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Research Article

Antiseptics and Antibiotics Used in Regenerative Endodontics

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ABSTRACT

Contemporary endodontics and the future of endodontics are based on regenerative strategies. Success of these regenerative endodontic treatments depends on disinfection of the root canal system. Current research in endodontics focuses on identifying the optimal methods of disinfection of root canal systems to achieve predictable results in revascularization therapy. Although the use of sodium hypochlorite for disinfection is mandatory, additional intracanal medicaments are also required to realize this goal. This article reviews the antiseptics and antibiotics used for achieving disinfection of root canals for regenerative procedures.

Key words: regenerative endodontics, revascularization, disinfection, sodium hypochlorite, antibiotics, chlorhexidine.

INTRODUCTION

Regenerative endodontic procedures can be defined as biologically based procedures designed to replace damaged structures, including dentin and root structures, as well as cells of the pulp-dentin complex. The objectives of regenerative endodontic procedures are to regenerate pulp-like tissue, ideally, the pulp-dentin complex; regenerate damaged coronal dentin, such as following a carious exposure; and regenerate resorbed root, cervical or apical dentin [1]. One of the presently viable regenerative procedures is revascularization of the root canal. This is done via a blood clot that is induced by over-instrumentation of the root canal system. The primary parameter influencing success of this revascularization treatment is the disinfection of the root canal space [2]. This article reviews the various agents used for root canal disinfection during revascularization treatment, along with a review of literature assessing these materials.

Need for disinfection during revascularization

The rationale of revascularization is that if a sterile tissue matrix is provided in which new cells can grow, pulp vitality can be reestablished. Revascularization protocols are derived from the observations of reimplanted and auto- transplanted teeth in experimental animals in which necrotic pulp, devoid of infection, provide a matrix into which the cells from the periradicular region could grow and reestablish pulp vascularity [1].

This sterile matrix that is created is the key to success of treatment. One area wherein maximum research is being carried out in the field of revascularization is the different antimicrobial agents used as intracanal medicaments to bring about the disinfection. Since almost no instrumentation is carried out (in contrast to routine root canal treatment where disinfection is brought about by the action of instruments synergistically with irrigants), the disinfection protocol relies on the chemical actions of the irrigants and medicaments. This may be likened to the Lesion sterilization and tissue repair (LSTR) therapy which employs the use of a combination of antibacterial drugs for the disinfection of pulpal and periradicular lesions [3].

Antiseptics used for disinfection in regenerative endodontics

Sodium hypochlorite

Hypochloric acid disrupts several vital functions of the microbial cell, resulting in cell death. NaOCl is commonly used in concentrations between 0.5% and 6%. It is a potent antimicrobial agent, killing most bacteria instantly on direct contact. It also effectively dissolves pulpal remnants and collagen, the main organic components of dentin. Hypochlorite is the only root canal irrigant of those in general use that dissolves necrotic and vital organic tissue. In some articles hypochlorite is reported to kill the target microorganisms in seconds, even at low concentrations, although other reports have published considerably longer times for the killing of the same species. It has been shown that 0.5% or 5% NaOCl, with or without EDTA for irrigation, resulted in considerable reduction of bacterial counts in the canal when compared with irrigation with saline [4]. This is in accordance with several published reports on the antibacterial activity of sodium hypochlorite in vitro. Hypochlorite is also the only irrigant capable of brining about destruction of root canal biofilms [5-7].

In vivo, the antimicrobial effectiveness of NaOCl is limited. The poorer in vivo performance compared with in vitro is probably caused by problems in penetration to the most peripheral parts of the root-canal system such as fins, anastomoses, apical canal and lateral canals. Also, the presence of inactivating substances such as exudate from the periapical area, pulp tissue, dentin collagen, and microbial biofilms counteract the effectiveness of NaOCl [8]. Long term exposure of dentin to a high concentration of

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sodium hypochlorite can have a detrimental effect on dentin elasticity and flexural strength, based on some in vitro studies [9,10]. Considering this limited antibacterial activity in lieu of the anatomical complexities of the root canal space, intracanal medicaments are used for antimicrobial action. However, the use of sodium hypochlorite in endodontics in general and in revascularization treatment, in particular is to be considered mandatory.

