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Original Article

A randomized control trial comparing the efficacy of 3Mixtatin and Modified 3Mix-MP paste using lesion sterilization and tissue repair technique to conventional root canal treatment in primary molars of children aged 4–8 years: An *in vivo* study

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ABSTRACT

Background: The aim of this study was to evaluate clinical and radiographic success rates of 3Mixtatin and Modified 3Mix-MP paste and compare it with conventional root canal treatment procedure in primary molars requiring pulpectomy.

Materials and Methods: In this *in vivo* study, 66 primary molars in 52 children aged between 4 and 8 years with primary molars having chronic periapical abscess were treated randomly with 3Mixtatin, Modified 3Mix-MP paste, and Metapex. The subjects were reviewed at 6 and 12 months both clinically and radiographically after pulpal therapy to evaluate and compare the healing process. The data obtained were subjected to statistical analysis at a significance level of 0.05.

Results: By the end of 12-month follow-up among the three groups, Group I seemed to be performing consistently better as compared to the other two groups when evaluated clinically and radiographically. However, Group III resulted in the greatest number of failures, with success rate being mere 42.9% at the end of follow-up period.

Conclusion: Radiographic and clinical healing occurred in all the three groups; however, based on our results, Group I seemed to be performing consistently better among the three groups at 12-month follow-up. Hence, it can be inferred that 3Mixtatin used as a localized agent is effective and comparable to both Modified 3Mix-MP paste and conventional pulpectomy procedure involving calcium hydroxide and iodoform paste in primary teeth.

Key Words: Metapex, primary teeth, pulpectomy

INTRODUCTION

Dental caries is perhaps the most prevalent chronic disease, as recognized by the American Academy of Pediatric Dentistry itself.[1] Pediatric dentists routinely counter primary teeth showing signs of irreversible pulpitis and pulpal necrosis. These teeth generally get subjected to two kinds of treatment, the preliminary being the pulp therapy, while extraction of the tooth seems to be the last resort.[2] Although extraction of the infected tooth followed by a space maintainer seems a viable treatment option, restoring a primary tooth to maintain space for the succedaneous tooth

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and prevention of alteration in tongue posture is a far superior treatment option.[3,4] Rarefication in the periradicular area of pulpally affected teeth is the most peculiar sign seen universally.[5]

No procedure is perfect, every procedure has some drawbacks associated with it and pulpectomy is also one of the procedures having some demerits associated with it, these have been discussed elsewhere.[6-10] Another less novel procedure, infrequently being practiced alongside pulpectomy is lesion sterilization and tissue repair (hereafter LSTR). Using triple antibiotic paste to eliminate the microbial flora inhabiting the infected pulpal space is generally the rationale orbiting the LSTR procedure. Conventionally, ciprofloxacin, metronidazole, and minocycline were added in a vehicle propylene glycol and macrogol; however, various authors have substituted the combination.[11-14]

Modern pediatric dentistry always keeps seeking methods that can regenerate remaining dental tissues to save the primary teeth and maintain its functional, developmental, and esthetic capabilities.[15] Subjected to which research keeps happening pertaining biocompatible materials such as bone morphogenic proteins (BMP),[16] Self-Assembling peptides, various Ayurvedic derivatives etc.[17] Statins is recently emerging as a material in dentistry, particularly in endodontic procedures. Its local application as a gel stimulates the regeneration of alveolar bone defects. Statins might also improve the function of odontoblasts, thus dentin formation.[18] In addition, statins have an anti-inflammatory effect by decreasing interleukin production.[19]

A plethora of studies[20-22] support employing LSTR as an effective treatment option in primary teeth as opposed to conventional pulpectomy procedure. These *in vivo* studies showed marked success of triple antibiotic paste used as LSTR technique when compared to conventional obturating materials with its success being significantly higher as opposed to another counterpart. However, these studies did not study a combination of drug that would directly augment bone formation while promoting aseptic conditions around the tooth. Therefore, the purpose of this study was to evaluate and compare 3Mixtatin with Modified 3Mix-MP paste and conventional pulpectomy procedure over 12-month follow-up. Here, 3Mixtatin is referred to as triple antibiotic paste with added Simvastatin.

