

PalArch's Journal of Archaeology of Egypt / Egyptology

ANTIBIOTICS AS ROOT CANAL MEDICAMENTS - A REVIEW OF LITERATURE

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Prathiba Reichal C, Anjaneyulu K, Lakshminarayanan Arivarasu. ANTIBIOTICS AS ROOT CANAL MEDICAMENTS - A REVIEW OF LITERATURE-- Palarch's Journal Of Archaeology Of Egypt/Egyptology 17(7), 661-673. ISSN 1567-214x

Keywords: Antibiotics, endodontics, medicaments, bactericidal activity.

ABSTRACT

Antibiotics are valuable armamentarium that are available to healthcare professionals for management of bacterial infections. Antibiotics can be applied both locally and systemically based on the trauma of the teeth during endodontic treatment. The local application of antibiotics is found to be more effective when compared with systemic application. The aim of the current study is to review the antibiotics that are used as medicaments in root canal treatments. The search of data and articles was performed from 1990 to 2015 through pubmed and google scholar. Various antibiotics have been tested in numerous studies and each study had some advantages. Various antibiotics have been tested in numerous studies and each study had some advantages. The antibiotics that are reviewed in this article are ledermix paste, metronidazole, tetracycline, clindamycin and triple antibiotic paste, antibiotic containing scaffolds and so on. PBSC and PBSN are the first proposed antibiotics used in dentistry, given by Grossman. Ledermix paste is used as a pulp capping agent due to presence

of demethylchlortetracycline. Septomixine forte contains polymyxine B Sulphate which is used as an intracanal medicament. Triple Antibiotic Paste and Antibiotic containing scaffolds are used for canal disinfection and pulp revascularization. These antibiotics are found to be effective in reducing the bacteria count in the root canal system of the infected teeth.

INTRODUCTION

Antibiotics are used as an adjunct to endodontic treatment in numerous ways. It is applied locally, systematically and prophylactically. The local or intracanal use of antibiotics in the form of medicaments is common. Inflammation of the pulp occurs mainly due to microorganisms. Although infection of the pulp is most frequently caused by advanced dental caries [1]. Cone-beam computer tomography is a method used to evaluate the root canal preparation since it reveals the traumatised fractures, resorptions of root, calcified teeth and avulsed teeth where the teeth is displaced from its socket [2][3][4]. Dental trauma is the most commonly seen injuries in childrens that leads to ellis fracture [5]. Complete structureless tooth can be treated by using laminates and veneers but infection of the pulp leads to contamination arising from dental plaque or saliva during cavity preparation, by micro leakage at the margins of restoration and by direct invasion of microorganisms. vitality of the pulp is tested by using sensor holder, thermal test and electric pulp test [6]. These agents are compounds that are capable of destroying microorganisms [7][8]. They can be in either chemical antiseptics or antibiotics. Chemical antiseptics are generally very effective antimicrobial agents which will kill microorganisms. These toxicities are time dependent so their use should be limited to short term contact. Antibiotics are of different classes that are found to be effective against microorganisms but are markedly less toxic to mammalian cells at similar concentrations [9].

Bacteria that are present within the root canals are accessible to mechanical instrumentation and irrigation. However, bacteria can also be seen within the accessory canals, lateral canals, dentinal tubule and other root canal. These areas are generally inaccessible to mechanical instrumentation and irrigation. Endoactivator and endodontic needles are used now-a-days for irrigating root canals prior to the application of medicaments [10]. Hence, the use of an antimicrobial medicament is indicated [11]. The filling of a prepared root canal with an antimicrobial medicament allows the medicaments components to diffuse through the dentin, the canal irregularities and the apical foramen to the periapical. This helps to expose the bacteria present in these periapical lesions by reducing the number of active bacteria [12]. Antimicrobial medications are also required to avoid inter-appointment contamination of root canal. The antibiotic chloramphenicol is used against staphylococci and *N.meningitidis*. Tetracycline, minocycline, doxycycline and bacteriodes are effective against enterobacteriaceae and many other bacteria that cause caries. The microbial world has responded to the introduction of antimicrobial substances into which ecological balances in a variety of ways [2]. It is apparent that the indiscriminate use of antimicrobial drugs by doctors everywhere has vitiated their benefits [4]. It is becoming increasingly more apparent that the administration of antibiotics without definite indication has very definite harmful effects. the first reported local use of an antibiotic in endodontic treatment was in 1950 when grossman used a polyantibiotic paste

known as PBSC (Penicillin, bacitracin, streptomycin and caprolate sodium). PBSC contains penicillin which targets gram-positive organisms, bacitracin target penicillin-resistant strains, streptomycin for gram-negative organisms and caprolate sodium to target yeast. Later nystatin replaced caprolate sodium as an antifungal agent in a similar medicament and named as PBSN (Penicillin, Bacitracin, Streptomycin and Nystatin) [13].

