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RESEARCH ARTICLE

COMPARATIVE EVALUATION OF 3MIXTATIN WITH MTA AND FORMOCRESOL FOR PULPOTOMY OF PRIMARY MOLARS: AN IN-VIVO STUDY

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Abstract

Background- Preservation of pulp vitality is of utmost importance to the normal physiological functioning of tooth in situ and physiological process of exfoliation in a tooth affected by disease or trauma. Pulpotomy serves such a purpose using various medicaments applied directly on vital pulp.
Aim- To compare and evaluate the clinical and radiographic success of 3Mixtatin with MTA and formocresol for pulpotomy of primary molars.
Materials &Methodology– Sixty primary molars were selected from 100 children aged between 5-9 years age who reported to Department of Pedodontics and Preventive Dentistry. All selected primary teeth were randomly divided in to three groups with 20 each depending on the type of pulpotomy medicament (Group I - Formocresol, Group II - MTA, Group III -3mixtatin) used. The children were then examined clinically and radiographically at 6 and 12 months.
Results &Observation– Overall clinical and radiographic success rate of three groups at 6 months and 12 months were Group I showed success rate of 91.7% ,81.7% Group II showed 100%, 91.7% Group III showed 95%,85% respectively.
Conclusion– 3mixtatin can be considered as additional pulpotomy medicament in primary teeth because of its bio-compatible and bio-inductive properties.

Introduction:

Formocresol (FC) has been widely used for pulpotomy in primary teeth for over sixty years, despite concerns over its harmful effects including pulpal responses, cytotoxicity, mutagenicity, and carcinogenic potential.[1] Over the past two decades, the focus has shifted to bio-inductive and regenerative materials like mineral trioxide aggregate (MTA), which induces faster formation of non-porous dentin bridges with reduced inflammation and pulpal necrosis. MTA's efficacy is attributed in part to its ability to release bioactive molecules such as transforming growth factor-β1 (TGF-β1) from human dentin and pulp cells, promoting odontoblastic differentiation. However, MTA has drawbacks related to its mechanical properties, handling, cost, and composition, including concerns about the toxicity of aluminum oxide present in it.[2]

The use of antibacterial drugs to treat carious lesions of primary teeth may sterilize not only the lesions but also such infected materials. In addition, it is suggested that bacteria may invade the pulp, even if it is covered with clinically

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sound layers of dentine, through dentinal tubules, and that such bacteria are sensitive to majority of drugs. So, the concept of mixed drugs also can be expected to kill these bacteria in primary teeth, since the bacteria in infected pulpal tissues of primary teeth were found to be sensitive to the mixed drugs rather than single drug therapy.[3]

In response to these limitations, there has been interest in 3Mixtatin as a novel pulpotomy medicament. 3Mixtatin combines three antibiotics—ciprofloxacin, metronidazole, and cefixime—in equal proportions along with simvastatin. Simvastatin, a component of statin, enhances osteoblast function and suppresses osteoclast function, potentially improving odontoblastic activity and dentin formation.

The present study aimed to evaluate the clinical and radiographic outcomes of 3Mixtatin compared to MTA and FC as pulpotomy agents in primary molars.

Patients and Methods:

The present in-vivo study was conducted in the Department of Pedodontics and Preventive Dentistry, Mamata Dental College and Hospital, Khammam, from October 2020 to December 2021 in collaboration with Department of Pharmacology, Mamata Medical College, Khammam, Telangana. Ethical clearance (EC/IRB: MDC-KT-19205303002D) was obtained from Ethical Review Committee and Institutional Review Board of Mamata Dental College and Hospital, Khammam, Telangana.

Preparation of 3mixtatin

3Mix was prepared by mixing three commercially available antibiotics namely ciprofloxacin (100mg) (Abott Healthcare Pvt Ltd) ,metronidazole (100mg) (J.B Chemicals & Pharmaceuticals Pvt Ltd)and cefixime(100mg) (Ranbaxy laboratories) in the ratio of 1:1:1.Two milligrams of simvastatin (Sun Pharmaceutical Ind. Ltd) were added to the drugs blend to form 3Mixtatin. Pure simvastatin powder was provided by the faculty of Pharmacy, and measurements were taken by an analytical balance with 0.1 mg accuracy. After removing the coating materials, drugs were pulverized by porcelain mortars and pestles to achieve fine powders. Preparation of 3Mixtatin was trained and supervised by an expert pharmacist. It was then stored in a tightly capped porcelain container.

