



Antibiotics: A changing scenario in Regenerative Endodontics

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ABSTRACT

The main aim of Endodontics is to either prevent the endodontic disease or to treat it. This is achieved by maintaining the pulp health in cases of pulp inflammation. If there is pulp necrosis, pulp health can be maintained by regenerating the healthy pulp tissue. Hence various researches and the clinical studies tried to regenerate the healthy functioning pulp-dentin complex. Regenerative dentistry aims to biologically replace the dental tissues along with their supporting structures. Regenerative Endodontics can be defined as “biologically based procedures designed to replace damaged structures such as dentin, root structures, and cells of the pulp-dentin complex.” Root canal anatomy is complex, hence even after mechanical instrumentation, there exists some portions of the root canal that remain untouched. Only instrumentation cannot completely eliminate the microbes existing into the root canal. Hence there is need to additionally irrigate the canals and also using medications is required to disinfect the root canal and promote healing. This article aims at focussing on various antibiotics used and role of these materials to disinfect the canals during revascularization treatment.



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INTRODUCTION

Regeneration in Endodontics is defined as “Biologically based procedures designed to physiologically replace damaged tooth structures, including dentin and root structures, as well as cells of the pulp-dentin complex.” Regeneration therapy is considered as the most promisable future in dentistry as well as in Endodontics. It is an evolving treatment option and aims at restoration of infected immature teeth. The main objectives of regeneration is to

effectively disinfect and create a microenvironment favourable for host cells and matrix. The presently viable regenerative procedure is revascularization. Tooth containing vital pulp is resistant to bacterial invasion (Baumgartner *et al.*, 2008). However necrotic pulp readily gets infected and colonized by bacteria. The infection in root canal of permanent teeth that is immature with open apex and succeeding periapical inflammation are usually instigated by diverse bacterial flora having both aerobic and anaerobic bacteria. Over time, the anaerobic infection dominates. There occurs symbiotic relationship that leads to virulence increase by organisms in that ecosystem. Hence the endodontic therapy aims at complete disruption of the ecosystem (Baumgartner *et al.*, 2008). Root canal anatomy is complex, hence even after mechanical instrumentation, there exists some portions of the root canal that remain untouched (Peters *et al.*, 2001). Only instrumentation cannot completely eliminate the microbes existing into the root canal. Hence there is need to additionally irrigate the canals and also using medications is required to disinfect the root canal and pro-

mote healing. This article aims at focussing on various antibiotics used and role of these materials to disinfect the canals during revascularization treatment.

'Rationale of using Antibiotics'

Antibiotics are used as a supplement to proper non-surgical or surgical endodontic therapy. Removing the microbes causing the infection should be the main aim. Antibiotics are given so that the contamination in the root canal and periapical area is suppressed. Systemic antibiotics act through blood stream. In an infected or necrotic pulp, the blood supply is lacking. Hence the systemic antibiotics are unable to kill the microbes. Hence for an antibiotic to be in direct contact with the bacteria, topical antibiotics might be efficient in a extremely inhibited and constricted pulp space (Mohammadi and Abbott, 2009a).

ADA codes for pulpal regeneration procedures

ADA in 2011-2012 documented pulp regeneration as an endodontic procedure and gave it codes.

1. First Phase (D3351)

This phase includes debridement and antimicrobial medication.

2. Intermediate Phase (D3352)

It includes replacement of antibacterial medication.

3. Final Phase (D3354)

Completion of the regenerative procedure.

Instrumentation of Root Canal Walls

"According to clinical considerations of American Association of Endodontists (AAE), root canal walls should be slightly instrumented or should not be instrumented at all". It stated that controlling the root canal contamination must be accomplished by irrigation solutions and intracanal medications (Law, 2013; Endodontic Diagnosis, 2013). So as to preserving the vitality of the stem cells present in apical tissues, mechanical debridement should be avoided, thereby encouraging regeneration (Law, 2013).

