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Clinical evaluation of Ideal Concentration of a Modified Triple Antibiotic Paste for Non-Instrumental Endodontic Treatment (NIET) in primary molars

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Abstract:
Aims: To assess the clinical and radiographic effectiveness of NIET utilizing 0.5 mg/ml, 2.5 mg/ml and 5 mg/ml concentrations of modified triple antibiotic paste (mTAP) consisting of amoxicillin, metronidazole and ciprofloxacin, in necrotic primary molars
Settings and Design: 96 non-vital primary molars in children aged 5 to 9 years were randomly allocated into three groups of different concentrations of mTAP (Group I: 0.5 mg/ml, Group II: 2.5 mg/ml and Group III: 5 mg/ml), based on MIC value of combination of antibiotics against *E. faecalis.*
Methods and Material: Different concentrations of mTAP were prepared, using raw powders of antibiotics with propylene glycol as vehicle. After NIET, clinical follow-up was done at 1, 3, 6 and 12 months whereas radiographic evaluations were conducted at 6 & 12 months.
Statistical analysis used: Chi-square test and Fisher's exact test was used to find association between categorical variables. A value of $P \leq 0.05$ was taken to be statistically significant.
Results: After 12 months follow-up, 2.5 mg/ml concentration group had highest clinical and radiographic success as compared to the other two concentration groups.

Conclusions: Modified triple antibiotic paste (mTAP) in concentration of 2.5 mg/ml, demonstrated good clinical and radiographic outcomes in NIET of necrotic primary teeth.
Keywords: Amoxicillin, Ciprofloxacin, Metronidazole, Non instrumental endodontic treatment

Introduction: Addressing pulp therapy in primary teeth poses multiple challenges due to factors such as variations in the morphology of primary teeth, complexity of behaviour management, intricate nature of root canals, the need for timely resorption of primary teeth, and challenges associated with the use of root canal filling materials.[1]The aim of a successful pulpectomy is complete elimination of all bacteria within the root canal systems.

Chronic alveolar infections or dentoalveolar abscess are often associated with necrotic primary teeth. Only systemic administration of antibiotics does not control the infection as lack of a blood supply to the pulp space limits the systemic delivery of antibiotics, resulting in a minimal concentration reaching the root canal. This limited concentration is unlikely to yield significant benefits. The use of local antibiotics presents a benefit by averting systemic consequences and complications, allowing for the application of significantly higher concentrations.[2,3]

Intracanal medicaments that counteract the virulence of pathogenic microorganisms have the potential to stimulate a host response conducive to the healing of periapical tissues.[4] In 1988 the cariology research unit at the Nîgata University School of Dentistry developed a concept known as Lesion Sterilization and Tissue Repair (LSTR) (also called NIET or Non-Instrumental Endodontic Treatment).[5] It is "a novel biologic strategy in the treatment of carious lesions with periapical involvement using a combination of 3 antibiotics (3-Mix)". The composition of 3-Mix was metronidazole, ciprofloxacin and minocycline.

The prime issue related to the use of triple antibiotic paste is the discoloration caused by the drug minocycline.[6] To counteract this, alternative medications such as clindamycin, cefaclor, amoxicillin have been tried. Amoxicillin been found to be highly effective against isolates from infected root canal systems that are composed primarily of facultative and obligate anaerobes.

Very few in vivo studies have been done with amoxicillin as part of triple antibiotic paste in primary teeth.[7]

The two ratios in the practice of NIET using triple antibiotic paste (TAP) combination are 1:1:1 (Hoshino *et al.,* 1988) and 1:3:3 (Takushige*et al.* 2004).[8] According to AAE Clinical Considerations for a Regenerative Procedure 2021, TAP should be used in the safest possible concentration (1-5 mg/mL)since higher dosages could have undesired results on the stem cells.[9] However, there is no definite dosage recommendation of TAP for NIET in primary teeth. Thus, there is a need to identify the ideal concentration of TAP which will bring both clinical and radiographic success while doing lesion sterilization and tissue repair in pulpally involved primary molars.

Subjects and Methods: This study was conducted among the patients visiting the OPD of Department of Paediatric and Preventive Dentistry of our institution. Requisite ethical clearance & permission to undertake the study was obtained from the Institutional Ethical committee (IRC no- GNIDSR/IEC/21-24/21). This study was registered in Clinical Trial Registry of India (Reg no: CTRI/2022/05/042944).

