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Evaluation of antibiotic mix in Non-instrumentation Endodontic Treatment of necrotic primary molars

ABSTRACT

Aim *To compare the clinical and radiographic success rates of an antibiotic mix consisting of metronidazole, minocycline and ciprofloxacin (3Mix-MP) and another mix where minocycline was replaced with clindamycin (3Mix-MP-R) in non-instrumentation endodontic treatment (NIET) of necrotic primary molars and to determine the effect of root resorption on the success of the treatment.*

Materials and methods *Forty-two necrotic mandibular primary molars from 22 healthy children were randomly assigned to either mixture. Blinded clinical evaluation was conducted after 1, 3, 6 and 12 months by the operator, and blinded radiographic evaluation was conducted at 6 and 12 months follow-ups by other two investigators with inter-examiner reproducibility of 0.95.*

Results *Overall success rates of 3Mix-MP and 3Mix-MP-R were 80.96% and 76.20% respectively, with no statistically significant difference. Radiographically, resorption of more than one third of the root length had a lower failure rate with no statistically significant difference ($p<0.5$).*

Conclusion *Primary teeth with necrotic pulp can be treated with 3Mix-MP or 3Mix-MP-R irrespective of the degree of root resorption.*

Keywords *Antibiotic mix; Necrotic primary molars, Non-instrumentation endodontic treatment; Root resorption.*

Introduction

Primary teeth are considered natural space maintainers; therefore they should be preserved within the dental arch in their functional form until exfoliation, in order to guarantee a proper dental, skeletal and physiological development of the child [AAPD, 2015-2016a]. In addition, the use of appliances such as space maintainers in teeth loss is considered a solution with various complications [Laing et al., 2009]. Likewise, the early loss of primary teeth can lead to problems such as space loss, disturbance in eruption sequence and development of bad habits [Waterhouse et al., 2011; AAPD, 2015-2016a]. Thus, a pulpectomy may be performed in order to preserve primary teeth with necrotic pulp [AAPD, 2015-2016b]. It is unwise to maintain untreated infected primary teeth in the mouth, even though they may be opened for drainage and often remain asymptomatic for an indefinite period of time. However, they are a source of infection and must be treated or extracted [Dean, 2016]. Pulpectomy also has a number of limitations. For instance, teeth with resorbed roots, significant mobility, or where furcal bone loss extends to the succedaneous permanent tooth cannot even be considered for pulpectomy. Due to these reasons, most paediatric dentists prefer extracting infected primary teeth and placing a space-maintainer [Waterhouse et al., 2011]. Reports on the decisions of dentists in the public sector have revealed their preference for extracting infected primary teeth over conducting conventional endodontic treatment [Trairatvorakul et al., 2005]. Thus, suggesting a need for a simple and less time-consuming technique to treat these teeth.

In recent years, the cariology research unit of the Niigata University, School of Dentistry in Japan, has developed the concept of lesion sterilisation and tissue repair (LSTR) [Takushige et al., 2004]. The LSTR therapy or the non-instrumentation endodontic treatment (NIET) in which 'no mechanical instrumentation is used' [Hoshino et al., 1990] involves topical application of a mixture of three antibiotics: metronidazole, minocycline, ciprofloxacin (3Mix), which are mixed with propylene glycol and polyethylene glycol (MP) as a carrier [Sato et al., 1996], the so called 3Mix-MP. This mixture has the ability to sterilise carious lesions, necrotic pulps and infected root dentin in primary teeth [Sato et al., 1996; Sato et al., 1993]. However, one problem with this mixture is the presence of minocycline which can lead to discolouration, especially in calcifying teeth [Kim et

al., 2010; Krastl et al., 2013]. Thus, it was necessary to investigate the efficacy of a substitute mixture, that is minocycline-free, but may be able to produce at least the same outcomes in comparison with the original mixture to be used for the treatment of primary teeth. The Children's Hospital of Wisconsin, Milwaukee (CHW) made changes in the 3Mix paste, replacing the minocycline with clindamycin and adding iodoform to the mixture to make it radiopaque [Burrus et al., 2014]. This mixture was termed as 3Mix- MP-R.

The purpose of this study was to conduct a clinical and radiographic evaluation of the endodontic treatment of mandibular primary molars with necrotic pulp by using two different mixtures of antibiotics: 3Mix-MP and 3Mix-MP-R. In addition, this study aimed at investigating the effect of root resorption on the success of the treatment.