However the bacteria colonized into the root canal may be resistant to the irrigants and medicaments used. Hence using irrigation alone without debridement might lead to persistence of infection into the root canal that leads to regeneration failure. Therefore it is a matter of controversy whether or not to mechanically debride the root canal walls for regeneration procedure. However minimal instrumentation of the canal can be helpful to properly debride the root canal and also preserve the vitality of the apical stem cells.

Irrigation solutions used for Regenerative Endodontic Therapy

Sodium Hypochlorite (NaOCl)

Sodium Hypochlorite is considered as important solution used for irrigation during root canal treatment. It is used usually in concentrations amid 0.5% and 6%. It is considered as powerful antibacterial agent, destroying most microbes on direct contact. It also efficiently dissolve the pulp tissue and its remains and collagen (chief organic component of dentin). It is reported that 0.5% or 5% NaOCl, with or without EDTA that results in efficient decrease in bacteria count into the root canal. Hypochlorite is considered as the only irrigant to bring about complete destruction of root canal biofilms (Siqueirajr et al., 2002). However it is important for NaOCl to be in close contact with the biofilm. It is noted that in most bordering areas of the root canal system including "fins, anastomoses, apical canal and lateral canals", there is problem in penetration of the NaOCl. Also the 'exudate from apical area, pulpal tissue, dentinal collagen and microbial biofilms' tend to counter the efficacy of Hypochlorite (Haa-pasalo et al., 2000). Exposure of root canal walls for longer period to Hypochlorite have unfavourable effect on dentin elasticity and flexural strength. Concentration of NaOCl greater than 3% have favourable antimicrobial action but is cytotoxic to PDL stem cells and stem cells of apical papilla (SCAP) (Martin et al., 2014).

Chlorhexidine (CHX)

Chlorhexidine is also being widely used either by itself or in combination with NaOCl in RET (Kontakiotis et al., 2015). The canal is irrigated with normal saline amid the two irrigants. CHX is a strong antibacterial agent with low cytotoxicity. Penetrating the cell wall or the outer membrane of the micro-organism, it targets the bacterial cytoplasmic membrane (Mohammadi and Abbott, 2009b). The material has a property of substantivity so there is slow release of the drug even after many days and removal of the drug. It has been reported that CHX when used as antimicrobial material in revascularization procedure showed continuous root development after 24 months (de Jesus Soares et al., 2013).

Ethylene diamine Tetra Acetic Acid (EDTA)

EDTA is also included into the irrigation protocol. It has been reported that irrigating the canal with 17% EDTA promote the survival rate of the SCAPs. It also reverses the cytotoxic consequence of higher concentrations of NaOCl solution on SCAPs. EDTA also releases the entangled growth factors from dentin, therefore this promotes the differentiation of DPSC

seeded onto the dentin surfaces into odontoblastic cells (Galler *et al.*, 2011). Hence EDTA is efficient in creating favourable environment for promoting of tissue regeneration. Its use might have a good influence in Regenerative Endodontic Therapy (RET) (Galler *et al.*, 2011).

Intracanal Medicaments

Rationale of combining antibiotics

Infections within the root canal are considered as polymicrobial including aerobic and anaerobic bacteria. Root canal anatomy is very complex hence using single antibiotic cannot completely eliminate bacteria. Also if non-specific antibiotic therapy is used, it could lead to destruction of normal microbial flora and also this will help the pathogenic flora to repopulate into the canal. In addition the combination of the antibiotics can also help prevent development of the bacterial resistance (Abbott, 2000).