Calcium hydroxide

Regenerative dental procedures have a long history, originating around 1952, when Dr. B. W. Hermann reported on the application of calcium hydroxide in a case report of vital pulp amputation. Calcium hydroxide has been used commonly as an intracanal medicament. This is mainly due to its high alkaline pH (about 11.5 - 12), which results in its antibacterial action. The disinfecting action of calcium hydroxide is effective for at least for one week and the effect drastically reduces thereafter [11]. Furthermore, calcium hydroxide has three important disadvantages: it is ineffective against Enterococcus fecalis which is the predominant microbe isolated in failed root canal treatment [12]; it is known to weaken the root structure [13] and, complete removal of the material is extremely difficult if not impossible [14]. Of these disadvantages, a point of concern in regenerative strategies is the potential weakening of tooth structure by this material. Revascularization strategies are employed in immature teeth with open apices, and these teeth inherently have thin dentinal walls that are predisposed to fracture.

It was also shown by Banchs and Trope that the stem cells at the periradicular region following differentiation result in continued root formation. These cells also help in res-establishing the vascularity of the pulp. Calcium hydroxide is cytotoxic to the cells of any viable pulp tissue and the stem cells from the apical papilla. This would be detrimental to the revascularization process [15].

Chlorhexidine gel

A recent report showed the efficacy of a 2% chlorhexidine gel in the revascularization treatment. Chlorhexidine (CHX) has antimicrobial properties and low cytotoxicity. It is also effective against most endodontic pathogens. CHX permeates the microbial cell wall or outer membrane and attacks the bacterial cytoplasmic or inner membrane or the yeast plasma membrane. In high concentrations, CHX causes coagulation of intracellular components [16]. Removal of the material is easy and the most importantly, the material exhibits substantivity ie., the antibacterial action is long-standing even after removal of the material. Chlorhexidine is also a matrix metalloproteinase inhibitor [17]. MMPs have been shown to be agents of tissue destruction and markers of inflammation. However, similar to other endodontic disinfecting agents, the activity of CHX depends on the pH and is also greatly reduced in the presence of organic matter.

Chlorhexidine may be a safe alternative if this medication came into contact with periapical tissues in immature teeth. CHX, in a clinical study showed that, when used as the antibacterial agent in revascularization treatment, resulted on continued root development at the end of 24 months [18]. Also, in contrast to calcium hydroxide, CHX did not cause obliteration of the root canal space by calcification. The root development was also reported to be faster than when other materials were used for root canal disinfection.

Antibiotics

Root canal infections are polymicrobial, consisting of both aerobic and anaerobic bacteria. Because of the complexity of the root canal infection, it is unlikely that any single antibiotic could result in effective sterilization of the canal. A combination would be needed to address the diverse flora encountered. The most commonly used medicament is a combination of three antibiotics, referred to as a triple antibiotic paste (TAP). This formulation was first used by Sato et al. and contains metronidazole, ciprofloxacin, and minocycline. This combination is commercially available as 3-MIX MP [19].

