinc oxide eugenol (IRM, Dentsply, Milford, DE, USA) was placed on the root pulp to ensure the proper seal, and the tooth was restored with amalgam (Permite; SDI Limited, Bayswater, Australia).

3Mixtatin group

After the hemorrhage control with moisten cotton pallet in normal saline, 3Mixtatin was mixed with normal saline to form a creamy mixture and was delivered to the pulp chamber to reach a thickness of 1-2 mm. The material was condensed lightly with a dry cotton pellet, followed by application of a layer of hard-setting zinc oxide eugenol (IRM, Dentsply, Milford, DE, USA) to ensure the proper seal. The teeth were then restored with amalgam (Permite; SDI Limited, Bayswater, Australia).

Mineral trioxide aggregate group

After achieving hemostasis with moisten cotton pellet in normal saline, the white MTA powder (Angelus Indústria de Produtos Odontológicos S/A, Londrina, Brasil) was mixed according to the manufacturer's instructions and placed in the pulp chamber, and condensed lightly with a moistened cotton pellet. A

layer of hard-setting zinc oxide eugenol (IRM, Dentsply, Milford, DE, USA) was applied on the MTA to ensure the proper seal. The teeth were then restored with amalgam (Permite; SDI Limited, Bayswater, Australia).

Follow-up study

The patients were recalled at 6, 12 and 24 months after treatment for comprehensive clinical and radiographic examinations which were conducted at each appointment by two experienced pediatric dentists that were blinded to the material applied to each group.

Presence of one of the following clinical and radiographic signs and symptoms was considered as the failure of treatment: sinus tract, tenderness to palpation and percussion, spontaneous pain or pain of long duration, swelling, presence of external or internal root resorption, inter-radicular radiolucency and periapical lesion. Pain of other sources mimicking irreversible pulpitis such as a gingival problem, food impaction, etc were ruled out.

Tenderness to percussion and internal root resorption were considered as clinical and radiographic criteria to assess the inter-examiner reliability using kappa agreement coefficient [21].

Statistical analysis

Chi-square or fisher's exact test was used to compare qualitative data. One-way ANOVA test was used to compare means. The data were analyzed using SPSS 18 software (IBM, Chicago, IL, USA). $P < 0.05$ was considered statistically significant.