Materials and methods

This study was conducted in the outpatient Department of Pediatric Dentistry, Faculty of Dentistry, Tishreen University (Latakia, Syria), between March 2013 and April 2015. Approval (No. 1331) from the Institutional Review Board was obtained before conducting the research. After examining the patients and recording the general medical and clinical history, so as to ensure that the children involved in the study had no medical problems or allergy to the drugs and chemical substances used. An informed written consent was obtained from all participating parents. Forty-two mandibular primary molars from 22 healthy children were analysed in the study. Teeth were randomly divided into two groups, where each group consisted of 21 teeth by a neutral assistant dragging a concealed lot from a box containing 2 x 21 lots.

Inclusion criteria were: pain or tenderness to percussion, abscess, fistula-opening, or clinical mobility that is incongruent with the physiological root resorption; evidence of periapical/bifurcation radiolucency, pathological external root resorption, or excessive bone resorption on radiographs. Teeth with one or more of the above mentioned clinical and radiographic signs and symptoms were included in the study. Non restorable teeth and teeth with perforation in the pulpal floor were excluded from the study.

The clinical signs and symptoms were recorded, and radiographs were taken prior to the treatment by one operator. The intra-examiner reliability for clinical and radiographic examination was calculated by Cohen's kappa statistic (1 and 0.90, respectively).

All treatments were performed by one operator. In each case, the treatment was completed at the same visit.

The following commercially available antibiotics were used: metronidazole (Fagyle®, Sanofi-Aventis, Oubari, Aleppo, Syria), minocycline (Minocin®, Bahri, Damascus, Syria), ciprofloxacin (Ciprobay®, Bayer, Germany), and clindamycin (Clindo®, ElSaad, Aleppo, Syria). After removing the capsules and the enteric coating, each drug was pulverissed using a porcelain mortar and pestle to obtain a fine powder. Then, each drug was stored separately in a tightly capped porcelain container to prevent exposure to light and moisture. The pulverised drugs were mixed together in a ratio of 1: 1: 1 in two mixtures for two distinct groups.

- 3Mix-MP Group: one part each of metronidazole, minocycline and ciprofloxacin were mixed together.
- 3Mix-MP-R Group: one part each of metronidazole, clindamycin, and ciprofloxacin were mixed together.

In both groups, the pulverised drugs were mixed with a vehicle (MP) which is a combination of propylene glycol [P] and polyethylene glycol (Macrogol, M) in a ratio of 1:7, that is one part of the vehicle with seven parts of the pulverised drugs in order to obtain an ointment with a consistency that can be formed into a small pellet. Iodoform was added to both mixtures making them radiopaque and allowing radiographic control of proper paste placement.

After administering local anaesthesia, each tooth was isolated using a rubber dam. The entire carious tissue was removed. Then the pulp chamber access was obtained and the remaining necrotic coronal pulp tissue was removed with a high-speed handpiece and a sterilised diamond round bur No.18 (DIAMANT®, HORICO, Germany). Next, by using a sterilised diamond round bur No.12 (DIAMANT®, HORICO, Germany), the root canal orifices were enlarged (1 mm diameter, 2 mm depth) to form medication cavities. Finally, the chamber walls were chemically cleansed using 35% phosphoric acid for one minute because of its ability to remove the smear layer [Matos et al., 1997; Takushige et al., 2004], washed with sterile water and dried with cotton pellets. If any refractory hemorrhage appeared, it was controlled by applying a cotton pellet soaked in 10% sodium hypochlorite and maintained for 1 minute. One of the two drug pastes (3Mix-MP or 3Mix-MP-R) was randomly placed in the medication cavity and over the pulpal floor. The operator and the children were blinded to the paste used. Then, the tooth was sealed with glass ionomer cement GIC (Medifil®, PROMEDICA, Neumünster, Germany) and restored with stainless steel crowns (SSCs) (3M ESPE, st. Paul, USA).

The patients were clinically checked after one and three months from the initial treatment to perform a clinical examination and to ensure the complete disappearance of clinical signs and symptoms. The cases were then followed-up clinically and radiographically at 6 and 12 months after the procedure. A blinded clinical evaluation was performed by the operator, whereas the radiographic evaluation was carried out independently by two experienced paediatric dentists (not the operator) blinded to the technique (techniques

	3Mix-MP	3Mix-MP-R	P value
	n =21	n=21	
Clinical signs and symptoms	n (%)	n (%)	
Pain and tenderness to percussion	21 (100)	20 (95.24)	0.311
Abscess	11 (52.38)	12 (57.14)	0.757
Fistula	4 (19.05)	5 (23.81)	0.5
Abnormal mobility	7 (33.33)	8 (38.1)	0.747
Radiographic signs	n (%)	n (%)	
Periapical/Bifurcation radiolucency	21 (100)	21 (100)	NA*
Root resorption < 1/3	10 (47.62)	9 (42.84)	0.757
Root resorption > 1/3	11 (52.38)	12 (57.14)	
* NA: not applicable			

TABLE 1 Preoperative clinical and radiographic signs and symptoms in both groups.

