

Triple Antibiotic Paste and Alternative Medicaments in Endodontics: A Literature Review

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Abstract—One of the major reasons for endodontic failure is inadequate disinfection of the root canals during canal preparation and cleaning. Despite the thorough instrumentation, chemo-mechanical preparation alone cannot eliminate residing bacteria, especially due to the complex anatomy of the root canal system. One effective intra-canal medicament is Triple Antibiotic Paste (TAP), which is a mixture of three antibiotics that has a combined effect to act as a potent antimicrobial agent against microbes. TAP has also been proposed as a root canal medicament in endodontic regenerative procedures, and the review assesses its efficiency in root canal disinfection in both primary and permanent teeth, along with its effects on regeneration/ revascularization procedures. Furthermore, the article discusses and compares other intra-canal medications used in contemporary endodontic practice, such as Calcium Hydroxide (CH) and Chlorhexidine Gluconate (CHX). The review emphasizes the importance of selecting the appropriate medicament and disinfectant to effectively treat odontogenic infections and maintain the vitality of diseased pulp when possible.

Keywords— Endodontics, Endodontic Regeneration, Root canal medicaments, Triple Antibiotic paste.

I. INTRODUCTION

Endodontic infections are challenging and lead to chronic problems and embraced complications. To maintain the tooth in a non-pathological status, it is obligatory to disinfect the root canals. Furthermore, developing teeth challenged with infection may retard root development and lead to subsequent problems in the long run. Endodontic infections are polymicrobial in nature and obligatory anaerobic bacteria standouts. *Prevotella species*, *Bacteroid melaninogenicus*, *Prophyromonas gingivalis*, *Prophyromonas endodontalis*, *Tannerella forsythia*, *Fusobacterium Nucleatum*, *Spirochetes*, some fungi and viruses predominate in primary endodontic infection. Some organisms are resistant to disinfection procedures and can survive after endodontic therapy, causing persistent endodontic infections. *Enterococcus fecalis* has been constantly identified in root canals in failed endodontic therapy. This microbe has features that make it a notable survivor of the root canal. Thriving under poor nutrition, surviving and making biofilms in medicated canals, phenotype switching into a viable but non-cultivable state, and utilizing tissue fluids from the periodontal ligament and dentinal tubules are some of these virulence factors. [1, 2]

Root canal disinfection is a critical step in endodontic treatment that involves eliminating microorganisms from the root canal system. The goal of root canal disinfection is to create an environment within the root canal system where microorganisms are unable to survive and minimize the available space by the endodontic procedure. This is accomplished through a combination of mechanical instrumentation, irrigation, and the use of intra-canal medicaments together with hermetic obturation of the Root Canals. Mechanical instrumentation involves the use of either rotary or hand endodontic files to remove infected pulp tissue,

debris, and bacteria from the root canal system. These instruments do not reach the complex anatomy of the root canal system such as fins, deltas and ramifications, leaving about 50% of the root canal system non-instrumented, necessitating thorough use of endodontic irrigation. [3] Apart from the bacteriocidal effect, a good irrigant helps to flush out and dissolve organic debris, remove the smear layer and neutralize endotoxins.

Despite sound chemo-mechanical preparation, there can be residual complex biofilms that are not easily disrupted. Intracanal medicaments are pharmacological agents that are placed inside the root canal after cleaning and shaping the canal system and left in the canal for some time. These medicaments are specially used when the pulp is necrotic, the canal is actively draining with acute symptoms, or there is a clinically or radiologically evident significant periapical infection. The medicaments destroy remaining viable bacteria in the radicular system, reduce peri-radicular inflammation and pain and halt inflammatory root resorption. Apexification and pulp revascularization are the other special indications for the use of root canal medicaments.

In contemporary endodontic therapy, CH has served as an excellent root canal medicament with satisfactory results. Nowadays, there are various preparations available in the market for the same purpose, aiming for even better results. Medicaments containing Chlorhexidine and Ethylene Diamine Tetra Acetic acid (EDTA) are some of those. Local administration of antibiotics is recommended to treat the majority of endodontic infections, rather than systemic antibiotic therapy. The rationale behind this is that the antibiotics will be effective in desired doses in the radicular system where systemically administered drugs will not reach, especially when the pulp is necrotic. Further, locally delivered antibiotics overcome the possibility of developing side effects, allergies, antibiotic resistance and poor patient compliance.