MATERIALS AND METHODS

This study was a randomized, single-blind, parallel controlled trial conducted in the Department of Pediatric and Preventive Dentistry during November 2017–April 2019, in children aged 4–8 years attending the Outpatient Department of Himachal Pradesh Government Dental College and Hospital, Shimla, participated in the study. Prior ethical approval from the Institutional Ethical Committee and consent from the parents/guardians were obtained.

Following criteria were followed for selection of teeth, children with cooperative behavior showing the following clinical characteristics were included in the study:

a. Spontaneous pain or tender to percussion
b. Deep carious lesion with pulp exposure
c. Presence of chronic apical abscess or sinus tract
d. Tooth should be restorable.

Radiographic characteristics:

a. Coronal-radiographic evidence of a deep carious lesions or lesion approximating pulp
b. Radicular discontinuity of lamina dura, furcation involvement less than or equal to half of shortest root in vertical dimension.

In addition, they include teeth involving physiological root resorption more than a third of its length or if they had the presence of obliteration of the root canal, excessive internal resorption, internal calcifications, and perforation into the bifurcation. Patients exhibiting any systemic illness or with previous history of allergy to the antibiotics used in the study were excluded from the study.

Considering $\alpha = 0.05$, power = 80%, and an effect size of 0.40, a minimum sample size of 66 was required. The flow of participants undergoing the intervention was followed from allocation to the final data analysis after 12 months [Figure 1]. Subjects were randomly allocated into three groups using a simple random technique in which three identical cards marked as I, II, and III were placed in front of the patient, these cards were concealed in identical, opaque, and sealed envelopes and the patient was asked to choose one. Once the patient chose the envelop, it was opened and the patient was assigned to that group. The operator was not blinded to the treatment because of different manipulation techniques implemented for the study groups. However, the patients were blinded to the treatment procedure rendering the study as a single blind.