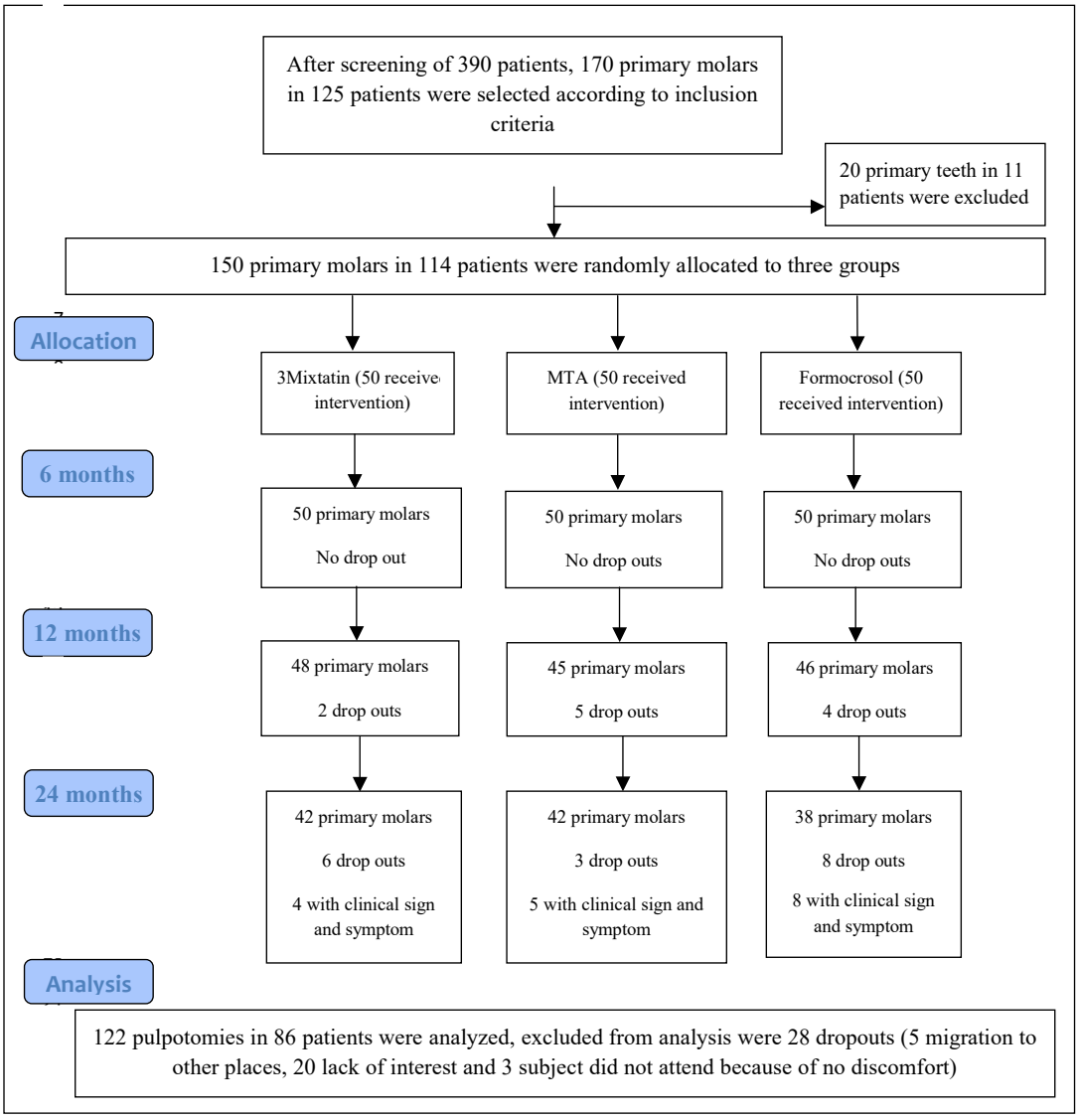
RESULTS

A total of 150 primary molars received pulpotomy. The final study sample consisted of 114 children (56 males, 58 females; aged between 3 and 6 years, mean age=5.14±1.12) with 90 mandibular molars and 60 maxillary molars. At 24-month follow-up, 122 teeth were available for assessment. There were no significant differences in children's age and gender among the study groups at baseline and 24-month follow-up (Table 1). Flow of the participants from baseline to 24-month follow-up and the reasons for drop-outs are shown in figure 1.

There was an excellent agreement between the examiners at baseline and 24-month follow-up (baseline kappa = 0.94, $P < 0.001$ and final follow-up kappa = 0.90, $P < 0.001$).

In the FC group, one (2%) tooth failed due to pain at 6-month follow-up and one (2.6%) tooth failed at 24-month follow-up.

Figure 1. Flow of participants from baseline to 24-month follow-up



Tenderness to percussion was detected in two teeth (4.34%) at 12-month follow-up and one teeth (2.6%) at 24-month follow-up. Three teeth showed internal root resorption, one (2.6%) teeth at 12-month and two (5.2%) teeth at 24-month follow-up (Table 2).

In the 3Mixtatin group, one (2%) tooth failed due to pain at 6-month follow-up. Two (4.1%) teeth had pain at 12-month and one (2.3%) at 24-month follow-up. No tooth in this group showed radiographic failure in the follow-ups (Table 2).

The results showed 100% clinical and radiographic success in the MTA group at 6 months follow-up. Two teeth (4.4%) at 12-month follow-up and two (4.7%) teeth at 24-month follow-up had pain. One tooth (2.3%) had fistula at the 24-month follow-up examination (Table 2).

The overall success rate was 78.9% for FC, 90.5% for 3Mixtatin and 88.1% for MTA group. There was no significant difference in overall success rate among the groups after 24-month follow-up (X^2=2.43, df = 2, P =0.27) (Table 2).

DISCUSSION

In the present study we assessed the efficacy of 3Mixtatin, a novel paste containing statin and 3Mix antibiotics, in pulpotomy of primary teeth. The results demonstrated similar success rate for pulpotomy in primary teeth in both 3Mixtatin and MTA groups after the 24-month follow-up. The overall failure rate was 21.1%, 11.9% and 9.5% for FC, MTA and 3Mixtatin cases, respectively. The success of 3Mixtatin in other procedures including direct pulp capping and pulpectomy has also been demonstrated in previous studies [14, 16].

This successful outcome of 3Mixtatin could be attributed to the bio-inductive effect of simvastatin [22]. Statin components are being used in regenerative dentistry due to their pleiotropic effect which enhances bone formation with improving osteoblasts function and suppressing osteoclasts function [12, 23]. It has been noted that statins promote osteoblastic differentiation from a population of undifferentiated cells [24, 25]. Several studies have shown that statin drugs can specifically stimulate high levels of BMP-2

Table1. Distribution of the characteristics of the study samples at baseline and 24-month follow-up

		Study Groups							
		Baseline				24-month follow-up			
		Overall	Formocresol	3Mixtatin	MTA	Overall	Formocresol	3Mixtatin	MTA
Age		5.14±1.12	5.05±0.89	4.89±1.08	5.15±1.2	7.58±1.6	7.14±1.5	7.73±1.14	7.35±1.07
Sex	Male	56	18	19	19	40	15	14	11
	Female	58	18	20	20	49	14	17	18
Pulpotomized teeth		150	50	50	50	122	38	42	42
Tooth type									
First molar		77	28	26	23	66	20	24	22
Second molar		73	22	24	27	56	18	18	20
Dental arch									
Maxilla		60	21	22	24	53	14	20	19
Mandible		90	29	28	26	69	24	22	23

Table 2. Frequency (%) of clinical and radiographic signs and symptoms in the study groups at follow-up visits.