Random selection of study samples from children of 5 - 9 years of age with pulpally involved primary molars visiting OPD was done, after obtaining informed consent from parents.

INCLUSION CRITERIA	EXCLUSION CRITERIA
1) Age group between 5-9 years 2) Children with deep caries involving pulp in primary molars 3) Irreversible pulpitis with apical periodontitis 4) Irreversible pulpitis with furcation involvement or periapical lesions 5) Primary molars with at least two-thirds of the roots present 6) Primary molars with restorable crown structure	1) Primary molars with dentigerous cyst 2) Differently abled children with a physical and mental disability 3) Children with systemic diseases 4) Prior episode of allergy to antibiotics administered in the study 5) Caries in primary molars exhibiting pre-shedding mobility (greater than 2º mobility) 6) Carious perforation of floor of primary molars 7) Primary molars with more than 2/3rd root resorbed 8) Primary molars without permanent successor teeth 9) Primary molars with gross destruction of alveolar bone 10) Primary molars with non restorable crown structure

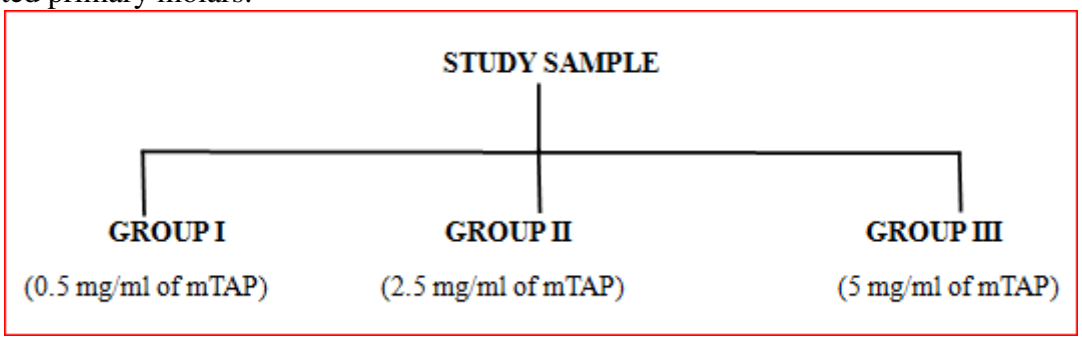
102 children aged 5-9 years were selected as study population based on inclusion and exclusion criteria. The sample size calculation was based on a similar trial previously conducted by Johns *et al.,* (2014) where the absolute difference in the primary outcome was reported to be 0.35 indicating the probability of successful treatment with conventional approach.[10] 96 carious, restorable primary molars having irreversible pulpitis with apical periodontitis, as determined through history, clinical examination and radiographic evaluation were selected as study sample based on selection criteria.

Clinical and Radiographic criteria for case selection: [11]

Clinical criteria: Spontaneous pain, tenderness to percussion, presence of abnormal mobility (mobility other than from normal exfoliation), presence of abscess or fistula.

Radiographic criteria: Coronally presence of deep carious lesion involving pulp, presence of radiolucency in the bifurcation/periapical region.

Distribution of Study sample: The total study sample was randomly divided into 3 groups (Group I, Group II and Group III) in 1:1:1 distribution, based on 3 final concentrations of modified triple antibiotic Paste (mTAP) which were used for performing lesion sterilization and tissue repair (LSTR) (also called NIET or Non-Instrumental Endodontic Treatment) in infected primary molars.



Preparation of Modified Triple Antibiotic Paste: To overcome the problem of staining of teeth caused by minocycline, it was replaced by another broad-spectrum antibiotic

amoxicillin in this study. Based on the study done by Santra A. *et al.* (2023), who evaluated the MIC value of combination of three antibiotics (amoxicillin, ciprofloxacin and metronidazole) against *E.faecalis* (515 µg/ml) {Amoxicillin 10 µg + Metronidazole 500 µg + Ciprofloxacin 5 µg}, the three final concentrations of modified triple antibiotic paste were prepared. The first concentration of modified triple antibiotic paste finalized was 0.5 mg/ml (515 µg/ml). The other two concentrations considered were 5 times and 10 times the previous concentration, i.e. 2.5 mg/ml and 5.0 mg/ml respectively.[12]