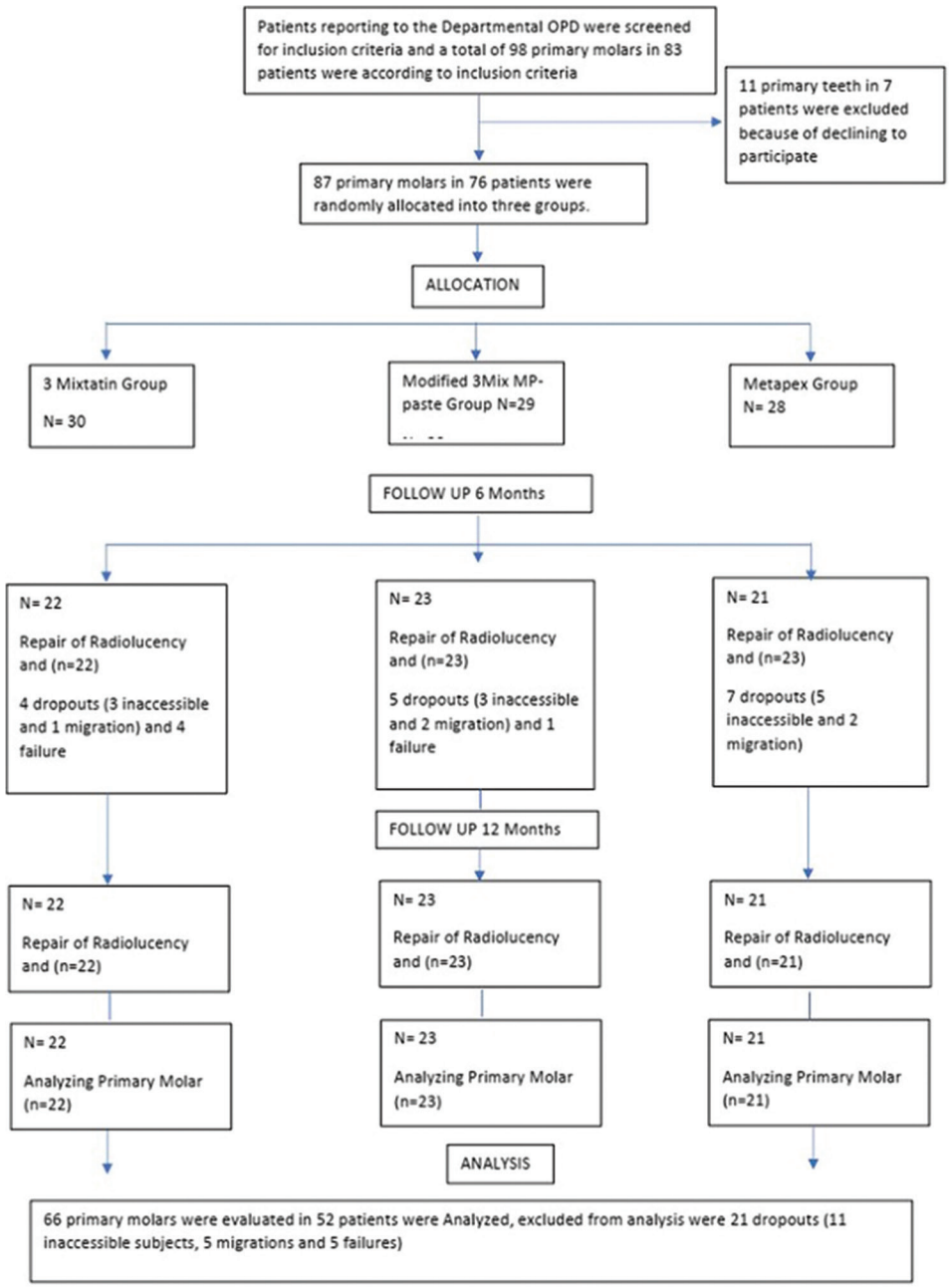

Figure 1: Flow of participants undergoing various treatment modalities.

Of the three groups, Group I comprised the 3Mixtatin group (n = 30), Group II comprised the Modified 3Mix-MP paste group (n = 29), and Group III comprised the conventional pulpectomy group receiving calcium hydroxide iodoform paste (Metapex, META Biomed Co. Ltd., Korea) as obturating materials (n = 28).

Baseline preoperative clinical and radiographic signs and symptoms were recorded on patient's history sheet including pain, presence of swelling, draining sinus, mobility, and lymphadenopathy, while radiographically teeth were evaluated for signs of periradicular changes. The teeth were later anesthetized using 2% lignocaine with 1:200,000 epinephrine (Becain-ADR, H.P., India) and isolation was done using rubber dam [Figure 2a].

Preparation of 3Mixtatin paste was done by mixing three commercially available antibiotics with Simvastatin powder (Simvotin, Solrex Pharmaceuticals Co. Baddi, Solan, India). Using a sharp B. P Blade, the enteric coating of the three antibiotic tablets was removed; they were pulverized individually

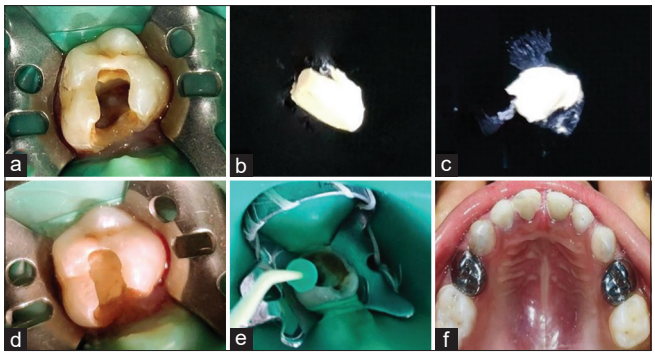

Figure 2: (a) Access opening in right maxillary second primary molar teeth, (b) Freshly Mixed 3Mixtatin paste, (c) Freshly Mixed Modified 3Mix-MP paste, (d) Triple antibiotic paste placed with in the pulp chamber, (e) Obturating the primary molar canals with prepacked syringe of calcium hydroxide and iodoform paste, (f) Restoration of primary molars with stainless steel crowns.