Calcium Hydroxide

Calcium Hydroxide is the prime root canal medication used in Endodontics. It is white, odourless powder, dissolves little in water, and has increased pH (Chandak *et al.*, 2018). 'Dr B.W. Hermann' in 1952 stated the use of calcium hydroxide in amputating the vital pulp. Calcium hydroxide has high alkaline pH (about 11.5-12), that has antimicrobial action. Its disinfecting action is efficient for at least one week and then consequence reduces extremely. 'Banchs and Trope' showed that stem cells at the periapical area along with segregation of the same results in constant root formation. These cells also re-establishes the blood supply to the pulp. Calcium hydroxide is not active against restricting the growth of *Enterococcus faecalis* which is considered as chief bacteria into the non successful root canal treatment. It also responsible for weakening of the root structure. It is extremely hard for removing the material from the root canal (Doyon *et al.*, 2005). In Permanent dentition with exposed apex, the dentin walls are thin. If used calcium hydroxide during revascularization strategy for such teeth can predispose to the fracture. Calcium hydroxide is stated to be cytotoxic to the SCAP and this might be harmful to the revascularization process (Banchs and Trope, 2004).

'Triple Antibiotic Paste (TAP)'

In 1951, Grossman was the first person to use antibiotics in Endodontics. It is recognized as "polyantibiotic paste (PBSC)". The PBSC consists of "penicillin, bacitracin, streptomycin and caprylate sodium". Penicillin was for Gram +ve organisms, bacitracin for penicillin resistant strains, streptomycin was for Gram -ve organisms and caprylate

sodium was to target yeasts" (Abbott, 2000). Now in recent years the TAP has been introduced containing 'ciprofloxacin, metronidazole, and minocycline'.

Composition of 3Mix-MP

"According to Hoshino et al"

- "Antibiotic (3Mix) – ratio 1:1:1"

"Ciprofloxacin 200mg, Metronidazole 500mg, Minocycline 100mg".

- "Carrier (MP) – ratio 1:1"

"Macrogol ointment, Propylene glycol".

"According to Takushige T et al"

The drugs are crushed and converted into powder and amalgamated in a ratio of 1:3:3 (3Mix) and dispartated either with macrogol-propylene glycol (3Mix-MP) or a canal sealer (3Mix-sealer).

Tetracycline

This includes " Tetracycline-HCl, Minocycline, Demeclocycline and Doxycycline". These are broad spectrum antibiotics and their efficacy is against wide range of microorganisms. They are bacteriostatic group of antibiotics. If it is bacteriostatic, there is no lysis of the bacterial cells and therefore no antigenic by product or endotoxin is released into the infected area. They inhibit mammalian collagenases preventing tissue degeneration and inhibiting clastic cells that result in anti-resorptive activities. It is used in Endodontics for eliminating the smear layer from instrumented canals, irrigating the retrograde cavity during periapical surgeries and also used as drug into the root canal (Abbott, 2000; Mohammadi and Abbott, 2009a). It can be used in combination with corticosteroids and this combination is shown to have antibacterial, anti-inflammatory, and also anti-resorptive action. This will help reduce inflammatory reaction in periapical area (Mohammadi and Abbott, 2009a). Lately " tetracycline nanoparticles loaded with calcium sulfate composite beads" is confirmed to be helpful in the treating periodontal diseases as well as intracanal medicaments to combat the infection around the periapical area (Ghangurde *et al.*, 2017).

Metronidazole

It is a nitroimidazole compound exhibiting broad spectrum against bacteria including protozoa and anaerobic bacteria but less effective against aerobic bacteria. It is widely used in periodontology in local as well as systemic forms due to its wide spectrum that is anaerobic bacteria, gram positive

and gram negative bacilli. Metronidazole act onto the bacteria cell by “permeation into the membrane and then binding to the DNA, thereby unsettling the helical structure causing rapid death”. It has been reported that combining metronidazole with ciprofloxacin showed decrease in bacterial biofilm including *E.faecalis*.

Ciprofloxacin

It is a second generation fluoroquinolone antibiotic. It is efficacious against “*E.coli*, *Legionella pneumophila*, *H.influenza*, *Pseudomonas aeruginosa*, methicillin sensitive but not methicillin resistant *Staphylococcus aureus*, *Streptococcus* species, *E.faecalis*” (Drusano et al., 1986).