Antibacterial drugs ciprofloxacin, metronidazole and amoxicillin in pure salt form, obtained from a chemical laboratory (Gluconate Health Ltd. New Delhi, India) were used in the study. Firstly, the stock solution of each antibiotic was prepared in distilled water/ethanol based on working concentration. Then, using propylene glycol as solvent, final working solution was prepared. To make the triple antibiotic paste in workable consistency, additives in the form of polymers were added to the prepared working solution to achieve a workable paste like consistency. The additives added were: Polyvinyl Pyrrolidone K-30 (PVP K-30), Hydroxy Propyl Methyl Cellulose (HPMC) and D-Lactose. The paste was transferred to a labelled container with date and concentration mentioned on the label [Figure 1]

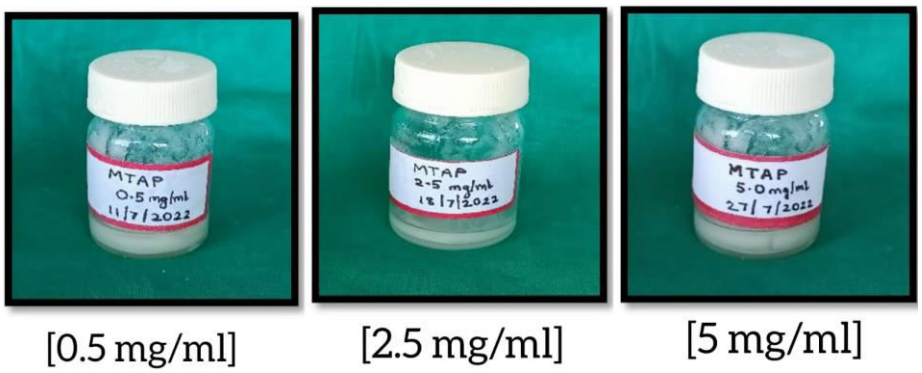


Figure 1: Freshly prepared 3 different concentrations of modified triple antibiotic paste (mTAP) [0.5 mg/ml, 2.5 mg/ml, 5 mg/ml]

Non-Instrumental Endodontic Treatment (NIET) procedure: [Figure 2]

- Freshly prepared modified triple antibiotic paste (within 24 hours)was used in the clinical procedure performed
- Local anaesthesia as appropriate (infiltrations for maxillary molars and inferior alveolar nerve block for mandibular molars) was induced using 2% lignocaine with 1:80000 adrenaline (Lignox, Warren Pharmaceuticals), whenever required
- Isolation was achieved with the help of rubber dam & sterile disposable plastic saliva ejector attached with high volume suction device. [Figure 2(a), Figure 2(b)]
- Removal of caries was done using sharp spoon excavator. Access cavity was prepared with round bur (No.4). Coronal pulp was amputated with a sharp spoon excavator and copious saline irrigation (0.9% w/v) was done. A cotton pellet soaked with 3% sodium hypochlorite was compressed over the pulp stumps for 1 minute to control hemorrhage.The orifices of the root canals were enlarged to form a medication cavity (1mm diameter& 2mm depth approximately) as a receptacle for the medicament. [Figure 2(c)]
- One-third of the cavity was then filled with either of the 3 different concentrations (0.5 mg/ml, 2.5 mg/ml and 5 mg/ml) of the modified triple antibiotic paste (mTAP) and then a coronal seal with glass ionomer cement was done. [Figure 2(d), Figure 2(e)]

- Semi-permanent restoration was done by cementing stainless steel crown (3M) on the second appointment after 15 days (2 weeks) on the treated teeth. [Figure 2(f)]
- Clinical outcome evaluation of individual study samples was performed at 1, 3, 6 and 12 months interval. Radiographic evaluation was done at 6 and 12 months interval.