to fine powders using mortar and pestle. The triple antibiotics comprised 500 mg of Ciprofloxacin tablet (Ciplox®, Alchemist Ltd., India), 500 mg of Ornidazole tablet (Ornida, Aristo Pharmaceuticals, India), and 100 mg of Cefixime tablet (Cefix, Zeiss Pharma Limited, Jammu, India); these were mixed in a ratio of 1:1:1. To the above mixture 2 mg of Simvastatin powder was added, together the combination was stored in a tightly capped amber colored bottle. Since 5 mg of Simvastatin tablet (Simvotin, Solrex Pharmaceuticals Co. Baddi, Solan, India) was available commercially, the tablet was pulverized in a similar manner and weighed on an analytical scale (Sartorius Electronic Weighing Scale, BSA, New Delhi, India) with 1 mg of accuracy. Upon its clinical application, the combination powder was mixed with normal saline to form a paste [Figure 2b] and placed in the following manner.[15]

Procedure for Groups 3Mixtatin and Modified 3Mix-MP paste (lesion sterilization and tissue repair technique)

Access opening to the pulp chamber was made using a round bur mounted on a water-cooled high-speed handpiece, upon gaining access to the pulp chamber, necrotic pulp tissue if present within the chamber was removed using a sharp spoon excavator, and no attempt was made to prepare the radicular section. Using a disposable syringe, a light flow of normal saline was delivered to wash away any remaining tissue. If hemorrhage was seen to be occurring within the pulp chamber, a moist cotton immersed in 1% Sodium Hypochlorite (Dentpro©, Jammu, India) was placed until hemostasis was achieved. Freshly prepared 3Mixtatin paste was placed within the pulp chamber using a small endodontic amalgam carrier and was condensed over the root canal orifices using a moist cotton pellet.

In case of Group II, i.e., 3Mix-MP paste group, a similar procedure was followed, except the vehicle used to prepare the paste was Macrogol (M) and Propylene Glycol (P) [Figure 2c]. Type IX Glass Ionomer Cement (3M ESPE Ketac molar, Germany) was used to fill the remaining of the pulp chamber [Figure 2d]. In both the groups, stainless steel crowns were placed over the treated tooth in the same appointment.

Clinical procedure for conventional pulpectomy receiving metapex as obturating material

Consequent to anesthetizing the tooth using 2% lignocaine with 1:200,000 epinephrine (Becain-ADR, H. P., India), isolation was done using rubber dam. An access cavity was made by a round bur mounted on a water-cooled high-speed handpiece. Pulp tissue present within the pulp chamber was removed using a sharp spoon excavator initially, later the radicular pulp was removed with a fine H-file. Thorough irrigation was done with 1% sodium hypochlorite and normal saline. The working length was determined using a diagnostic radiograph. The biomechanical preparation was done using H-Files (21 mm) in pull back motion. The canals were enlarged to two or three instrument size greater than the first file used. Simultaneously, irrigation was done using 1% sodium hypochlorite and normal saline solution. The prepared canals were dried using paper points and calcium hydroxide and iodoform paste (Metapex) was injected to fill up the canal space [Figure 2e]. Following obturation of the canals, the remaining pulp space was filled with Type IX Glass Ionomer Cement. The patients were recalled after 15 days and final restoration of the tooth was done using stainless steel crowns [Figure 2f].