	3Mix-MP	3Mix-MP-R	P value
Follow-up period	n (%)	n (%)	
6 months*			0.61
Decrease in radiolucency	17 (94.44)	16 (80)	
Static radiolucency	1 (5.55)	2 (10)	
Increase in radiolucency	0 (0)	2 (10)	
Radiographic success rate			0.61
12 months			0.657
Decrease in radiolucency	11 (61.11)	11 (55)	
Static radiolucency	3 (16.67)	3 (15)	
Increase in radiolucency	1 (5.56)	4 (20)	
Normal exfoliation	3 (16.67)	2 (10)	
Radiographic success rate	17 (94.44)	16 (80)	0.205

TABLE 2 Radiographic evaluation of radiolucency status and radiographic success rates in both groups at 6 and 12 months follow-up.

were indistinguishable and coded). The inter-examiner reproducibility was calculated by Cohen's kappa statistic and was indicated excellent with a measurement agreement of 0.95.

The clinical success criteria were absence of pathological clinical signs and symptoms of the oral disease (pain or tenderness to percussion; abscess, fistula, and/or abnormal mobility). If one or more of the above mentioned clinical signs were present, the case was considered a failure and the tooth was extracted. Radiographically, the cases were considered successful when the size of the periapical/bifurcation radiolucency reduced or remained the same compared to the preoperative status. Increase in radiolucency compared with the preoperative status was considered as radiographic failure. In case of normal exfoliation, the case was considered successful both clinically and radiographically. At the end of the follow-up period, the overall clinical and radiographic failure rates in the study were calculated. The cases were considered as total (overall) failures if they failed clinically at the 3, 6 or 12 months; or when they failed radiographically at the 12 months follow-up.

Statistical tests used to analyse the findings were Chi-Square test or Fisher's Exact test when the conditions of the Chi-Square test could not be realized. A p-value <0.05 was considered statistically significant. The statistical analysis was conducted using Stata (version 6.0) and under the supervision of an independent data analyst from the Department of Family and Society Medicine at Tishreen University.

Results

Before the treatment, no statistically significant differences existed between the two groups in terms of the distribution of the preoperative clinical and radiographic signs and symptoms and the degree of root resorption (Table 1).

After one month from treatment all the cases in both groups (100%) were completely free of clinical signs and symptoms.

At the three-month follow-up, three teeth (14.28%) in the 3Mix-MP group exhibited clinical symptoms (one tooth [3.6%] had a fistula, and two teeth showed abscess [9.52%]), while one tooth (5%) in the 3Mix-MP-R group showed an abscess. These teeth were extracted. After 6 and 12 months from treatment all teeth (100%) in both groups were completely clinically asymptomatic.

No statistically significant differences were noticed between the two groups regarding the appearance of radiolucency and the radiographic success rates after 6, and 12 months of treatment (p >0.05; Table 2).

At the end of the follow-up period, the overall failures were 4 out of 21 teeth (19.04%) (3 teeth failed clinically during the follow-up period and one teeth failed radiographically at 12 months in the 3Mix-MP group; and 5 out of 21 teeth (23.80%) (one teeth failed clinically during the follow-up period and four teeth failed radiographically at 12 months) in the 3Mix-MP-R group. Therefore the overall success rates for 3Mix-MP and 3Mix-MP-R were 80.96% and 76.20% respectively, with no statistically significant difference (p = 0.71).

Although resorption of more than one third of the root length had a lower failure rate radiographically, there were no statistically significant differences in the relation between root resorption and clinical and radiographic success of the treatment between the two groups. Moreover, no statistically significant differences

	Radiographic success			Clinical success		
	3Mix-MP	3Mix-MP-R	P value	3Mix-MP	3Mix-MP-R	P value
follow-up period	n (%)	n (%)		n (%)	n (%)	
6 months						
root resorption<1/3	8 (100)	9 (100)	NA	8 (100)	8 (88.88)	0.53
root resorption>1/3	10 (100)	11 (100)	NA	10 (100)	10 (90.90)	0.52
P value	NA*	NA*		NA*	0,71	
12 months						
root resorption<1/3	8 (100)	9 (100)	NA*	7 (87.5)	6 (66.67)	0.335
root resorption>1/3	10 (100)	11 (100)	NA*	10 (100)	10 (90.91)	0.524
P value	NA*	NA*		0,444	0,217	
*Na: not applicable						

TABLE 3 The correlation between root resorption and the success of the treatment

were noticed regarding the association between root resorption degree and the clinical and radiographic success of the treatment within each group individually during all the follow-up periods (p >0.05; Table 3).