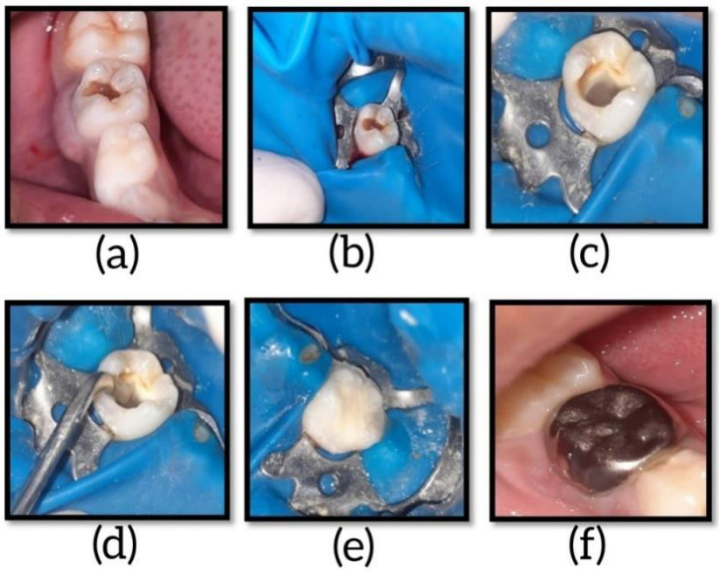


Figure 2: (a) Case selection, (b) Application of rubber dam, (c) Access opening and pulp extirpation, (d) placement of mTAP in access cavity, (e) GIC filling of access cavity, (f) Restoration of teeth with stainless steel crown

Clinical evaluation and the radiographs were taken by the same observer pre and post operatively at subsequent appointments to minimize error. While taking radiographs, the kilovoltage and milliamperage settings were kept exactly the same for each study sample throughout the study. The radiograph was taken using long cone paralleling technique using a RVG sensor positioner for each study sample to minimize any magnification and distortion error.

The statistical analysis was done using IBM SPSS statistics 27.0 (IBM Corporation, Armonk, NY, USA). Test of proportion (z-test) was used to compare the clinical signs among the groups. Chi-square test and Fisher's exact test was used to find the association between the categorical variables. A value of $P \leq 0.05$ was taken to be statistically significant.

Results: After excluding the patients who did not follow-up at any stage of the study, a total of 84 samples (28 in each group) were included in the data analysis. Clinical evaluation of the cases was done during follow ups at an interval of 1, 3, 6 and 12 months, whereas radiographic evaluation was done at an interval of 6 and 12 months. The treated cases were considered clinically successful if there was absence of spontaneous pain, tenderness to percussion, swelling/abscess and abnormal mobility [Figure 3-5]. Radiographically, success in the cases was considered when radiolucency decreased or remained same [Figure 3-5]. Increase in radiolucency at subsequent visits was considered a radiographic failure.

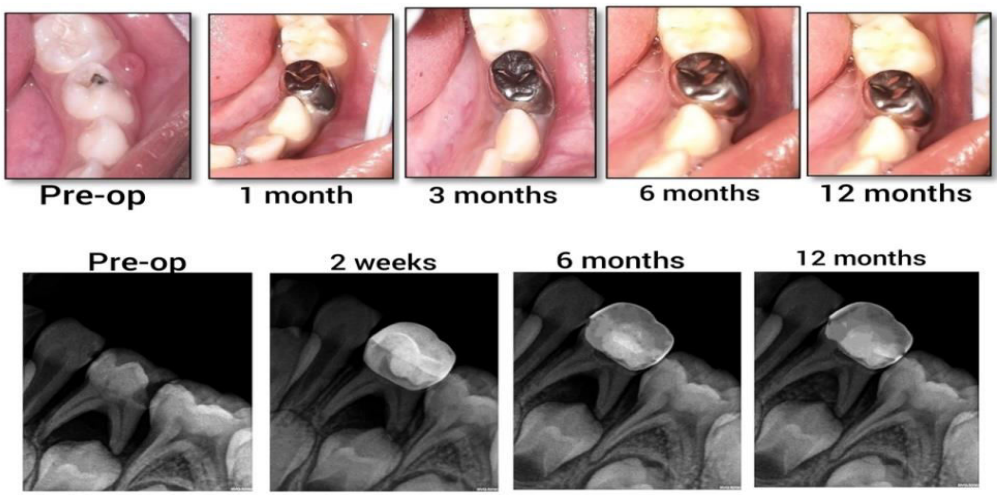


Figure 3: Clinical and Radiographic success of a study sample of Group I (0.5 mg/ml)