Septomixine Forte (Septodont, Saint-Maur, France) and Ledermix (Lederle Pharmaceuticals, Wolfratshausen, Germany) are agents made by combining antibiotics with a corticosteroid. But these agents have a narrow antibiotic spectrum. Understanding of growth, survival and virulence factors of precise microorganisms involved in endodontic infections helps select the best intra-canal medicament. [4] The use of intra-canal medicaments for a minimum of 7 days is recommended by the American Association of Endodontists for regenerative procedures. But the long-term use is not recommended due to adverse effects on the microhardness of radicular dentine, especially by CH and TAP. [5]

II. MEDICAMENTS USED

Hoshino and colleagues largely contributed to developing the TAP to eradicate bacteria from the radicular system, especially for regenerating purposes. [6] TAP has a broad spectrum activity as it combines the antibacterial properties of three antibiotics: Ciprofloxacin, Metronidazole and Minocycline. Ciprofloxacin is a second-generation fluoroquinolone with a broad spectrum of activity and excellent tissue penetration. Metronidazole is a nitroimidazole compound that has a bactericidal effect on cells by binding and destroying DNA, ultimately causing rapid cell death. It has excellent action against anaerobes and protozoa. Minocycline has a broad spectrum of bacteriostatic activity by binding to 30S ribosome and inhibiting protein synthesis. It is a semisynthetic derivative of tetracycline that possesses many unique properties apart from its bacteriostatic action, including preventing tissue degeneration by the inhibition of collagenases and anti-resorptive properties by the inhibition of clastic cells. [7]

CH was first introduced by Herman as a pulp-capping material decades before the introduction of TAP. [8] CH dissociated into OH⁻ and Ca²⁺ ions in contact with aqueous fluids. Being a strong base with a pH of 12.5-12.8, CH provides various therapeutic effects, making it a popular root canal medicament even today. CH denatures and destroys the cytoplasm, proteins and DNA of endodontic pathogens and provides initial bactericidal action and bacteriostatic effect later when pH drops with time. [9]

III. PREPARATIONS

According to Hoshino et al, 1996 the TAP preparation contains an Antibiotic mix: Carrier = 5: 1 can heal periapical lesions. [6]

Antibiotic mix - Ciprofloxacin: Metronidazole: Minocycline = 1: 1: 1 or 33%: 33%: 34%

Carrier - Macrogol ointment and propylene glycol 0.1-1.0 mg/ml concentration

To overcome some of the side effects of Conventional TAP, modified TAP (MTAP) is described in the literature combining Ciprofloxacin, Metronidazole, and Clindamycin 30% of each with 10% of iodoform to improve its radiopacity. [10, 11]

CH preparations: CH powder is mixed with various types of vehicles such as water-soluble substances, viscous vehicles and oil-based vehicles. The type of the vehicle directly

influences both physical and chemical properties and thereby determines its clinical application. As an example, viscous and oily vehicles extend the time of medicaments remaining within the canal and outstretch the action of CH compared to water-based preparations. [12]

IV. INDICATIONS

A. Root canal Disinfection

As previously mentioned, TAP is effective in disinfecting and overcoming the resistance of poly microbes within the radicular system by its broad spectrum activity against anaerobes, aerobes, actinomyces and other bacteria. TAP has been stated as the most efficacious root canal medicament to overcome bacterial resistance in one systematic review. [10] When compared with Calcium Hydroxide (CH), TAP has twice the depth of penetration in dentine and bacterial destruction, so is recommended as a root canal disinfectant in re-treatment cases as well. Even though TAP has shown superior action compared to CH against *E. fecalis*, which is a commonly identified pathogen in re-treatment cases, TAP is slightly inferior to combined preparations of CH and chlorhexidine (CHX) for the same. [13] MTAP has proven to have better root canal disinfection properties than TAP with fewer adverse effects. [14]

B. Management of periapical lesions

TAP is indicated in the treatment of periapical abscesses, periapical granulomas or even large periapical lesions (possibly small radicular cysts). [15] Another systematic review by Kumar et al, 2021 stated that TAP can be successfully used to manage large periapical lesions non-surgically where other conventional root canal medicaments failed. [11] The protocol for non-surgical management, in some reported cases, is intra-canal aspiration followed by TAP paste for 2 weeks. It is a conservative approach compared to surgical endodontics. When non-surgical endodontic therapy fails, TAP can still be utilized in multidisciplinary treatment, such as endodontics combined with surgical enucleation. [4]

C. Endodontic flare-up

An endodontic flare-up is an acute escalation of a periapical pathology following the initiation of orthograde root canal therapy. This is not an uncommon occurrence and the reported incidence is 2-20%. [2] Some studies show the use of TAP as an intra-appointment intra-canal dressing can reduce the incidence of an endodontic flare-up. [17] Further, TAP is effective in controlling ongoing endodontic flare-ups faster than CH. The reason behind this is the synergistic effects of the superior antibacterial action of the antibiotic mixture and the anti-inflammatory action of Minocycline. [18, 19]