Discussion

The bacterial components of the intraoral pathology and the pulpal and periradicular infections have been extensively analysed in the literature in order to discover the target bacteria in endodontic treatment. Based on these findings, the required drugs were selected [Hoshino, 1985; Ando and Hoshino, 1990; Hoshino et al., 1992]. Metronidazole has a wide bactericidal spectrum against anaerobes commonly found in infected oral tissues, so it was the first chosen antibiotic. However, metronidazole was unable to eradicate all the bacteria in the lesions, even at high concentrations; in fact, some bacteria were resistant to it [Hoshino et al., 1988; Hoshino et al., 1989]. Several *in vivo* and *in vitro* studies were conducted and showed that mixed drugs (3Mix-MP) were effective against oral bacteria including those present in carious lesions, infected dentin, and necrotic pulp in primary teeth [Sato et al., 1992; Takushige et al., 2004]. .

Our study was conducted to compare the efficacy of the original compound (3Mix-MP) versus the modified one (3Mix-MP-R).

The cause of early clinical failure after 3 months from treatment for the 4 cases can probably be attributed to the insufficient marginal sealing of the stainless steel crowns due to the deep extent of subgingival caries which could result in the leakage of the medical substance. This occurred in two cases in the study by Takushige et al. [2004], leading to failure.

After one year of observation, the radiographic success rate in the clindamycin group was less than that of the minocycline group, but the difference is not statically significant.

In the first group, where 3Mix-MP was applied, our results were different from Takushige et al. [2004], as these authors recorded a 100% success rate, which could be attributed to the fact that they retreated a number of cases that exhibited clinical symptoms after the treatment, whereas we did not conduct any retreatment of such cases. Moreover, Takushige et al. [2004] did not have radiographic evaluation data. As for the difference in the percentages of the drugs, Takushige et al. [2004] used a ratio of 1:3:3 .whereas we used a 1:1:1 ratio. Thus, the effect of this difference remains unknown. Regardless of the retreatment of several cases in the study of Takushige et al. [2004], the high overall success rate may indicate the clear efficacy of the mixture.

Several studies have compared the efficacy of the 3Mix-MP with other mixtures of antibiotics in endodontic treatment of primary teeth with necrotic pulp. Each of the studies by Pinky et al. [2011] and Nanda et al. [2014] compared the efficacy of the 3Mix-MP with another mixture in which metronidazole was substituted by ornidazole. In both studies, no statistically significant differences were observed between the two groups, with increased radiographic success rates for the new mixture [Pinky et al., 2011; Nanda et al., 2014].

The results of our study in 3Mix-MP group were different from those obtained by Pinky et al. [2011] for the same mixture. Their clinical and radiographic success rates were 100% and 90%, respectively. This discrepancy may be a result of the differences in the sample selection criteria or in the clinical procedure followed, as Pinky et al. [2011] excluded teeth with advanced bone resorption, used a 1:3:3 ratio to mix the drugs, and placed the final restoration over 3 stages by placing ZOE on top of the drug mixture followed by GIC after 15 days, and then the SSC after 30 days. However, in our study we placed the GIC and SSC in the same treatment session. Pinky et al. [2011] did not mention the occurrence of any leakage

before placement of the SSC nor did they discuss the occurrence of any reaction between the eugenol and the remaining pulp tissue and the 3Mix [Kayalvizhi et al., 2013].

In the study by Nanda et al. [2014] the drugs were combined in a 1:3:3 ratio, yet the radiographic success rate in the 3Mix-MP group was 81% after 12 months, which is similar to the findings of our study in the 3Mix-MP group with 80.96%; whereas their clinical success rate was 100%.

In a study by Nakorchai et al. [2010] the clinical and radiographic success, for the 3Mix-MP were compared to those of Vitapex for endodontic treatment of primary teeth with pulpal involvement. Their radiographic success rates were 76% in the 3Mix-MP group, which is a little lower than our values, noting that they did not enlarge the canals orifices as we did.