Evaluation criteria	After 6 months			After 12 months			After 24 months			Overall		
	Formocresol	3Mixtatin	MTA	Formocresol	3Mixtatin	MTA	Formocresol	3Mixtatin	MTA	Formocresol	3Mixtatin	MTA
Pain	1	1	0	0	2	2	1	1	2	2	4	4
Tenderness	0	0	0	2	0	0	1	0	0	3	0	0
Sinus tract	0	0	0	0	0	0	0	0	1	0	0	1
Mobility	0	0	0	0	0	0	0	0	0	0	0	0
PDL widening	0	0	0	0	0	0	0	0	0	0	0	0
Internal root resorption	0	0	0	1	0	0	2	0	0	3	0	0
External root resorption	0	0	0	0	0	0	0	0	0	0	0	0
Periapical radiolucency	0	0	0	0	0	0	0	0	0	0	0	0
Overall failure	1	1	0	3	2	2	4	1	3	8	4	5

expression in osteoblasts which in turn induces the transformation of mesenchymal stem cells into osteoblasts, and thereby, increases the formation of bone tissues [26-28]. Therefore, they might increase dentin formation by improvement in odontoblastic function [29]. Statins also increase neuronal cells and induce angiogenesis which may lead to dentin and pulp regeneration [30]. Furthermore, the body of evidence exhibits the anti-inflammatory properties of statins. It has been noted that statins inhibit the production of pro-inflammatory cytokines like interleukin-6 (IL-6) and IL-8 by down-regulating their stimulators [31, 32]. They also reduce the pro-inflammatory chemokines and inflammatory markers such as CRP and tumor necrosis factor (TNF-a) and their receptors [33].

Moreover, the successful outcome of 3Mixtatin in our study could also be attributed to its 3Mix antibiotic content which is capable to eliminate bacteria from infected dental tissues [34]. Elimination of the pathogenic microorganisms is an integral part of pulp treatment in primary teeth. The bactericidal efficacy of 3Mix antibiotics in their topical application has been shown in carious primary teeth [35]. The results from in-situ experiments suggest that these mixed drugs penetrate into the lesions and sterilize them. Furthermore, triple antibiotic paste has been used successfully in regenerative endodontic treatment of teeth with large peri-radicular lesions [36]. Therefore, it is reasonable to assume that all of these pathways lead to the observed higher success rate of pulpotomized primary molars treated by 3Mixtatin.

Of further note, consistent with previous findings, our result demonstrated the high clinical and radiographic successes of pulpotomized primary molars treated with MTA. Currently available evidence suggests a significantly higher success for MTA compared with formocresol, ferric sulfate and calcium hydroxide as a pulpotomy medicament in primary teeth [37]. MTA serves as a biologically active substrate for the cells and has been shown to stimulate the propagation of human osteoblasts and induces thick dentine bridges [38]. MTA has shown higher radiographic success rates than other agents in pulpotomized primary molars at 1-year follow- up, with the rates ranging from 96% to 100% [39, 40]. MTA and MTA-like products have excellent biocompatibility and great sealing ability that could create a strong barrier against future bacterial leakage towards the remaining pulp in canals [41, 42]. In our study, the successful results of 3Mixtatin in pulpotomy of primary teeth are probably related to the antibacterial, anti-inflammatory and bio-inductive properties of 3Mixtatin [16]. On the other hand, treatment with FC was selected to represent the control group. FC pulpotomy is considered to be the most common pulp therapy material for primary teeth which yields successful results [2]. However, there is much controversy surrounding its application because of mutagenic and carcinogenic potential and hazardous effects on the permanent successors [6].

In overall, our findings demonstrated remarkable results of 3Mixtatin in pulpotomy of primary teeth at the 24-month follow-up. Therefore, 3Mixtatin can be considered as effective material in pulpotomy of primary teeth because of its successful results as well as biocompatible and bio-inductive properties.

It is important to note the limitations of this study that will shape the future direction of the present work. A more precise and detailed understanding of the effect of 3Mixtatin in pulpotomized primary teeth can be obtained by histologic examination of the treated teeth. Therefore, long term follow-ups until the exfoliation of treated teeth are suggested to more accurately assess the histologic results in different groups. In addition, animal studies are suggested to histologically investigate the mechanism of action of 3Mixtatin on pulp tissue.

CONCLUSION

The present study showed that 3Mixtatin can be utilized as a pulp capping material in pulpotomy of primary teeth owing to its successful clinical and radiographic outcomes after 24 months of follow-up period.

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