Review Article

Lesion Sterilization and Tissue Repair: A Literature Review

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Abstract

Background: Lesion sterilization and tissue repair (LSTR) is also known as non-instrumental endodontic treatment which claims to be a "new biologic approach in the treatment of carious lesions with periapical involvement using a mixture of 3 antibiotics (3-Mix)." LSTR involves the use of three antibiotics/antibacterial drugs, namely, Metronidazole, Ciprofloxacin, and Minocycline. Propylene glycol is used as solvent. Concept of LSTR was developed by cariology research unit at the Niigata University School of Dentistry in 1988 in this a fresh creamy consistency is prepared and placed in the pulp chamber which is subsequently sealed with a GIC restoration and stainless-steel crown. The present review article concentrates on the basic concept of LSTR including its technique, advantages and disadvantages.

Keywords: Lesion, Metronidazole, Minocycline, Repair, Tooth.

Introduction

Pulp therapy becomes an enigma for the dentist as it cannot be performed in all patients because it is compromised by factors such as extensive root resorption, inadequate bone, and periodontal support, a child belonging to pre-cooperative age group etc.[1] In routine dental practice, clinicians come across a number of cases where a deciduous tooth is affected by dental caries followed by periradicular change and is beyond conservation by traditional endodontic procedures.[2] In such a situation, extraction becomes the only indicated treatment option.[1]

However, the premature loss of primary teeth can bring about disturbances such as ectopic eruption, alteration in eruption sequence, space loss, development of deleterious habits, functional, and speech impairment. Primary teeth play an integral role in the development of occlusion.[3] Most promising space maintainers are successfully disinfected and restored primary teeth. The typical tooth morphology of primary teeth is that it has tortuous root canals, ramifications, the presence of multiple accessory canals, and ample medullary bone spaces that favor spreading of infection. Due to proximity of the developing permanent tooth germ to the roots of the primary teeth and inability to obtain hermetic seal, as there is lack of apical closure due to physiologic root resorption of the primary tooth proper endodontic treatment cannot be performed.[2-5]

In lesion sterilization and tissue repair (LSTR), combination of antibiotics (Metronidazole, Ciprofloxacin, and Minocycline) is used for controlling of oral infections such as dentinal, pulpal, and periapical lesions.[6] In this, lesion is disinfected and tissue regeneration is promoted by the host's natural tissue recovering process. Three types of antibiotics are combined to ensure complete removal of all pathogenic microorganisms in pulpal and periapical lesions.[7]

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Discussion

This oral disinfection procedure was first invented by the Cariology Research Unit of Niigata University School of Dentistry the triple antibiotic paste (TAP) contains 1 part of ciprofloxacin and three parts of metronidazole and three parts of minocycline by weight. Ciprofloxacin is a synthetic fluoroquinolone and has a bactericidal effect. Metronidazole is a nitroimidazole compound having a broad spectrum of activity against protozoa and other anaerobic bacteria. Minocycline is a synthetic derivative of tetracycline with a similar spectrum of action.[6,8]

Indications[6]

1. Primary teeth affected with pain and tender on percussion
2. Teeth with Grades I and II mobility

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3. Presence of abscess
4. Presence of sinus tract
5. Presence of radiolucency in furcation area
6. Pulpless primary teeth in hemophilic patient
7. Immature primary teeth with necrotic pulp and incompletely formed roots.

Contraindications[6]

1. Patient sensitive or allergic to ciprofloxacin, minocycline, or metronidazole
2. Radiographic evidence of excessive internal or external root resorption
3. Primary tooth nearing exfoliation
4. Perforated pulpal floor
5. Excessive bone loss in furcation area involving underlying tooth germ
6. Non restorable crown of permanent tooth where post-placement and core buildup are not possible.