Although all the previous studies reported acceptable clinical and radiographic success rates for the LSTR treatment using the 3Mix-MP, Trairiavorakol and Detsomboonrat [2012] suggested that non-instrumentation endodontic treatment with the 3Mix-MP in primary teeth cannot substitute the conventional endodontic treatment as a long term treatment. This study revealed a good clinical success rate of 76% but a low radiographic success rate of 36.7% after 2 years of follow-up. This low rate could be attributed to the fact that these authors considered a case to be radiographically successful only when the decrease of radiolucency was observed. Conversely, in our study the case was considered a radiographic failure only if the radiolucency increased compared to its initial preoperative status, according to Payne et al. [1993], who mention that most clinicians are prepared to accept pulp-treated primary teeth that have a limited degree of radiolucency in the absence of clinical signs and symptoms, and most of the pulp therapy studies in the existing literature have considered such teeth to be successfully treated. In the study by Trairavorakol and Detsomboonrat [2012], the radiographic success rate after 12 months of treatment was 45.8%, which corresponded to the radiographic improvement of the case in our study which was 61.11% at 12 months follow-up and 52.39% as an overall rate at the end of the study (taking into consideration the teeth that failed clinically in the 3 months follow-up period). Moreover, in the study by Traivavorakol and Detsomboonrat [2012] only 60 of a total of 80 teeth were available for the final follow-up and no explanation was given for the dropouts [Kayalvizhi et al., 2013]. However, the length of the observation period may have an impact on the overall success rate.

In the second group of our study, we used the 3Mix-MP-R, a mixture which to date none of the previous studies had used, except a report of 3 clinical cases by Burrus et al. [2014] that revealed a complete success. The radiographic improvement of the 3 aforementioned cases was met by a similar improvement in more than half of the cases in our study after a 12 months follow-up.

Clindamycin is used in paediatric dentistry as one of two options for patients with allergic reactions to penicillin and/or cephalosporin antibiotics, since it is effective for infections (eg, abscesses) caused by gram-positive aerobic bacteria and gram-positive or gram-negative anaerobic bacteria [AAPD, 2015-2016c]. These characteristics make clindamycin an appropriate alternative that is equivalent to the main mixture according to the results of our study. Moreover, clindamycin is used in antibiotic prophylaxis regimens for patients at high risk of infections who are in need for a dental procedure [AAPD, 2015-2016d].

According to our study, the degree of root resorption has no effect on the success of the treatment for both antibiotic mixtures as no statistically significant differences were found when root resorption was more or less than one third of the root length. This is corroborated by the findings of the study by Takushige et al. [2004], which leaves the degree of root resorption unlimited in the sample selection criteria and hence all the teeth were successful.

Furthermore, we found out that despite the lack of statistical differences in terms of the degree of root resorption, teeth with a resorption of less than 1/3 of the root length had a higher rate of radiographic failure. This indicates that this treatment is effective for teeth with advanced root resorption and to which conventional endodontic treatment is contraindicated. More studies are required to support this observation.

To enhance the diffusion of the antibacterial drugs, (3Mix) the antibiotics used in our study were mixed in both groups with excipients (carrier) comprised of propylene glycol and polyethylene glycol (Macrogol) [MP], as the study by Cruz et al. [2002] demonstrated the efficacy of propylene glycol in carrying 3Mix and penetrate through the dentinal tubules. Similarly, a study by Phides and Hoshino [2008] suggested MP as a good vehicle to carry medications through root canal obturation.

Based on this study and many former studies, the NIET treatment can be considered successful and effective especially in cases with poor prognosis because of its high antibacterial efficacy. Another advantage of this technique is being non-instrumentational. This means that it can be applied to patients with root resorption of more than 1/3 of the root length and can prevent the excessive enlargement of root canals and unnecessary irritation to the periapical tissue, thus preventing damage to the permanent tooth bud. It also requires less chair time (one session), and therefore is more likely to be acceptable for non-cooperating children.

Although the NIET treatment in our study provided promising results for both mixtures, this study should be repeated using a larger sample size and over a

longer time period to confirm these results.

Conclusion

After 12 months of clinical and radiographic follow-ups, we can conclude that primary teeth with necrotic pulp can be treated with an antibiotic mixture composed of ciprofloxacin, metronidazole and minocycline or an antibiotic mixture composed of ciprofloxacin, metronidazole and clindamycin. Both combinations of antibacterial drugs can be used in endodontic treatment of primary teeth irrespective of the degree of root resorption.

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