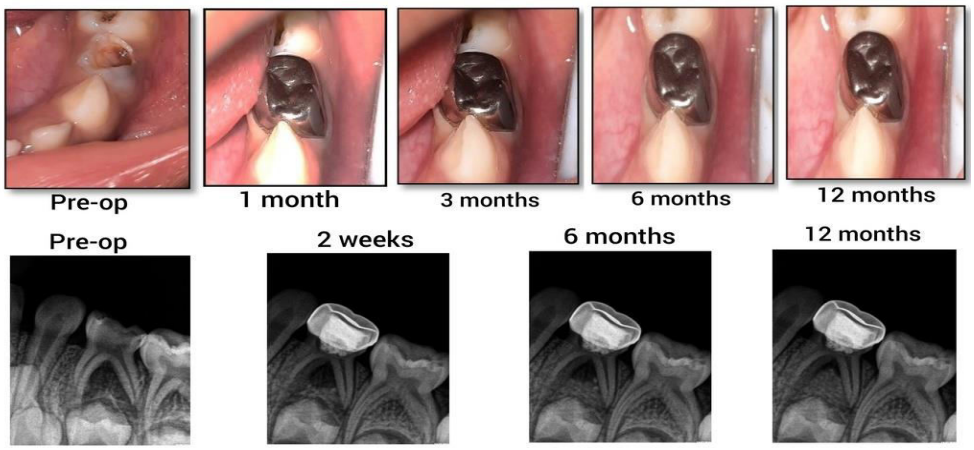


Figure 4: Clinical and Radiographic success of a study sample of Group II (2.5 mg/ml)

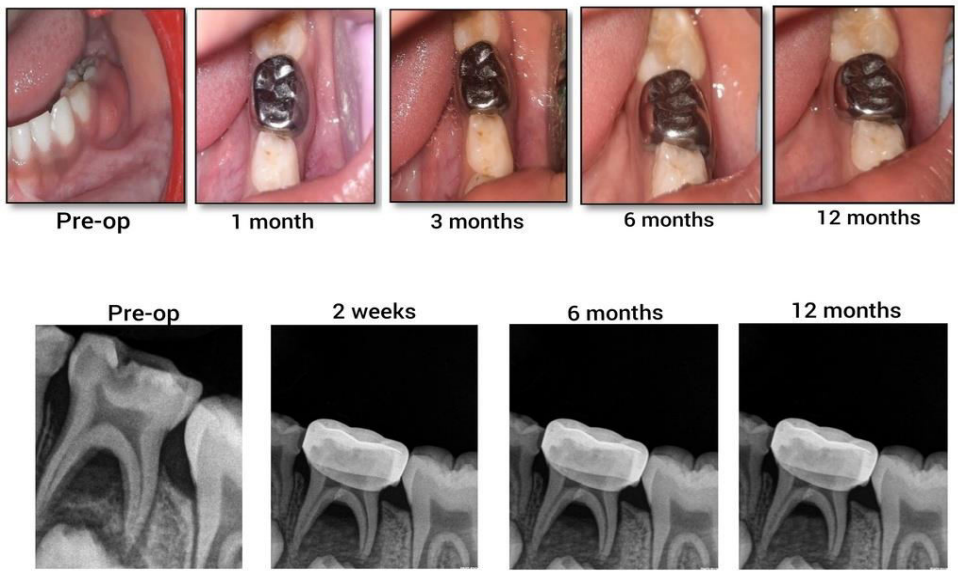


Figure 5: Clinical and Radiographic success of a study sample of Group III (5 mg/ml)

Post operative clinical evaluation: Clinical evaluation showed that group II (2.5 mg/ml) had no cases of T.O.P and abnormal mobility & only 2 cases of pain and abscess, after 12 months follow-up period as seen in [Table 1]. Group I (0.5 mg/ml) and group III (5 mg/ml) had few cases with clinical signs and symptoms after 12 months follow-up period. From [Table 1], it

can be concluded that group II (2.5 mg/ml) had higher efficacy as compared to the other two groups in overall resolution of clinical signs and symptoms.

1 month post operative clinical evaluation showed higher clinical success rate of group I (0.5 mg/ml) as compared to group II (2.5 mg/ml) and group III (5 mg/ml). Whereas, group II (2.5 mg/ml) had highest clinical success rate as compared to the other two groups after 3, 6 and 12 months follow-up periods. [Table 2] and [Graph 1] depicts the clinical success of 3 groups after different follow-up periods.

