RESEARCH ARTICLE

Comparison of Modified Triple Antibiotic Paste in Two Concentrations for Lesion Sterilization and Tissue Repair in Primary Molars: An *In Vivo* Interventional Randomized Clinical Trial

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Abstract

Introduction: "Lesion sterilization and tissue repair" (LSTR) is a non-instrumentation endodontic treatment modality that has recently gained popularity with promising results in several clinical trials. However, there is a dearth of evidence regarding the concentration of modified triple antibiotic paste (MTAP) to be used for the procedure.

Aim and objective: To compare the clinical and radiographic efficacy of 1 mg/mL and 1 g/mL concentrations of MTAP (ciprofloxacin, metronidazole, and clindamycin) used in LSTR of primary molars.

Materials and methods: Sixty-four infected primary molars in children between 4 years and 10 years of age were randomly allocated to two groups. Lesion sterilization and tissue repair at 1 mg/mL concentration of MTAP (group I) and 1 g/mL concentration of MTAP (group II) was performed. Clinical and radiographic outcomes were evaluated using Coll and Sadrian's criteria at 10 days, 1 month, and 3 months and the results were tabulated.

Statistical analysis: The data obtained were subjected to statistical analysis with IBM.SPSS statistics software 23.0 Version. To test the significance in categorical data, a Chi-square test was used. The probability value of 0.05 was considered significant.

Results: At the end of 3 months review, clinical success rates of group I and group II were 84.4 and 90.6%, respectively, and radiographic evaluation showed group I–78.1% and group II–90.6%.

Conclusion: Both 1 mg/mL and 1 g/mL concentrations of MTAP used in LSTR of primary molars had similar success rates with no statistically significant difference.

Clinical significance: Lesion sterilization and tissue repair when found to be equally effective in less concentration may aid in achieving adequate infection control with the least detrimental effect on the remaining vital pulp and periradicular structures. In addition, this circumvents the systemic administration of potent antibiotics thus combating antibiotic resistance.

Keywords: Antibiotic resistance, Ciprofloxacin, Clindamycin, Concentration, Irreversible pulpitis, Lesion sterilization and tissue repair, Metronidazole, Primary teeth, Randomized clinical trial.

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Introduction

In developing countries like India, the first dental visit is more for curative purposes than preventive. In such a scenario, it is not unusual to encounter a young child with huge swellings presenting for treatment. In addition, pulpal infection in primary teeth occurs faster when compared with permanent teeth owing to the morphological and structural differences between both. Several studies have reported that the enamel layer of deciduous teeth is thinner when compared with its permanent counterpart.[1] Thus, pulpal involvement of caries in primary teeth is meteoric.

The conventional treatment options for such cases will be multi-visit pulpectomy with stainless steel crown (SSC) or extraction followed by a space maintainer. However, pediatric dentists are more inclined to pulpectomy than extractions considering the many benefits of preserving deciduous teeth until their normal time of exfoliation.[2] But several factors make conventional pulpectomy arduous. To begin with, the time taken to effectively complete the procedure could challenge the cooperative ability of a child. Second, pulpectomy of abscessed teeth often requires multiple visits which have to be supported with systemic antibiotics. This again is a topic of debate in the era of escalating antibiotic resistance. Thus to overcome these hurdles,

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the concept of lesion sterilization and tissue repair (LSTR) which involves the topical placement of triple antibiotic pastes (TAPs) evolved which aims to disinfect the canal space thus promoting repair of damaged tissue.[3]

The two ratios in the practice of this drug combination are 1:1:1[4] and 1:3:3.[3] However, there is no definite recommendation on the dilution of TAP. Recent studies by Prather BT et al. have proved that TAPs at greater concentrations were found to be harmful to the stem cells of the apical papilla (SCAP).[5] This instigated further studies to identify the ideal concentration of TAP which acts sufficiently on the pathogenic microflora and is simultaneously gentle on the pulpal and periapical tissues. Results of these studies have concluded that antibiotic combinations even at the concentration of 0.1 mg/mL were effective against predominant endodontic pathogens.

Therefore, the present study aims to compare the clinical and radiographic efficacy of 1 g/mL and 1 mg/mL concentrations of modified triple antibiotic paste (MTAP) (ciprofloxacin, metronidazole, and clindamycin) for LSTR.

Materials and Methods

This study was conducted among the outpatients of the Department of Pediatric and Preventive Dentistry. Ethical clearance was obtained from the Institutional Review Board (SRM IRB NO: SRMDC/IRB/2017/MDS/No.802) and was prospectively registered under the Clinical trials registry (CTRI/2018/08/015435).