D. Management of inflammatory root resorption

TAP has been described as an intra-canal medicament to halt external inflammatory root resorption as it has an extensive antibacterial effect on bacteria residing in necrotic pulp, dentinal tubules and even in the periapical area. Once the causative agents are removed, the inflammatory resorption will automatically halt. Further, Minocycline has an additional unique property in arresting the inflammatory resorptive

process by inhibiting collagenases and clastic cells. [12] Similarly, CH is also widely used to manage root resorption. CH reverses inflammatory resorption by neutralizing the acidic environment, retarding osteoclastic activity and promoting repair through Alkaline Phosphatase activity. [9]

E. Management of root fractures

Multiple published case reports suggest that both CH and TAP are perfect inter-appointment root canal dressings to treat teeth with horizontal root fractures. Following treating the coronal fractured part with TAP for 2 weeks, A Mineral Trioxide Aggregate (MTA) plug can be used to seal the root canal at the fractured end. All case reports showed great success with the elimination of symptoms and repair of the fracture site. [12, 20]

F. Deciduous teeth in pulp therapy procedures

For successful vital pulp therapy procedures, materials like formocresol, ferric sulfate, and MTA are used. Ledermix or medication containing paraformaldehyde are used as medications on the hyperalgesic pulp to reduce the inflammation and make the pulp non-vital, respectively, whenever it is impossible to obtain anesthesia or when the patient is unable to cooperate for the duration of the pulp therapy procedure. When the patient is pain-free at the following visit, the routine pulp therapy process is then completed. [23]

CH is a widely used pulp therapy material in deciduous teeth with satisfactory long-term results. [9] It is used in pulp capping, pulpotomy and following pulpectomy. Some studies report incidences where root resorption is accelerated following pulpectomy with CH dressing. TAP is recommended in many studies as an inter-appointment dressing in pulpectomy procedures of primary teeth with different success rates. [21] Even though the success rate is not great as pulpectomy procedures, TAP can be used for non-instrumented endodontic procedures, especially for teeth with pre-operative external or internal resorption with a good outcome. [22] Lesion sterilization and tissue repair is one such procedure where receptacles are made at the floor of the pulp chamber by enlarging the canal orifices and TAP is placed directly over those, before restoring with Glass Ionomer Cement (GIC). This technique is described in the 2020 American Academy of Pediatric Dentistry (AAPD) pulp therapy guidelines. [23] The success rate is further improved when MTAP is used instead of TAP. [11]

G. Regeneration and revascularization of permanent immature teeth

Traditional approaches to treating immature non-vital permanent teeth are the use of inverted gutta-percha cones, the use of customized cones and apexification with Calcium Hydroxide. Later, CH got replaced with MTA apexification as it introduced numerous benefits over CH, such as being quick to achieve apexification, inducing a more thickened and completed apical barrier, the need for fewer visits and eliminating undesired effects of CH. (Discoloration, reducing fracture resistance of radicular dentine) Yet, there are a few

drawbacks in apexified immature teeth including large root canals, thin fracture-prone roots, and short root length, thus reduced crown: root ratio. [24]

Regenerative endodontics is a biologically driven approach to managing immature permanent teeth, where disinfected radicular space is filled with the host's tissues, allowing the tooth to undergo apexogenesis and root maturation with the elimination of clinical symptoms of apical periodontitis. [23] Apart from these advantages, this technique can be practiced for instances where apexification is challenging or even impossible to achieve, due to very immature roots. (Cvek stage 1 to 3). [24] This revolutionary approach has attracted the attention of many clinicians with promising results. [25] All three terms, "endodontic regeneration", "revascularization" and "revitalization" is synonymously used for this therapy. The term "Revitalization" is adopted by the European Society of Endodontology (ESE) position statement in 2016 as root canal space is occupied by not only blood vessels but some other soft tissues and hard tissues as well. [26]

The first goal in revitalization is to properly disinfect the canal. With the use of TAP, this can be achieved, even in non-instrumented canals as it can combat the diverse microbial population encountered within infected canals and radicular dentine. [7, 24] Then bleeding into the canal is evoked by over-instrumenting beyond the apical end, so undifferentiated stem cells are accumulated in the canal space. These cells in the fibrin scaffold will undergo differentiation in the presence of growth factors in the blood into root-forming cells. [27] Compared to TAP, CH has the additional effect of enhancing the release of growth factors such as TGF- β 1 which promote migration, proliferation and differentiation of stem cells. The presence of bacterial antigens of residual bacteria in the root canal system retards the final phenotype conversion of stem cells, thus compromising the success of revitalization therapy. One study demonstrated that TAP was a more effective medicament than CH in terms of vitality and adhesion of stem cells with regard to regeneration. In this regard, TAP may be better than CH for revitalization procedures. [28, 36]