Post operative radiological evaluation: Radiographic evaluation showed that at 6-months follow-up, bone regeneration was the highest in group II (32.1%), static bone was the highest in group I (82.2.2%), increased bone loss was the lowest among group II (10.7%) [Table 3]. At 12-months follow-up bone regeneration was the highest in group II (42.9%), static bone was the highest in group III (64.2%), increased bone loss was the lowest among group II (7.1%) as seen in [Table 3]. Fisher's exact test showed positive association, however was not statistically significant.

Success rate of group II (2.5 mg/ml) was higher than that of group I (0.5 mg/ml) and Group III (5 mg/ml) but not statistically significant. According to the [Table 4] and [Graph 2], the group II (2.5 mg/ml) showed the highest success rate among the 3 groups over the different follow-up periods.

On comparison between clinical and radiographic efficacy of the three concentrations at 6 and 12-months follow-up period, it can be concluded that samples with radiographic failure did not always present with clinical failure and this observation was statistically significant.

	Pain			**TOP**			**Swelling/Abscess**			**Abnormal Mobility**		
	Gr-I (n=28)	Gr-II (n=28)	Gr-III (n=28)	Gr-I (n=28)	Gr-II (n=28)	Gr-III (n=28)	Gr-I (n=28)	Gr-II (n=28)	Gr-III (n=28)	Gr-I (n=28)	Gr-II (n=28)	Gr-III (n=28)
Pre-op	19 (67.8%)	19 (67.8%)	22 (78.6%)	15 (53.6%)	17 (60%)	15 (53.6%)	24 (85.7%)	22 (78.6%)	24 (85.7%)	6 (21.4%)	15 (53.6%)	17 (60.7%)
1 month	7 (25%)	4 (14.3%)	9 (32.1%)	4 (14.3%)	4 (14.3%)	4 (14.3%)	4 (14.3%)	15 (53.6%)	4 (14.3%)	4 (14.3%)	4 (14.3%)	4 (14.3%)
3 months	4 (14.3%)	0	0	0	0	0	2 (7.1%)	2 (7.1%)	4 (14.3%)	2 (7.1%)	0	2 (7.1%)
6 months	4 (14.3%)	2 (7.1%)	2 (7.1%)	4 (14.3%)	2 (7.1%)	4 (14.3%)	7 (25%)	2 (7.1%)	4 (14.3%)	6 (21.4%)	0	4 (14.3%)
12 months	4 (14.3%)	2 (7.1%)	2 (7.1%)	2 (7.1%)	0	2 (7.1%)	6 (21.4%)	2 (7.1%)	6 (21.4%)	6 (21.4%)	0	4 (14.3%)

Table 1:Evaluation of clinical symptoms for Group I (0.5 mg/ml), Group II (2.5 mg/ml), and Group III (5 mg/ml) at various time periods

	Clinical Follow-up							
	1 month		3 months		6 months		12 months	
	Failure	Success	Failure	Success	Failure	Success	Failure	Success
Group I	13 (46.4%)	15 (53.6%)	4 (14.3%)	24 (85.7%)	15 (53.6%)	13 (46.4%)	11 (39.2%)	17(60.7%)
Group II	15 (53.6%)	13 (46.4%)	2 (7.1%)	26 (92.8%)	4 (14.3%)	24 (85.7%)	2 (7.1%)	26 (92.9%)
Group III	15 (53.6%)	13 (46.4%)	4 (14.3%)	24 (85.7%)	6 (21.4%)	22 (78.6%)	7 (25%)	21 (75%)

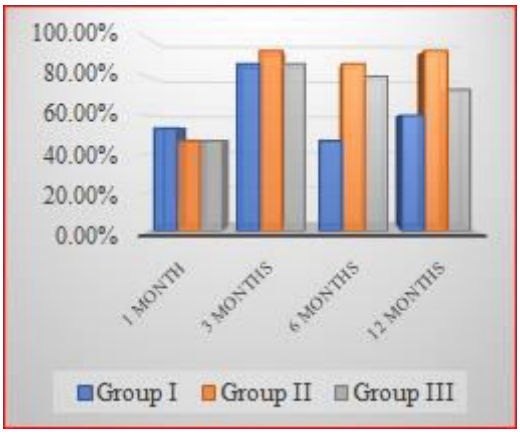
Table 2: Comparison of clinical evaluation (success & failure rate) among three groups (Group I- 0.5 mg/ml, Group II-2.5 mg/ml, Group III-5 mg/ml) at different time periods