Children reporting to the department with deep caries in primary molars were assessed for eligibility and those fulfilling the inclusion and exclusion criteria were included in the study with a 1:1 allocation ratio and parallel study design.

Sample Size Estimation

The sample size was estimated to be 64 (group I: 32 and group II: 32).

The calculation was based on proportion for two groups and the values were adopted from similar trials reported in the literature and the calculation was done using (nMaster software Version 2.0) with α set to 5% and $\beta = 90$.

Inclusion Criteria

- Age group between 4 years and 10 years.
- Children with deep caries involving pulp in primary molars.
- Irreversible pulpitis with periapical or furcal lesions.
- Primary molars with at least two-thirds of the roots.

Exclusion Criteria

- Special children with a physical or emotional alteration.
- Children with systemic diseases.
- Previous history of allergy to antibiotics used in the study.
- Caries in primary teeth exhibiting pre-shedding mobility.

Preparation of the Medicament[3]

For the preparation of the material, 1 g of each antibiotic powders (USP-graded ciprofloxacin, metronidazole, and clindamycin) mixed at the ratio of 1:1:1 yielding 3 g of stock compounded antibiotic powder (3Mix) which was stored in an airtight container for not more than a week.[6] A high-precision scientific balance was used for all the measurements and the materials were handled in aseptic condition throughout the procedure.

From this compounded powder, 1 g was mixed with 1 mL of propylene glycol to prepare 1 g/mL concentration. Similarly, 1 mg/mL solution was prepared by dissolving 1 mg of the compounded powder in 1 mL of propylene glycol as mentioned above. To this concentration corrected 3Mix-propylene glycol mixture, macrogol powder was added till the mixture achieved a workable consistency. This 3Mix-propylene glycol and macrogol (3MixMP) mixture was freshly prepared just before commencing the clinical procedure. Any excess material from this mixture was discarded.

The samples were included based on the criteria mentioned and randomly allocated into two groups by a staff member who was not related to the study. Block randomization was practiced to uniformly allot the samples to both groups. The principal investigator enrolled the participants and assigned them to interventions according to the randomization. All the procedures were performed by the principal investigator and the follow-up visits were evaluated by another blinded investigator.

Procedure

The procedure with all possible consequences was explained to the parent/guardian and written consent was taken. Appropriate behavior management techniques were used and topical anesthesia at the injection site was achieved through the application of 2% lignocaine gel for 2 minutes. Local anesthesia as appropriate (infiltrations for maxillary molars and inferior alveolar nerve block for mandibular molars) was induced using 2% lignocaine at 1:80,000 adrenaline. After ensuring adequate anesthesia, caries was excavated following isolation, and an access opening was done using a sterile No. 4 round bur with a high-speed handpiece. The pulp chamber was deroofed with a safe-ended access bur. The access cavity was enlarged as prescribed by Takushige et al. in 2004[3] to create a medication cavity. Coronal pulp was amputated with a spoon excavator and copious saline irrigation was done. The pulp stumps were treated with a 3% sodium hypochlorite soaked cotton pellet for 1 minute to control hemorrhage. One-third of the cavity was then filled with the triple antibiotic paste (3MixMP) of the given concentration and then a coronal seal with glass ionomer cement was done.

On the 10th-day follow-up visit, after confirming the resolution of the clinical symptoms, crown preparation was done and SSC was luted. All the recruited samples were followed up and assessed at 1 and 3 months intervals for clinical and radiographic evaluation.

The follow-up evaluation was done by an investigator who was blinded to the intervention performed. The assessment was based on Coll and Sadrian's recommendation.[7]

The results thus obtained were tabulated and statistically analyzed. Descriptive data on age and gender were projected in frequency tables and a Chi-square test was employed to analyze inter- and intragroup comparisons.

Results

Sixty-four samples were recruited and randomly allocated into two groups with a ratio of 1:1. The study was conducted from September 2018 to May 2019 and was successfully completed with 10 days, 1 month, and 3 months of follow-up with an attrition rate of 10%.

Participants of the study are children aged 4–10 years with a mean age of 6.11 $\pm$ 1.5 of which 23 were girls (48.9%) and 24 were boys (51.0%). Sixty-four carious primary molars from 47 children were thus recruited.

Six samples recruited withdrew from the study due to various personal reasons with no exclusions by the investigator. The trial was not ended or stopped early.

The samples were assessed for clinical and radiographic success; the results were tabulated and subjected to statistical analysis (SPSS version 23.0).