Preparation of TAP[1,9,10]

Takushige *et al*. proposed the most common combination which includes metronidazole, ciprofloxacin, and minocycline. The commercially available antibiotics available in either enteric coated tablet or in capsule form are taken in separate dappen dishes. The enteric tablet coating is removed by scraping the coating with a blade and for the capsule the outer capsular material is removed. Components are powdered separately in clean mortar and pestle and wettness should be avoided. Storage of powder should be done in tightly capped porcelain containers and stored in dark place or in the refrigerator to prevent exposure to light and moisture. After proper pulverization, each of the components is taken in a clean glass slab/mixing pad. Then, a part of the solvent is dispensed. The triple antibiotic mixture has maximum effect when seven parts of powder are mixed with one part of solvent. So after dispensing, the powder is divided into seven parts and each part mixed separately with the solvent to ensure uniform consistency of the mix. The final preparation will be a soft ball-like structure of 1 mm diameter. If the mix is soft add more three mix powder to this. If the preparation becomes flaky, dry and too hard, then add more solvent. Airtight container should be used for storage. If the mix turns translucent on storage, it has to be discarded.

Different combinations of antibiotics in the 3-Mix

Sato *et al*. carried out a series of *in vitro* experiments using the 3-Mix with and without Rifampicin. Later they combined Ciprofloxacin and Metronidazole along with a third antibiotic, namely Amoxicillin, Cefaclor, Cefroxadine, Fosfomycin, or Rokitamycin.[11,12] Ruparel *et al*. in an *in vitro* study substituted Minocycline with Cefaclor and referred to it as the modified TAP and tried another combination referred to as the double antibiotic paste (DAP). The DAP can be referred to as the 2-Mix, because it consisted only of Ciprofloxacin and Metronidazole. They also tried Augmentin on its own and its effect on the survival of stem cells of apical papilla.[13] Algarni *et al*. used antibiotic gels containing Clindamycin modified 3-Mix and compared it to the 2-Mix. Park *et al*. reported a case using an Amoxicillin modified 3-Mix for revascularization of necrotic immature permanent tooth and overcame discoloration aspect after 1 year clinical follow-up.[14]

Procedure[1,2,10]

After preparation of TAP, access cavity is prepared. LA is given and rubber dam isolation is done. Preparation of access cavity using round bur followed by removal of necrotic tissue and irrigation done using saline and sodium hypo-chlorite. The ethylenediaminetetraacetic acid is a better choice as it removes the smear layer leading to clean and patented dentinal tubules, which could allow deeper penetration of antibiotics into the dentinal tubules. Sodium hypochlorite is an effective hemostatic agent, can be used to control hemorrhage, if present. Furthermore, it does not interfere with pulpal healing and clots can be removed; moreover, it stops the pulpal hemorrhage that compromises pulpal healing and is nontoxic to pulpal tissue. Next step is the preparation of medication cavity using a round bur at the canal orifice which is 2 mm deep, and 1 mm wide, and is meant for retaining the triple anti-biotic paste at the canal orifice. After proper drying, the paste is placed in the cavity, and permanent restoration is done using glass ionomer cement followed by stainless steel crown placement. In an *in vivo* study conducted by Prabhakar *et al*. on 60 infected primary molars, even though the teeth with root canals left unprepared also exhibited a clinical and radiographic success, the success rates were more for the biomechanically prepared ones than the others.

Advantages[6]

- Easy and simple, one visit technique, painless, and economical
- No instrumentation needed
- No irritation of the periapical tissues
- No obturation required.

Disadvantages

Systemic antibiotics for local application raise concerns due to its adverse effects. The foremost disadvantage is tooth discoloration caused by minocycline. As a remedy, Thibodeau and Trope suggested use of cefaclor instead of minocycline.[1,15] To compensate for the radiolucent appearance of the TAP which makes it difficult to assess the quality of the filling, iodoform could be added to impart radio-opacity.[16]

These concerns of TAP include allergic reactions, the probability for the emergence of antibiotic-resistant bacterial strains, drug side effects, and the risk of developmental anomalies in permanent teeth if used in primary teeth and cyst formation if the focus of chronic infection is left. The positive side to the above-said statement is the volume of these drugs used in LSTR is minimal, and there are no reported side effects.[17]

Hollow tube effect concern subsists in LSTR treated teeth because of the unfilled roots. The root canal that is not filled could be infused with tissue fluids; further, it gets stagnated

and ultimately form a nidus for infection; whether this occurs in all cases or could be suppressed by host immunity is yet to be determined.[1]