H. Other uses of different medicaments

TAP is incorporated into gutta-percha points (medicated gutta-percha points) and Zinc Oxide based root canal sealers to reduce the incidence of root canal reinfection and provide an extended antibacterial property. Although CH incorporated root canal sealers provide the advantages of providing an antibacterial effect and facilitating root end healing by dissociating into Ca^{2+} and OH^- , the same dissociation makes CH based sealers lose their solid content and create voids. [29]

TAP has been tested as an intra-canal medicament applied to a scaffold. [30] This facilitates antibiotics to persist in low concentration for an extended period without further dilution and is cytotoxic. [4] Incorporation of TAP into Glass Ionomer cement empowers the restorative material with antibacterial properties without reducing its' mechanical properties or chemical bonding to tooth substance. These materials have been tested in atraumatic restorative technique in primary molars with satisfactory results. [31, 32]

V. DRAWBACKS OF INTRA-CANAL MEDICAMENTS

I. Discoloration of dentine

Use of iodoform containing CH pastes as intra-canal dressing can result in discoloration of the crown leading to a major esthetic problem. Leaving CH residues in the crown and prolong use is the main reason for that. Equally, one of the major drawbacks of TAP is that Minocycline is incorporated into the dentine matrix by chelation into Calcium ions causing discoloration. There are multiple strategies to overcome this incident. Avoiding the use of Minocycline is one way of doing that. Instead, Double Antibiotic Paste (DAP) containing only Metronidazole and Ciprofloxacin can be used without significant alteration of the antibacterial spectrum. Several other antibiotic preparations, replaced Minocycline with Clindamycin, Augmentin, or Cefaclor (second-generation Ciprofloxacin) minimized the possibility of tooth discoloration with even better antibacterial effects. [11, 33] Another described method is sealing off dentinal tubules by applying a coat of bonding agent. Once the discoloration is already established, internal bleaching is an effective remedy to reduce or eliminate the discoloration. [34]

II. Negative effect on dentine microhardness and flexural strength

TAP has an undesirable demineralizing effect on dentine, subjecting it to altering mechanical properties and increasing brittleness. Studies state that the Calcium chelation effect of Minocycline and low pH (pH = 2) of TAP causing dentine erosion are reasons behind this. When used in higher concentrations, like 1g/ml TAP, reduction in microhardness is significant and when compared with MTAP of the same concentration, it is found at 500µm from the pulp-dentinal complex. [35] To minimize this detrimental effect, Methylcellulose based TAP (1mg/ml) is recommended.

Due to the dentine protein denaturing effect prolonged use of CH is not recommended. Andreasen et al, 2002 reported a 50% reduction in the flexural strength of dentine 1 year following CH treatment. [37] But another study reported that a similar reduction of flexural strength can occur even after 7-84 days of application. [38]

III. Undesirable effect on stem cells

TAP, used for root canal disinfection in endodontic revitalization therapy, has a toxic effect on apical papilla cells. This toxicity is more profound in higher TAP concentrations such as 1g/ml. Hence, lower concentrations (0.1-2 mg/ml) of TAP are recommended to overcome the negative cytotoxic effect. [10, 39]

IV. Removal of the Medicament

At the final session of regenerative endodontic therapy, any leftover antibiotic paste should be entirely eliminated to maximize the survival rate of stem cells. But the removal of TAP is a challenging task due to the binding capacity of TAP to radicular dentine. Various irrigation and instrumentation techniques have been tried, aiming to complete the removal of TAP including the Endovac system, Endoactivator, photon-induced photo-acoustic streaming, XP endo finisher file, and combined use of NaOCL and EDTA. Topçuoğlu et al stated

that the use of 1.5% NaOCl combined with EDTA to be effective than the use of NaOCl alone. [40] Regardless of the irrigation and instrumentation technique used, TAP cannot be 100% removed from the radicular dentine. [41] CH is also a challenging intracanal medicament in terms of removal and inadequate removal could compromise the sealing of the canal by root canal sealers. All the above methods described for TAP removal are used similarly for CH removal, although the most commonly used technique is using a master file to the working length with EDTA and sodium hypochlorite. [9, 42]

VI. CONCLUSIONS

Intra-canal medicaments play a major role in the endodontic treatment both in the deciduous and permanent dentition. The evidence-based application of these medicaments proves a successful long-term outcome. TAP and CO are the major medicaments in clinical practice with promising results. The added advantage of intra-canal medicaments is the minimal systemic effects as the materials are used only within the canal. The ongoing research in regeneration procedures using intra-canal medicaments would make a major change in endodontic management.

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