Upon completion of the procedure, the treated teeth were evaluated clinically and radiographically at 6- and 12-month [Figure 3a-l]. At the time of revisits, the teeth were examined clinically for any signs of inflammation including pain (visual analog scale score), presence of swelling, draining sinus, and mobility (Millers Classification); Miller recognized three grades of tooth mobility, where Grade I was first distinguishable sign of movement, Grade II was movement of tooth which allows crown

to deviate 1 mm of its normal position, and Grade III shows noticeable and increased movement of tooth more than 1 mm in any direction or the tooth can be depressed into the socket. A reduction in grade of mobility from preoperative baseline was treated as success while increased mobility was recorded as failure, while radiographically teeth were evaluated for signs of resorption both internal and external, and Orstavik *et al*.[23] criterion was used to check for periradicular changes. The criterion is a periapical index scoring system which has a 5-point scale radiographic interpretation designed to determine the absence, presence, or transformation of a disease state. It assigns the radiographs as favorable and unfavorable depending on healing occurring from immediate postoperative stage to first and second follow-up visits. The details of which are explained in Table 1. In case tooth got extracted prior to follow-up visit, the cause was noted and considered as failure.

Radiographic images were evaluated by the operator and an examiner for the above criteria's. To assess intrarater agreement, 4 weeks after the first session, the operator again scored all the study images. While for the interrater agreement, scores were assigned individually by both the examiners and evaluated to Cohen's kappa analysis. Those cases in which consensus could not be reached unanimous agreement were made by both the operator and the examiner.

RESULTS

The treatment outcomes were analyzed based on clinical and radiographic findings, data were tabulated and recorded as preoperative and follow-up findings both clinically and radiographically. The radiographic evaluations were carried out by two co-investigators. Cohen's kappa statistic for intra- and inter-examiner reliability was 0.886 and 0.891, respectively, which indicates almost perfect agreement. Categorical variables were reported as counts and percentages. Group comparisons were made using the Chi-square test or Fisher's exact test. $P < 0.05$ was considered significant. All the statistical tests were two-sided and were performed at a significance level of $\alpha = 0.05$. Analyses were conducted using IBM SPSS STATISTICS (version 22.0, IBM, Chandigarh, India). The distribution of tooth type in the sample is shown in Table 2.

Postoperative clinical findings

All the teeth present in the groups were evaluated clinically at 6- and 12-month intervals. Among the total 87 primary molars, 66 primary teeth contributed to a follow-up of 1 year with 21 teeth resulting as dropout cases. Of these 66 primary molars, 34 were primary first molars and 32 were primary second molars among these teeth, nine teeth depicted signs of pain and increased mobility in which four teeth contributed to Group II while Group III had five teeth contributing to 23.8% failure clinically at 6-month interval. Furthermore, the teeth showing clinical signs of failure had risen at 12-month interval in which Group I had 2 teeth showing signs of pain and swelling, while Group II had additional 2 teeth with pain and mobility adding up to six in total teeth showing clinical signs of failure, although these findings were statistically insignificant. In Group III, teeth with clinical signs of failure had risen from five teeth to ten teeth making 47.6% of total failure. These findings were statistically highly significant ($P = 0.005$) when comparing teeth at 6- and 12-month intervals in Group III. The comparison among the groups is seen in Table 3, a graphical representation is viewed in Figure 4.

Postoperative radiographic findings

All the teeth present in the groups were evaluated radiographically at 6- and 12-month intervals. Although when the teeth were evaluated within individual groups at 6- and 12-month intervals, more failure of teeth was seen radiographically in Group III in comparison to Group I and Group II and the findings were statistically insignificant. However, due to increased periapical radiolucency and external root

Table 1: Depicts periapical index helps to determine radiographic outcomes

Outcome	Score at immediate postoperative and follow up	Clinical impression
Favorable		
Healed	3, 4, 5 at IPO and then 1-2 at follow-up	Complete disappearance of radiolucency restoration of lamina dura
Healing	3, 4, 5 at IPO improves but isn't 1-2 at follow-up	Lucency apparent but smaller
Unfavorable		
Not healed/healing	5-3 at IPO stays 5-3 at follow-up or 1-2 at IPO and then 3, 4, 5 at follow-up	Lucency the same or larger