Table 1 depicts the clinical success of 1 mg/mL and 1 g/mL concentration of MTAP in LSTR. All samples showed 100% success in both 10-day and 1-month follow-up. At 3-month follow-up, 1 mg/mL concentration had success of 84.4% and 1 g/mL concentration had 90.6% which had no statistical significance ($p < 0.05$).

Table 2 demonstrates the radiographic success of 1 mg/mL and 1 g/mL concentration of MTAP in LSTR. Similar to clinical evaluation, radiographic success at 10-day and 1-month follow-up was 100% for both groups. At 3 months, 1 mg/mL concentration had success of 78.1% and 1 g/mL concentration had 90.6% which again had no statistical significance ($p < 0.05$).

Table 3 gives the comparison between clinical and radiographic efficacy of both the concentrations at a 3-month follow-up which was statistically significant. That is samples with radiographic failure did not always present with clinical failure and this observation was statistically significant.

Discussion

Successful pulp therapy in primary teeth depends mainly on the reduction and elimination of root canal infection. Necrotic primary teeth, especially of long-standing nature and symptomatic with periapical bone destruction tend to harbor a high bacterial load and more complex anaerobic bacterial flora.[6] Hence, intracanal medicaments which neutralize the virulence of pathogenic microorganisms can induce a host response that favors periapical tissue healing.[8]

The earliest use of antibiotics as intracanal medicament dates back to 1951 where Grossman used the polyantibiotic paste[9] which was followed by other broad-spectrum antibiotics as a single agent or in combination with other agents to overcome the polymicrobial endodontic infections. The most recent addition to this list of intracanal medicaments is the introduction of TAP by Sato et al. in 1992[10] consisting of ciprofloxacin, metronidazole, and minocycline.

The efficacy of MTAP has been confirmed by *in vitro* studies conducted by several authors such as Sato et al.[10] and Alam et al.[11]

However, clinically the addition of minocycline is found to be associated with certain complications like discoloration of the tooth structure, antiangiogenic activity, and chelation of radicular dentin leading to demineralization and weakening of root structure.[12]

A recent *in vitro* study by Karczewski et al.[13] assessed the antimicrobial efficacy, dentin discoloration, and cytotoxicity of Clindamycin MTAP and concluded that clindamycin could serve as a viable replacement to minocycline in TAP.

Thus, in the present study, a combination of ciprofloxacin, metronidazole, and clindamycin was adopted. The drug combination was chosen based on their spectrum of action against endodontic pathogens.

The concentrations compared in the current study were derived from previous literatures where most studies postulated a paste-like consistency of MTAP which would be equivalent to a concentration as high as 1 g/mL. However, a higher concentration of MTAP was

Table 1: Clinical follow-up comparing 1 mg/mL and 1 g/mL concentration

	Clinical follow-up					
	10 days		*1 month*		*3 months*	
Groups	*Success*	*Failure*	*Success*	*Failure*	*Success*	*Failure*
Group I—1 mg/mL	32 (100%)	0	32 (100%)	0	27 (84.4%)	1 (3.1%)
Group II—1 g/mL	32	0	32	0	29 (90.6%)	1 (3.1%)
Total	64	0	64	0	56	2

p value 0.962

Table 2: Radiographic follow-up comparing 1 mg/mL and 1 g/mL concentration

	Radiographic follow-up					
	10 days		*1 month*		*3 months*	
Groups	*Success*	*Failure*	*Success*	*Failure*	*Success*	*Failure*
Group I—1 mg/mL	32 (100%)	0	32	0	25 (78.1%)	3 (9.4%)
Group II—1 g/mL	32	0	32	0	29 (90.6%)	1 (3.1%)
Total	64	0	64	0	54	4

p value–0.921)

Table 3: Comparison between clinical and radiographic efficacy at a 3-month follow-up

3-month follow-up							
Group I (1 mg/mL)				*Group II (1 g/mL)*			
Clinical		*Radiographic*		*Clinical*		*Radiographic*	
Success	*Failure*	*Success*	*Failure*	*Success*	*Failure*	*Success*	*Failure*
27 (84.4%)	1 (3.1%)	25 (78.1%)	3 (9.4%)	29 (90.6%)	1 (3.1%)	29 (90.6)	1 (3.1%)
		$\chi^2 = 41.87$				$\chi^2 = 61.00$	
		$p < 0.001$*				$p = 0.00$*	

*Statistically significant

found to have detrimental effects on the periradicular tissues and also reduces the microhardness of the root dentin. An *in vitro* study by Prather et al. in 2014[5] suggested that antibiotic paste at a concentration as less as 1 mg/mL had sufficient antimicrobial action at the same time, had no detrimental effects on the microhardness of the root structure.