TAP is considered as effective material for disinfection of necrotic pulps, thereby creating a proper environment for tissue regeneration process. Bose et al found that RET using TAP and calcium hydroxide caused noteworthy growth of the root compared to MTA apexification. When applied TAP, the percentage of dentin thickness was increase compared to calcium hydroxide or formocresol. “ (Lovelace et al., 2011) showed that after disinfection of the root canal, evoking hemorrhage induced collection of undifferentiated stem cells into canal from periapical area”. Such cells participate in regenerative process after efficient decontamination. Hence it has been stated that root canals sanitized with NaOCl and TAP had little chances to develop periapical lesion and also had greater chances of boosting the growth of the root and canal wall thickness (Lovelace et al., 2011).

The major disadvantage of using TAP was sever discoloration caused due to minocycline component present in it that fixes to calcium of dentin and forms insoluble complexes. Hence, to prevent discoloration, pulp chamber has to be closed with dentin bonding agent ensuring that TAP remains below CEJ. While removing the TAP clinician should remove the entire TAP from the pulp chamber and wipe clean with cotton pellets soaking into absolute alcohol.

Modified TAP was introduced in that minocycline was replaced with clarithromycin, cefuroxime or cefaclor or clindamycin to prevent discoloration.

Alkaline Materials used in Regenerative Endodontic Therapy

Mineral Trioxide Aggregate (MTA)

“Tricalcium silicate, dicalcium silicate, bismuth oxide, calcium sulfate dehydrate or gypsum and tricalcium aluminate” are the major component of the MTA. MTA is considered as bioactive material that produces calcium hydroxide. This Calcium Hydroxide releases calcium ions that help in attachment of

the cells and their proliferation. It has a high pH that is 12.5 that exerts antimicrobial properties. MTA is used as coronal barrier over scaffold or blood clot preventing coronal leakage and entry of microorganisms (Kontakiotis et al., 2015).

Biodentin

“Tricalcium silicate, dicalcium silicate, zirconium oxide, calcium carbonate, calcium oxide and iron oxide” are the major components of Biodentin. It is also used as a barrier over blood clot.

Scaffolds containing antibiotics used in Regenerative Endodontic therapy

In current years, there is progress of new experimental strategies for regenerating dental pulp and disinfection of the canal that leads to improved treatment outcome of regenerative therapy. The initial study for scaffolds united “MET and CIP” in a decomposable polymer to get “Bimix (MET/CIP) antibiotic containing nanofibers” and used in applying as “drug delivery systems” in RET. The EB method is for proper root canal disinfection forming a fibrin based scaffold for interaction with endogenous stem cells and growth factors. The EB method has rather used triple antibacterial (“ciprofloxacin [CIP], metronidazole [MET], and minocycline [MINO]”) or a double -antibacterial (MINO free). A biocompatible nanofiber based intracanal drug delivery system was put forward so as to create environment that is devoid of bacteria for tissue regeneration (Shimizu et al., 2012). Using these therapeutic nanofibers, a 3D tubular construct was made that may be effortlessly inserted in the canals of necrotic teeth. It has been reported that when exposing infected dentin to “triple antibiotic-eluting nanofibers” showed noteworthy bacterial demise Shimizu et al. (2012). This helps release of antibiotics and therefore disinfecting canal and also helps enhance cell adhesion.

CONCLUSIONS

Eliminating bacteria from root canal play a major role in endodontic treatment success. Combining irrigation and disinfection has been proved effective in regenerative therapy. Sodium hypochlorite is mandatory to accomplish this objective. Disinfection can be accomplished by using intracanal medicaments like calcium hydroxide and TAP. Newer blends of antibiotics can be assessed for effective revascularisation therapy.

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Conflict of Interest

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