A total of 60 primary molars from 100 children aged 5-9years age who reported to Department of Pedodontics and Preventive Dentistry were assessed for enrollment, meeting the inclusion criteria for the study purpose: cooperative; presence of carious or mechanical pulp exposure in asymptomatic vital primary teeth; presence of at least two-thirds of the root length radiographically; restorable tooth. The final selection for inclusion in the study was done intra operatively, only when hemostasis was adequately achieved within 5 minutes after coronal pulp amputation. The exclusion criteria were as follows: history of systemic diseases; teeth showing clinical and radiographical evidence of pulp degeneration such as history of spontaneous or nocturnal pain, tenderness to percussion or palpation, pathologic mobility, swelling or fistulous tract, periodontal ligament (PDL) space widening, internal root resorption, external root resorption, furcal radiolucency/inter-radicular bone destruction and/or periapical bone destruction[4]; teeth without permanent successor and teeth requiring more than 5 minutes to achieve hemostasis during clinical procedure.[5]All selected primary teeth were randomly divided into three groups with 20 each depending on the type of pulpotomy medicament used. Group1-Formocresol (Sultan health care), Group2-MTA (Shivam industries), Group3-3Mixtatin. In cases that more than two eligible teeth were available in the same patient, the teeth were assigned randomly to the study groups.

Methodology:

In all groups, the standard pulpotomy procedure was performed. 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 saline was then placed against the stumps of the pulp at the openings of the root canals for 5 minutes. After hemostasis, the pulpotomy materials were applied based on the study group as specified below.

Group-1: 20 teeth which required pulpotomy procedure using no.2 cotton pellet moistened with FC was squeeze dried and 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 was placed on the root pulp to ensure the proper seal, and the tooth was restored with amalgam.

Group-2: 20 teeth requiring pulpotomy, after achieving hemostasis with moisten cotton pellet in normal saline, the white MTA powder was mixed according to the manufacturer's instructions and placed in the pulp chamber and condensed lightly with a moist cotton pellet. A layer of hard-setting zinc oxide eugenol was applied on the MTA to ensure the proper seal. The teeth were then restored with amalgam.

Group-3: A total of 20 teeth were included in this group. After the hemorrhage control with moisten cotton pellet 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, and a thin layer of resorbable collagen membrane was placed followed by application of a layer of hard-setting zinc oxide eugenol to ensure the proper seal. The teeth were then restored with amalgam.

For standardization, the most effective long-term restoration has been shown to be a stainless-steel crown that seals the tooth from microleakage. Hence all the teeth were given stainless steel crown taking into account, age of the patient.

Clinical and radiographic follow-up:
Clinical and radiographic examinations were conducted at six and twelve 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 were tabulated and subjected to statistical analysis.

Results:

Statistical analysis was performed using IBM SPSS for windows version 18 (IBM, Chicago, IL, USA). Chi-square and fisher's exact test were used to compare qualitative data. One-way ANOVA test was used to compare means. $p< 0.05$ was considered statistically significant. Table 1, Graph 1 shows the comparison of clinical success rates among the three groups at 6 months & 12 months implying no statistical significance observed at the end of 6 months (P=0.355) and 12 months (P=0.484). Table 2, Graph 2 shows the comparison of radiographic success rates among three groups at 6 months & 12 months implying no statistical significance observed at the end of 6 months (P= 0.227)and 12 months (P=0.553).Table 3, Graph 3 gives the overall clinical and radiographic success rate of three groups at 6 months and 12 months. Group 1 shows success rate of 91.7% at 6 months & 81.7% at 12 months. Group 2 shows success rate of 100% at 6 months and 91.7% at 12 months. Group 3 shows success rate of 95% at 6 months and 85% at12 months.