Journey from 3-Mix to 2-Mix

Ruparel *et al*. in their *in vitro* study paved the way for 2-Mix consisting of ciprofloxacin and metronidazole but its bactericidal efficacy was not tested.[13] In the 2-Mix, minocycline was removed and consist of ciprofloxacin and metronidazole only. Sabrah and Yassen compared the antimicrobial activity of the 3-Mix and, 2-Mix with calcium hydroxide against *Enterococcus faecalis* and *Porphyromonas gingivalis* and it was found that calcium hydroxide does not have effective bactericidal properties and that the 2-Mix has comparable antibacterial activity to the 3-mix, so it can replace the 3-Mix.[18] Kim *et al*. confirmed that a low concentration of 1 mg/mL of the 2-Mix had fewer negative effects on attachment and proliferation of DPSCs to dentin.[19] Hence, these *in vitro* studies suggested that the 2-Mix could be used where 3-Mix was indicated.

Advantages of 2-Mix[20]

Main disadvantage of 3 Mix is staining due to minocycline which is overcome by usage of 2-Mix. Also advantages of 2Mix over 3-Mix were its comparable antibacterial efficacy, longer residual antibacterial effect, and fewer detrimental effects on DPSCs. It also had similar antibacterial efficacy. Disadvantages of Macrogol, that is, Polyethylene glycol such as, respiratory tract irritation, skin irritation, eye irritation, and central nervous system depression; whereas long-term exposure could cause liver damage, reproductive, and mutagenic effects; could be overcome too.

Mechanism of action of 2-Mix[21]

The mode of action for 2-Mix is same as for 3-Mix, that is, it sterilizes the infected tissues; both pulpal and periapical. Concerns and issues against the use of 2-Mix are similar to that of 3-Mix for LSTR which are mentioned in the following text but reduced number and lower concentrations of antibiotics should overcome significant side effects.

Related studies on LSTR

Akgun *et al*. (2009) used TAP as a disinfectant for traumatize immature tooth with a periapical lesion and found that after 4 months, the patient had no symptoms, and a radiograph showed that the radiolucency had completely resolved.[6]

Agarwal *et al*. (2011) assessed the clinical efficacy of pulpotomy procedures using Pulpotec, LSTR using 3 mix, and zinc oxide eugenol (ZOE) pulpectomy. 60 pulpally involved teeth were selected and randomly divided into three groups. Clinical evaluation at 1 month showed only 70% success in the LSTR group (Group 3) compared to 100% success in the other two groups. By the end of 12 months, the LSTR group displayed a poorer success rate compared to the ZOE pulpectomy group.[22]

Enterococcus faecalis the main endodontic pathogen in canals as well as peri-radicular tissues is highly virulent. Enterococcus groups were viable even after copious irrigation was performed. Hence; Alam *et al*. studied by *in vitro* methods the susceptibility of *E. faecalis* to the triple antibiotic paste. He concluded that the 3-mix, at 100 µg/mL, is completely capable of inhibiting the growth of all strain when combinations was used.[23]

Takushige *et al*. (2004) evaluated the effectiveness of 3-mix with MP paste and of a root canal sealer on the clinical outcome of LSTR in 56, 4 to 18-years-old patients. Out of 87 primary teeth, the clinical symptoms disappeared in 83 teeth, but in four cases it resolved only after retreatment using the same procedure. Draining sinuses and gingival abscesses disappeared after few days, and the permanent successor erupted without any problems. The mean function time of the teeth was 680 days, except for one case with congenitally missing permanent teeth. All the cases were evaluated as successful.[2]

Future perspective[1]

The effects are ambiguous in relation to the damage the procedure may cause to the underlying tooth bud, its effect on the growth and development in children, the necessity for the concurrent usage of systemic antibiotics and so on. Thus for prudent case selection and more effective management, long-term studies are recommended in future.

Conclusion

Sterilization of infected tissue is the main concern for the success of endodontic treatment as any residual microorganisms can cause reinfection and failure of endodontic treatment. This causes waste of time, money, and energy and frustrating condition for the patient and dental surgeons. Moreover, pediatric patients usually have a short attention span and do not like long treatment duration and repeated visits. Therefore, TAP can be successfully used for treatment of immature vital tooth. Further *in vivo* and *in vitro* studies are required for the success of TAP.

Conflicts of Interest

The authors declare they have no potential conflict of interests regarding this article.

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