IPO: Immediate post-operative radiographs

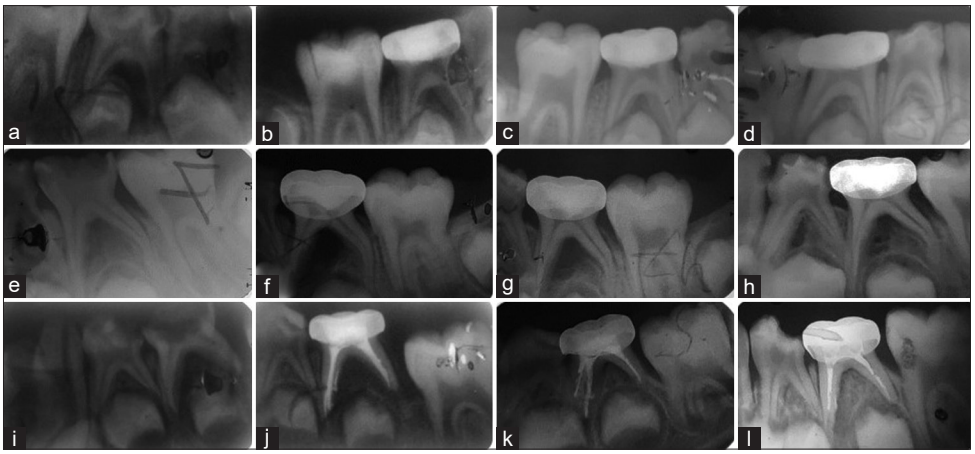

Figure 3: (a) Group I (3Mixtatin) preoperative radiograph, (b) Postoperative radiograph, (c) Radiograph at 6-month interval, (d) Radiograph at 12-month interval, (e) Group II (Modified 3Mix-MP paste) Preoperative Radiograph, (f) Postoperative Radiograph, (g) Radiograph at 6-month interval, (h) Radiograph at 12-month interval, (i) Group III (calcium hydroxide iodoform paste) preoperative radiograph, (j) Postoperative radiograph, (k) Radiograph at 6-month interval, (l) Radiograph at 12-month interval.

Table 2: Depicts various tooth type distributed among the groups of the sample

Tooth type	Arch type	Group I (3Mixtatin), *n* (%)	Group II (Modified 3Mix-MP paste), *n* (%)	Group III (Metapex), *n* (%)	Total, *n* (%)
Primary first molar	Maxillary arch	3 (13.6)	5 (21.7)	7 (33.3)	15 (22.7)
	Mandibular arch	5 (22.7)	8 (34.7)	6 (28.5)	19 (28.7)
Primary second molar	Maxillary arch	5 (22.7)	2 (8.6)	0	7 (10.6)
	Mandibular arch	9 (40.9)	8 (34.7)	8 (38.0)	25 (37.8)
Total, *n* (%)		22 (100)	23 (100)	21 (100)	66 (100)

MP: Macrogol and propylene glycol

Table 3: Frequency (%) of clinical signs and symptoms in the study and control groups

	6 months, *n* (%)	12 months, *n* (%)	*P*
Group I (*n*=22)			
Success	22 (100.0)	20 (90.9)	0.284
Failure	0	2 (9.1)	
Group II (*n*=23)			
Success	19 (82.6)	17 (73.9)	0.085
Failure	4 (17.4)	6 (26.1)	
Group III (*n*=21)			
Success	16 (76.2)	11 (52.4)	0.005*
Failure	5 (23.8)	10 (47.6)	

*Significant. Statistical analysis: Chi-square test. $P \leq 0.05$ is called statistically significant

resorption manifesting in Group III, its comparison to Group I and Group II showed statistically significant differences during intergroup analysis. These are shown in Table 4 and Figure 5.