Discussion:

Clinically, diagnosing the extent of pulp inflammation in primary and young permanent teeth with carious pulp exposures can be challenging. It's difficult to differentiate between partial or total chronic pulp inflammation and select the appropriate treatment.[4] Formocresol (FC) remains endorsed by the American Academy of Pediatric Dentistry for pulpotomy procedures and continues to be taught in dental education.[7] Considering these facts, exposure of children to the formaldehyde component of formocresol during a pulpotomy is insignificant and inconsequential.[8] Recent advancements in dentistry have introduced bio-inductive and regenerative materials like mineral trioxide aggregate (MTA), shifting focus from preserving to regenerating residual pulp tissue.[2] Successful dental pulp healing hinges not only on the biological effects of the medicament used but also on the ability of both the dressing and final restorative material to create a biological seal against immediate and long-term microleakage at the restoration interface (Jabbarifar et al., 2004; Chacko &Kukirose, 2006; Percinoto et al., 2006).[9]

3Mixtatin, a novel pulpotomy agent, combines these antibiotics to eliminate bacterial contamination, a primary cause of treatment failure in primary teeth. Additionally, it incorporates simvastatin to act as an anti-inflammatory, bio-inductive, and angiogenesis-stimulating agent. Simvastatin, a component of statins, is gaining prominence in regenerative dentistry due to its ability to enhance osteoblast function, suppress osteoclast activity, and promote dentin formation.[10] Experimental and clinical studies indicate that statins like simvastatin also possess potent anti-inflammatory properties, reducing levels of pro-inflammatory cytokines levels.[11] Simvastatin enhances the proliferation and recruitment of osteo progenitor cells which is critical step in the early stages of bone healing.[12] Strong evidence has been provided that statins enhance osteoblast differentiation and mineralization resulting in bone formation. Moreover, statins increase bone formation indirectly by inhibiting inflammation that is responsible

for an imbalance in bone metabolism. Statins also inhibit osteoclasts activation by preventing downstream intracellular signaling pathways in osteoclasts and modulate the maintenance of skeletal integrity. In this context, the results of Okamoto et al. study showed that simvastatin treated dental pulp stem cells (DPSCs) promoted odontogenesis via upregulation of two odontogenic markers, dentin sialo phosphoprotein (DSPP), and osteocalcin (OCN), as well as enhanced mineralized tissue formation invitro and invivo.[11]

Min et al reported that simvastatin enhanced odontogenic differentiation and expression of angiogenic factors in human dental pulp stem cells (hDPSCs) through mechanisms that involved haemeoxygenase-1(HO-1) and its product carbon monoxide (CO). Furthermore, Pettiete et al. reported a significant loss of vertical height of the pulp chamber and increases in pulp calcification in patients who were treated with statins. They concluded that systemic statins could be a contributing factor in increased odontoblastic activity.[10]

An additional mechanism to explain the effect of 3mixtatin would be the ability of statins in stimulating angiogenesis which contributes to the wound healing process.[13] Although low doses of simvastatin are proangiogenic, a dual and dose-dependent biphasic effect of statins on angiogenesis is reported. On the other hand, it has become increasingly clear that statins have anti-inflammatory properties. This beneficial role of statins has been proved by their inhibitory effects on pro-inflammatory cytokines production such as interleukin-6(IL-6) and IL-8 and by downregulation of nuclear factor kappa ß and activator protein 1 that are IL stimulators. Statins also exert their anti-inflammatory effect by reducing the pro-inflammatory chemokines and inflammatory markers such as C-reactive proteins (CRP) and tumor necrosis factor (TNF-a) and their receptors. In similar line, Lin et al. study showed that the use of statins was consistently associated with suppresses of the progression of apical periodontitis by diminishing cysteine-rich 61 (Cyr 61), a potential osteolytic mediator in inflammatory bone diseases.

In the present study, Group 1 results shows 93.4% and 83.4% clinical success at the end of 6 months and 12 months respectively in which 2 cases comes under failure among which one case was with pain, one case was with tenderness. The radiographic success was 90% and 100% at 6 months & 12 months respectively in which 2 cases comes under radiographic failure in which one case with resorption and one case with inter radicular radiolucency. The results of the present study were in accordance with Havale et al in which clinical failure symptoms attributed to chronic inflammation of pulp and periapical tissue leading to oedema, which progresses into pathologic mobility.[15]