Another study by Algarni et al. in 2015[14] has shown that 1 mg/mL concentration of TAP loaded onto methyl cellulose-based material had a significant antibiofilm effect against the most resistant endodontic pathogen—*E. faecalis*.

Thus, the present trial compared the conventional 1 g/mL with the recently proposed 1 mg/mL concentration.

The results of this study had no failures reported in the 10 days review which suggests that both concentrations of the drug were equally effective in minimizing the bacterial load thereby improving its clinical status. Similar results were observed at 1-month follow-up.

Six of the recruited 64 samples were not available for a 3-month follow-up. Thus, four samples were lost in group I, and two samples were lost in group II. Of the reported 28 samples in group I (1 mg/mL), one sample reported swelling in relation to the treated tooth and was counted as a clinical failure. Extraction of the symptomatic tooth was done due to accelerated root resorption. A space maintainer was provided following extraction. Two other samples from the same group reported exaggerated root resorption but were not associated with pain or swelling. Hence, no intervention was done and the children were instructed to report for timely follow-up or immediately in the event of pain/swelling. Thus, three samples from group I including the clinical failure case were counted to be radiographic failures. This failure could be attributed to less concentration of the available drug in 1 mg/mL concentration of 3MixMP for sustained release.

Of the 30 cases reported to a 3-month follow-up in group II (1 g/mL), one patient reported pain and pathological root resorption. This case was counted as clinical and radiographic failure and extraction followed by space maintenance was done.

On comparing the clinical results with a radiographic observation of each group, a statistically significant result was obtained (Table 3). That is, clinical performance was statistically better in both groups when compared with the radiographic assessment, proving that the samples with radiographic failure did not always present with clinical failure and this observation was statistically significant.

The results of this study was in correspondence with the results obtained by Takushige et al.,[3] Prabhakar et al.,[15] Nakornchai et al.,[16] Pinky et al.,[17] Jaya et al.,[18] Duanduan et al.,[19] Nanda et al.,[20] Dasari et al.,[21] Shojaee and Motamedifar,[22] and Ali et al.[23] in treating infected primary molars following non-instrumentation endodontics employing a combination of antibiotics reported satisfactory results and suggested LSTR be a viable cost and time-efficient alternative to conventional pulp therapy.

However, few authors have contradicted this suggestion. Trairatvorakul and Detsomboonrat[24] conducted a 27-month follow-up study on LSTR with ciprofloxacin, metronidazole, and minocycline combination and have stated that though the treatment showed good clinical success, radiographic success is less when compared with conventional pulp therapy. Similarly, Daher et al.[25] in their 2-year follow-up study on LSTR with chloramphenicol, tetracycline, and zinc oxide eugenol paste (CTZ paste) stated lower survival rate and radiographic success.

Doneria et al.[26] compared the clinical and radiographic success of zinc oxide-ozonated oil, vitapex, and 3MixMP and concluded that treatment with 3MixMP was not as successful as the former obturation materials.

Similar to the above mentioned, the present study also had compromised radiographic success when compared with the clinical performance.

Apart from the questionable radiographic success, LSTR in both higher and lower concentrations shows promising results in prolonging the survival span of infected primary molars where conventional pulpectomy would be questionable. In addition, LSTR circumvents the need for extensive canal instrumentation which further weakens the dentinal walls. Also, local administration of the antibiotics for disinfection can override the use of systemic antibiotics.

Conclusion

The results of the present study prove that there is no much difference between the higher and lower concentrations of 3MixMP and can be efficiently used in LSTR of primary molars. However, further studies with longer follow-up with less concentration of 3MixMP would be more conclusive on the actual efficacy of the medicament. Beyond the concentration, the LSTR procedure on children was found to be less time-consuming and the non-instrumentation concept greatly reduced the risk of aspiration or breakage of the instrument. In addition, the risk of pushing debris apically or damaging the permanent tooth bud due to over instrumentation can be avoided. Standardizing this treatment modality would be of great aid in reducing the chairside treatment time of younger children with lacking cooperative ability.

Clinical Significance

Though the long-term efficacy of this treatment modality is yet to be explored, LSTR even at a lower concentration of MTAP effectively reduces clinical symptoms and also helps control the infection without systemic administration of potent antibiotics thus giving scope to lessen the impact of antibiotic resistance.

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