		Group I (n=28)	**Group II (n=28)**	**Group III (n=28)**	**p-value**
Pre op	**Radiographic features**	28 (100%)	28 (100%)	28 (100%)	
After 6 months	Regeneration	0	7 (32.1%)	7 (25%)	0.087
	Static Bone	23 (82.2%)	18 (64.2%)	17 (60.7%)	
	Increased bone loss	5 (17.8%)	3 (10.7%)	4 (14.3%)	
After 12 months	Regeneration	7 (25%)	12 (42.9%)	7 (32.1%)	0.06
	Static Bone	17 (60.7%)	14 (50%)	18 (64.2%)	
	Increased bone loss	4 (14.3%)	2 (7.1%)	3 (10.7%)	

Table 3: Comparison of different features of periapical radiolucency among the groups over pre operative period, 6-month and 12-month follow-up periods

	Radiographic follow-up			
	6 months		12 months	
	Success	Failure	Success	Failure
Group I	23 (82.2%)	5 (17.8%)	24 (85.7%)	4(14.3%)
Group II	25 (89.3%)	3 (10.7%)	26 (92.8%)	2 (7.1%)
Group III	24 (85.7%)	4(14.3%)	25 (89.3%)	3 (10.7%)

Table 4: Comparison of radiographic evaluation (success & failure rate) among three groups (Group I- 0.5 mg/ml, Group II-2.5 mg/ml, Group III-5 mg/ml) at different time periods



Graph 1: Comparison of clinical evaluation (success rate) among three groups at different time periods (Group I- 0.5 mg/ml, Group II-2.5 mg/ml, Group III-5 mg/ml)

Graph 2: Comparison of radiological evaluation (success rate) among three groups at different time periods (Group I- 0.5 mg/ml, Group II-2.5 mg/ml, Group III-5 mg/ml)

Discussion: The effectiveness of pulp therapy in primary teeth primarily relies on reducing and eliminating root canal infections. Primary teeth that are necrotic, particularly those of prolonged duration and symptomatic with periapical bone destruction, often host a substantial bacterial load and a more intricate anaerobic bacterial environment.[13] Therefore, intracanal medicaments that neutralize the virulence of pathogenic microorganisms may stimulate a host response that promotes healing of periapical tissues.[14]

The latest inclusion in the array of intracanal medicaments came with the introduction of TAP by Sato *et al.* in 1992, which comprises ciprofloxacin, metronidazole, and minocycline.[15]In clinical observations, the inclusion of minocycline has been associated with particular complications, including tooth discoloration, antiangiogenic effects, and the chelation of radicular dentin.[16] To overcome this, alternative medications such as clindamycin, cefaclor, amoxycillin have been proposed. Pandey MB.*et al.* (2023) used amoxicillin instead of minocycline clinically.[17] Present study used amoxicillin instead of minocycline to prepare the triple antibiotic paste, for performing NIET.

Among all primary endodontic infection cases, *E. faecalis* was predominantly found to be associated with asymptomatic cases than with symptomatic ones. Cogulu *et al.* found 8-10% *E. faecalis* bacteria in necrotic asymptomatic deciduous molar teeth.[18] An in-vitro study by Santra A. *et al.* (2023) found out that the Minimum Inhibitory Concentration (MIC) value of combination of amoxicillin, ciprofloxacin and metronidazole is 515 µg/ml against *E. faecalis* biofilm.[12] In their study, they concluded that a combination of amoxicillin 10 µg + metronidazole 500 µg + ciprofloxacin 5 µg was most effective for elimination of *E. faecalis* (99.98%), which would aid in dose determination of triple antibiotic paste for further clinical

trial. Based on this study which was taken as reference study, the first concentration of modified triple antibiotic paste finalized in the present study was 0.5 mg/ml (515 µg/ml). The other two concentrations considered were 5 times and 10 times the previous concentration, i.e. 2.5 mg/ml and 5.0 mg/ml respectively.