DISCUSSION

Signs and symptoms exhibited by a tooth reflect its status of vitality. Understanding of the mechanism that protects, controls, and regulates resorptive process may help in maintaining a primary tooth as long as it is necessary. Thus, the rationale of this study was to preserve the primary teeth with pathological interradicular or periapical root resorption by targeting the undifferentiated mesenchymal cells leading to osteoblast differentiation and activation. Moreover, application of antibiotics topically to eliminate bacterial contamination and reduce inflammation is warranted as it serves as the main cause of treatment failure in primary teeth. LSTR is a technique which facilitates not only disinfection of the canal but also serves as an equivalent to conventional pulp therapy.

In addition, in Group I, the combination used, i.e., 3Mixtatin, incorporates Simvastatin, an antihyperlipidemic drug, into the triple antibiotic paste, Simvastatin was used as an anti-inflammatory and bioinductive agent, whereas 3Mix served as an antibacterial agent. The bioinductive effects of simvastatin result in inhibition of bone resorption and promotion of osteoblast proliferation and differentiation.[24] Concurrently, BMP acts as an inducer for osteoblastic differentiation from a

Table 4: *P* value of radiographical signs and symptoms in the study and control groups (inter-group comparisons)

Groups	Follow-ups	
	6 months (*P*)	12 months (*P*)
Group 1 versus Group 2	0.011*	0.020*
Group 1 versus Group 3	0.002*	0.001*
Group 2 versus Group 3	0.398	0.238

*Significant. Statistical analysis: Mann-Whitney U-test. $P \leq 0.05$ is called statistically significant

population of undifferentiated cells. Many studies support the fact that statin drugs stimulate a high level of BMP-2 expression in osteoblasts, this, in turn, induces the transformation of mesenchymal stem cells into osteoblasts, which result in increased bone formation.[25] Moreover, statins stimulate angiogenesis which contributes to wound healing process.[26]

Although on reviewing literature, a number of studies have made comparison among various triple antibiotic combinations using the LSTR technique. However, only one studies by Aminabadi *et al*. uses 3Mixtatin to treat interradicular or periapical root resorption and/or perforation in primary molars and it reported a high clinical and radiological success rate of 96.9% at the end of 12 months.[15] Comparing these results to our study, our group of 3Mixtatin showed a lesser success rate both at 6- and 12-month intervals. This variance in results may be attributed to difference in the combination and dosage of drugs used.

While comparing Modified 3Mix-MP paste (Group II) to studies in the literature, our study showed a clinical success of 82.6% and 73.9% at 6- and 12-month intervals, while the radiographic success was 74% and 61%, respectively. A study by Raslan *et al*.[27] (80.96%) showed a similar clinical success rate, while studies by Prabhakar *et al*.[28] (97.7%), Doneria *et al*.[21] (95.5%), and Pinky *et al*.[29] (90%) showed a higher success rate. On radiographic evaluation, our study showed comparable results with the studies done by Nakornchai *et al*.[20] (76%) and Lokade *et al*.[30] (76.2%) at similar intervals, while it was lower as compared to Pinky *et al*.[29] (90.0%), Raslan *et al*.,[27] (94.44%) and Prabhakar *et al*.[28] (83.3%).

In our study, Group III seemed to be underperforming, as the clinical success when compared to studies by Nurko and Garcia-Godoy[31] (100%), Mortazavi and Mesbahi[32] (100%), and Ozalp *et al*.[33] (100%) was lower at 12-month interval. In additional, when evaluated radiographically, the success rate of