Metronidazole is a nitroimidazole compound. It is selectively toxic to anaerobic microbes. It also exhibits broad spectrum antimicrobial activity against against protozoa and anaerobic bacteria. The presence of certain redox proteins reduces the nitro group of this compound and generates free radicals that enter the cell and induce DNA damage. This results in rapid cell death [20]. Tetracyclines, which includes doxycycline and minocycline are primarily bacteriostatic, inhibiting protein synthesis by binding to 30S ribosomes in susceptible organisms. They exhibit broad spectrum of activity against gram positive and gram negative microorganisms. Minocycline is a semisynthetic derivative of tetracycline with a similar spectrum of antibacterial activity. Tetracycline inhibits collagenases and matrix metalloproteinases,and is not cytotoxic. It also increases the level of interleukin-10, an anti-inflammatory cytokine [21, 22]. Ciprofloxacin is a synthetic floroquinolone with rapid bactericidal action. It inhibits the enzyme bacterial DNA gyrase, which nicks the double stranded DNA, introduces negative supercoil and then reseals the nicked end. The bactericidal action probably results from digestion of DNA by exonucleases whose production is signaled by the damaged DNA. It exhibits very potent activity against gram negative bacteria but very limited activity against gram positive bacteria. Most of the anaerobic bacteria are resistant to ciprofloxacin. Hence it is often combined with metronidazole in treating mixed infections. Metronidazole and ciprofloxacin can generate fibroblasts, all of which will enhance success of the regenerative procedure [21-23]. It has also demonstrated that while each of these antibiotics did not result in complete bacterial elimination, a combination resulted in complete elimination of microbiota [23].

Hoshino et al. recommended a ratio of 1:1:1 of metronidazole (500 mg), minocycline (100 mg) and ciprofloxacin (200 mg) for the 3Mix formulation. The carrier or vehicle recommended was propylene glycol, in the ratio 1:1, with polyethylene glycol or macrogol. This combination is termed MP [23]. The standard recommended

mix contains 1 part of MP mixed with 7 parts of 3Mix. This formulation was modified by Takushige et al., who recommended mixing the antibiotics is a formulation of 3:3:1, wherein 3 parts of metronidazole and 3 parts of minocycline are mixed with 1 part of ciprofloxacin. This can be mixed with MP or root canal sealers. However, the mixture with sealers is presently not recommended [24].

Comparing TAP, calcium hydroxide, and formocresol as intracanal medicaments in non-vital young permanent tooth, the triple antibiotic group showed the highest percentage increase in the dentin wall thickness compared with the other two groups [25]. It was also reported that TAP can help promote functional development of the pulp–dentin complex. TAP contains both bactericidal (metronidazole, ciprofloxacin) and bacteriostatic (minocycline) agents and hence may be considered the material of choice to allow for successful revascularization.

It has however been argued that antibiotic pastes may cause bacterial resistance or allergic reactions. Infact the original antibiotic combination used in endodontics (Grossman's paste which was composed of Penicillin, Bacitracin, Steptomycin and Nystatin or caprylate sodium) fell out of favor for this reason. Also, minocycline may cause tooth discoloration because of photoactivation. Minocycline binds to calcium ions via chelation to form an insoluble complex. It should be limited to the root canal because of the potential risk of tooth discoloration [26]. Lenherr et al investigated the discolouration potential of various endodontic materials in bovine tooth model. The most severe discolouration was reported to be detected after 12 months in triple antibiotic paste group followed by ledermix paste indicating the effect of tetracycline [27]. A biantibiotic paste, omitting minocycline from the formulation has also been recommended but this mixture does not have the antobacterial potency of TAP. Cephalosporins (cefaclor) has also been suggested as an alternative to minocycline in the triple antibiotic paste [28]. Arestin [29] and amoxicilllin [30] have also been recommended as alternatives to minocycline. However, no clinical trials exist on the efficacy of these alternative formulations on the success of revascularization treatment and hence this combination can neither be recommended nor refuted at the present moment.

CONCLUSIONS

Disinfection of the root canal system is the key to success of revascularization treatment in endodontics. Sodium hypochlorite has to be used mandatorily to achieve this goal. Disinfection should also be achieved by using intracanal adjuncts like triple antibiotic paste or chorhexidine. Long term clinical trials are needed to evaluate if chlorhexidine gel is as effective as the triple antibiotic paste in revascularization. New combinations of antibiotics should also be evaluated for successful revascularization therapy.

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