In the present study, Group 2 showed 100% and 93.4% clinical success at the end of 6 months and 12 months respectively. In this group, no cases showed failure clinically. The radiographic success was 100% and 90% at 6 months & 12 months respectively. One case showed radiographic failure in which it showed inter radicular radiolucency. The results of the present study were also in agreement with a study conducted by Aeinehchi et al.[16]

In the present study, Group 3 showed 96.6% and 86.6% clinical success at the end of 6 months and 12 months respectively. In this group, clinically 2 cases showed failure among which two cases showed tenderness. The radiographic success was 93.4% and 83.4% at 6 months & 12 months respectively. At the end of the study, 2 cases had showed radiographic failure. The present study was in agreement with a study conducted by Aminabadi et al which could be attributed to the bio-inductive effects of simvastatin on inhibition of bone resorption and osteocyte apoptosis and promoting osteoblast proliferation and differentiation. Statins increase bone formation indirectly by inhibiting inflammation that is responsible for an imbalance in bone metabolism. Statins also inhibit osteoclasts activation by preventive downstream intra cellular signaling pathways in osteoclasts and modulate the maintenance of skeletal integrity.[10] The overall clinical and radiographic success rate of three groups at 6 months and 12 months. Group 1 shows success rate of 91.7% at 6 months & 81.7% at 12 months. Group 2 shows success rate of 100% at 6 months and 91.7% at 12 months. Group 3 shows success rate of 95% at 6 months and 85% at 12 months.

Therefore,3Mixtatin can be considered as an additional pulpotomy medicament in primary teeth because of its biocompatible and bio-inductive properties. 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.

Legends

Table 1: - Comparison of clinical success rate of the study groups at 6 months and 12months.

Clinical success	Group 1	Group 2	Group 3	Pvalue
6months	93.4%	100.0%	96.6%	0.355NS
12months	83.4%	93.4%	86.6%	0.484NS
P value	0.228NS	0.150NS	0.161NS	

Chi square test, p<0.050 set as statistically significant, NS= Nonsignificant

Graph 1: - Comparison of clinical success rate of the study groups at 6 months and 12months.

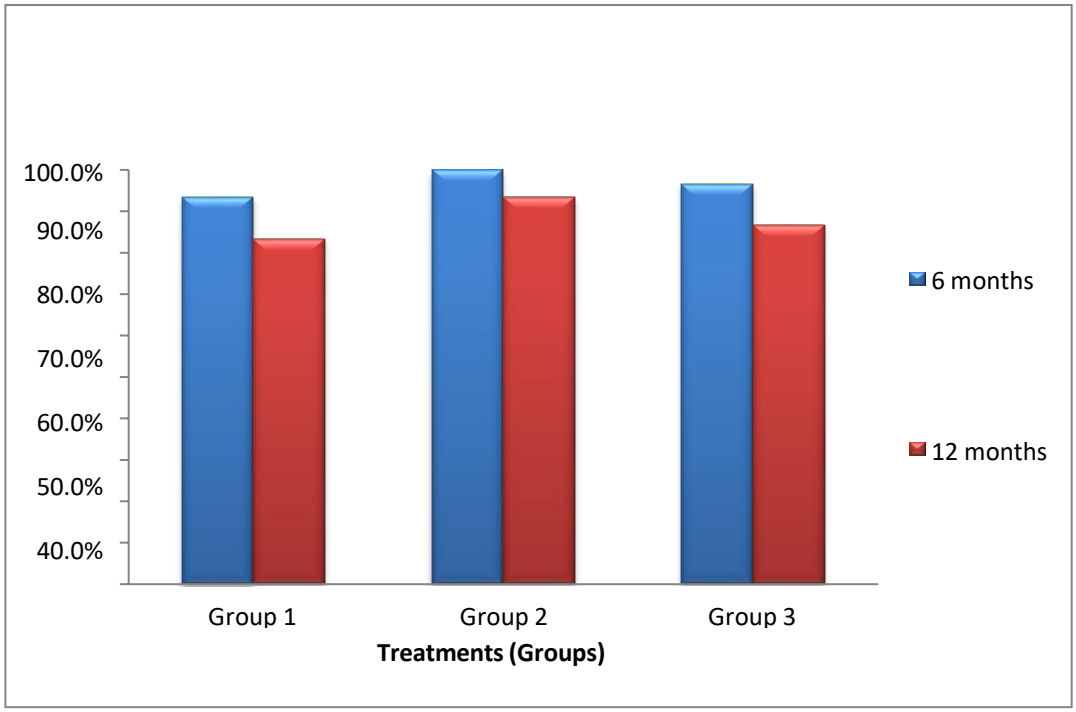

Table 2: - Comparison of radiographic success of the study groups at 6 months and 12 months.