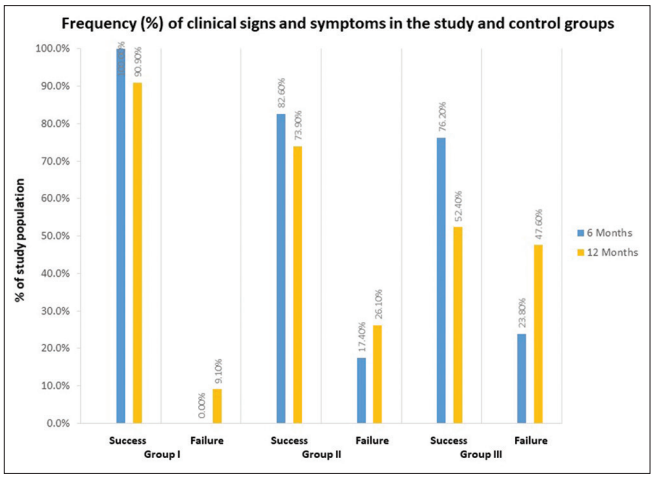

Figure 4: Depicts clinical success and failure among three groups at 6- and 12-month intervals.

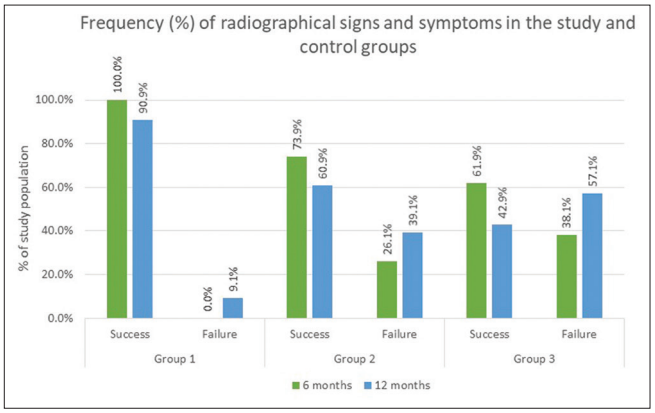

Figure 5: Depicts radiological success and failure among three groups at 6- and 12-month intervals.

Group III had greatly reduced from 61.9% at 6-month interval to 42.9% at 12-month interval which is lowest in the available literature. This marked decrease in reported success rate was thought to be attributed due to the use of calcium hydroxide in primary molars that had undergone severe inflammatory process. While the use of calcium hydroxide is indicated in primary teeth with inflamed pulp tissue, response to calcium hydroxide to this inflammation can be two faced. In our study, it was seen that use of calcium hydroxide in molars with poor prognosis potentiated the inflammatory response and resulted in increased root resorption and signs of inflammation and hence decreased success rate clinically and more so radiographically. Internal resorption and increase in interradicular radiolucency were found to be the common cause of failure among all the groups when evaluated radiographically. These above findings have been a common cause of failure in various published literature as well.[21,22,28,33] Identical to other studies,

pain, mobility, and sinus formation were some other clinical causes of failure among the primary molars.

The findings of our investigation have led to a paradigm shift in the pupal treatment of primary teeth as 3Mixtatin had significantly proven more successful when compared to Modified 3 mix-MP paste and conventional root canal therapy. However, such conclusive inference should be weighed against limitations such as small sample size and great number of lost follow-up. Further studies are warranted to develop substantial evidence for use of 3Mixtatin in a more generalized practice.

CONCLUSION

Within the limits of present *in vivo* study, we concluded the following:

- 3Mixtatin paste can be considered effective and superior pulp therapy agent using LSTR technique when compared to calcium hydroxide paste in primary teeth
- On the basis of the overall success rates at 12-month follow-up of all the three medicaments, the following order of performance can be inferred:
  - Clinical performance: 3MIXTATIN > MODIFIED 3MIX-MP PASTE > CALCIUM HYDROXIDE AND IODOFORM PASTE
  - Radiographic performance: 3MIXTATIN > MODIFIED 3MIX-MP PASTE >> CALCIUM HYDROXIDE AND IODOFORM PASTE.

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Nil.

Conflicts of interest

The authors of this manuscript declare that they have no conflicts of interest, real or perceived, financial or non-financial in this article.

Clinical significance

- Statins are class of drugs with proven bone regenerating potentials and a viable treatment options in retaining primary molars with poor prognosis until physiologic exfoliation
- Calcium hydroxide and iodoform paste may result in exaggerated inflammatory response when used in primary molars undergoing severe inflammatory process.

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