In 2014, Prather *et al.* conducted an in vitro study indicating that an antibiotic paste at a concentration as low as 1 mg/mL exhibited effective antimicrobial action, while concurrently demonstrating no adverse effects on the microhardness of the root structure.[19] In 2015, Algarni*et al*. conducted a study demonstrating a notable antibiofilm effect against the highly resistant endodontic pathogen, *E. faecalis*, using a 1 mg/mL concentration of TAP loaded onto a methyl cellulose-based material.[20] So, the present study compared the clinical and radiographic efficacy of a lower concentration (0.5 mg/ml) with those of higher concentrations (2.5 mg/ml and 5.0 mg/ml) of modified triple antibiotic paste (mTAP) containing amoxicillin, ciprofloxacin and metronidazole, to find out the best possible result while doing Non-Instrumental Endodontic Treatment (NIET) in carious, restorable primary molars having irreversible pulpitis with apical periodontitis.

All the previous studies have pulverized the commercially available tablets and removed the enteric coating of tablets to prepare the paste form. [21,22] The uniqueness of the present study was that antibiotic powder in pure form, which had been procured from chemical lab (Gluconate Health Ltd.), was used to prepare the triple antibiotic paste. In the present study, three additives (polymers) which are routinely used in manufacturing commercial tablets, Polyvinyl Pyrrolidone K-30 (PVP K-30), Hydroxy Propyl Methyl Cellulose (HPMC) and D-Lactose; were added to the final working solution to obtain the paste consistency by mixing the ingredients in a mortar and pestle. All these polymers are additives used commercially in manufacturing tablets and are declared safe for human trials and use by FDA, EU and DCGI.[23,24,25]

Cruz *et al.* recommended carriers like macrogol and propylene glycol (3MIX–MP), illustrating that these carriers effectively transport the medicament deep into the dentinal tubules, facilitating the thorough eradication of bacteria.[26] The vehicle used in the present study was propylene glycol as studies have shown that it penetrates well into dentinal tubules, thus proving its effectiveness as an ideal vehicle.[27]

3-month post operative clinical follow up revealed significant improvement in clinical success rate in all the three concentration groups. 6-month and 12-month clinical success rate of Group II was higher than that of group I and Group III and was found to be statistically significant. A study by Shankar K. *et al.* (2021) using mTAP containing ciprofloxacin, metronidazole and clindamycin showed that at the end of 3 months review, clinical success rates of 1 mg/ml conc. group and 1 gm/ml conc. group were 84.4 and 90.6%, respectively. [28]

On comparing the radiographic features among three groups at 6 and 12-months follow-up period, highest bone regeneration was seen in Group II (2.5 mg/ml) subjects and increased bone loss was seen mostly in Group I (0.5 mg/ml) subjects. This difference could be attributed to less concentration of the available drug in 0.5 mg/mL concentration of mTAP for sustained release. Lower success rates were obtained in another study by Tairatvorakul C. *et al.* (2012) with an observation of 75% of clinical success and poor radiographic success of 36.7% with 3-Mix.[29]

In a 2020 Systematic Review and Meta-Analysis on Nonvital Pulp Therapy for Primary Teeth by Coll A. James *et al*., it was found that for teeth exhibiting both external and internal root resorption, the success rate of NIET was 76 percent, surpassing the pulpectomy success rate of 47 percent.[30] The meta-analysis revealed a statistically significant difference between the success rates of NIET and pulpectomy, with NIET being the more favourable option.

So, NIET shows promising outcomes in extending the lifespan of infected primary molars, especially in situations where conventional pulpectomy might be deemed uncertain.

Furthermore, NIET eliminates the necessity for extensive canal instrumentation, thus avoiding additional weakening of the dentinal walls. This technique could be applicable in children with special needs, where conventional endodontic treatment is challenging due to underlying medical conditions.

Conclusions: The present study would help to identify the ideal concentration of triple antibiotic paste which will bring both clinical and radiographic success while doing Non-Instrumental Endodontic Treatment (NIET) in primary molars. Modified triple antibiotic paste (mTAP) using amoxicillin, ciprofloxacin and metronidazole in concentration of 2.5 mg/ml have shown good clinical and radiographic success in treating necrotic primary teeth. Long duration study on a larger population and study samples can be performed with 2.5 mg/ml concentration of modified triple antibiotic paste in future, to further enrich the effectivity of the study technique.

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