Radiographic success	Group 1	Group 2	Group 3	Pvalue
6months	90.0%	100.0%	93.4%	0.227 NS
12months	80.0%	90%	83.4%	0.553 NS
P value	0.278NS	0.076NS	0.228NS	

Chi square test, p<0.050 set as statistically significant, NS=Nonsignificant

Graph 2: - Comparison of radiographic success of the study groups at 6 months and12months.

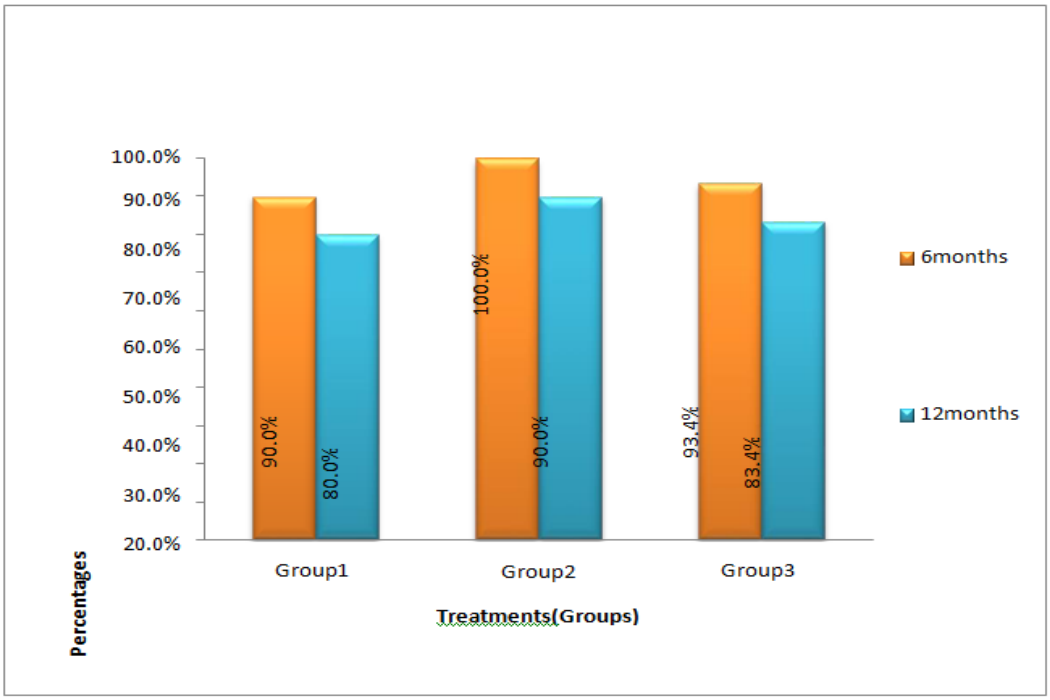

Table 3: - Clinical and radiographic success and failure rates of all the study groups at 6 months and 12 months

Treatment	Clinical				Radiographic				Overall			
	6months		12months		6months		12months		6months		12months	
	S	F	S	F	S	F	S	F	S	F	S	F
Group1	93.4%	6.6%	83.4%	16.6%	90.0%	10.0%	80.0%	20.0%	91.7%	8.3%	81.7%	18.3%
Group2	100.0%	0.0%	93.4%	6.6%	100.0%	0.0%	90.0%	10.0%	100.0%	0.0%	91.7%	8.3%
Group3	96.6%	3.4%	86.6%	13.4%	93.4%	6.6%	83.4%	16.6%	95.0%	5.0%	85.0%	15.0%

S=Success rate in percentage, F=Failure in percentage

Conclusions and Summary:

Within the limitations of the study though 3Mixtatin can be used as an additional pulpotomy medicament, good quality studies with limited comparison and interpretation, long term evaluation with clinical and radiographic follow-up should be done along with histological evaluation to consider 3Mixtatinas an ideal pulpotomy medicament.

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