Ledermix paste, a combination of ledermix with calcium hydroxide, septomixine forte, clindamycin, metronidazole and triple antibiotic paste are the antibiotic medicaments used in dentistry. Ledermix paste is composed of demethylchlortetracycline, and demeclocycline, which is a product of mutant strain of streptococcus aureofaciens and triamcinolone. Triamcinolone is an anti-inflammatory corticosteroid. The paste contains neomycin-sulphate and chloramphenicol as the antibiotics, and prednisolone as corticosteroid [14].

Ledermix will diffuse through the dentinal tubules. This diffusion is not blocked either by the smear layer or by cementum. The paste can be used effectively against progressive root resorption in traumatised teeth, thereby eliminating inflammatory root resorption without damaging periodontal membrane [15]. Similarly, tetracyclines are broad spectrum antibiotics that are primarily used as bacteriostatics. Tetracyclines are found to be effective against gram-negative bacteria. Tetracycline include - HCl, minocycline, demeclocycline and doxycycline as their broad spectrum antibiotics [16]. Tetracycline has additional properties other than antibacterial effects. They are inhibitions of mammalian collagen and clastic cells that help in preventing tissue breakdown and provide an anti-resorptive property. Inflammatory diseases are found to be blocked by tetracyclines, thereby enhancing the formation of collagen and bone formation [17]. Septomixine forte contains two antibiotics namely neomycin and polymyxin B Sulphate. This antibiotic only has a limited spectrum of activity. Neomycin is effective against gram-negative bacteria and is ineffective against bacteroides [18]]. Clindamycin is effective against many usual oral pathogens including actinomyces and peptococcus. It is a particularly effective invitro against black pigmented prevotella and porphyromonas species [19]. The aim of the current study is to review the different types of antibiotics that are used as root canal medicaments in the field of dentistry.

PBSC AND PBSN

In 1951, the father of Endodontics, Gossman proposed the antibiotic known as PBSC that contains Penicillin, Bacitracin, Streptomycin and Caprolate sodium. Initially, it was used as a local antibiotic in endodontics [7]. It potentially had many therapeutic effects but there were also drawbacks like allergic reactions and frail activity towards anaerobic bacteria. Hence, in 1951 the Food and Drug Administration (FDA) prohibited PBSC from endodontics. Later, PBSN (Penicillin, Bacitracin, Streptomycin and Nystatin) was introduced which is an antifungal property [20].

Ledermix paste:

Ledermix paste was first developed by Schroeder and Triadan in 1960 and was marketed in 1962. Ledermix is a glucocorticoid and its development is based on the use of a corticosteroid to prevent inflammation and pain [21]. Ledermix paste is used in the combination of corticosteroid, tetracycline antibiotic, triamcinolone acetonide, demeclocycline HCl, with 1% of concentration in a polyethylene glycol base. The paste diffuses through the dentinal tubules and cementum to reach the periodontal and periapical tissues. The concentration of demeclocycline with ledermix paste is high enough to be effective against susceptible bacteria. However, the concentration is not sufficient to enter into the peripheral parts of dentine and periradicular tissues [22]. Inhibitory levels of demeclocycline is achieved in the dentine that is present adjacent to the root canal. Heling and pecht have reported that both ledermix paste and tetracycline of 3% in a hydrous base are effective in reducing the amount of *Staphylococcus aureus* in the dentinal tubules. It is stated that side effects are less common in ledermix paste since the amount of paste entering into the periradicular tissues are too small [23].

Ledermix paste has no damaging effects on the periodontal membrane and it is effective against progressive root resorption in traumatically injured teeth [24]. Wong and Sae-Lim of 2002 evaluated the effect of immediate placement of intracanal ledermix paste on root resorption of delayed replanted monkey teeth [25]. the ledermix group showed significantly more complete healing [26]. Chen et al of 2008 evaluated the individual influence of triamcinolone and demeclocycline on external root resorption after extended extraoral dry time of 60 minutes. The teeth treated with ledermix paste, triamcinolone and demeclocycline had more significant healing when compared with gutta percha and replanted after 60 minutes [27].

Ehrmann et al of 2003 investigated the relationship of postoperative pain associated with three different treatment regimes for infected teeth with acute apical periodontitis after complete biochemical debridement of the root canal system in patients needed for emergency relief of pain. It was reported that the patients with teeth dressed with ledermix paste had less pain than that experienced by patients who were dressed with Calcium hydroxide or no dressing at all [28]. Kim et al of 2000 found that discolouration of tooth are reported after the application of Ledermix when exposed to sunlight. A dark grey-brown staining is evidently seen in both mature and immature, but the immature tooth is severely discolored. Staining of the crown occurred only when the pulp is filled with ledermix paste and not in the root. Hence, it was suggested that placement of ledermix was restricted to below the gingival margin, so that such effects can be minimised [29].

Septomixine forte

Septomixine forte contains two antibiotics namely, neomycin and polymyxin B sulphate. These two had only a limited spectrum of antibiotic property. Neomycin is effective against gram-negative bacteria and is ineffective against bacteroides and their related species. Polymyxin B Sulphate is ineffective against gram - positive bacteria and it was demonstrated by Tang et of 2004 [30]. Septomixine forte is ineffective in inhibiting residual intracanal bacterial growth.

Clindamycin

Clindamycin is found to be effective against many of the usual oral pathogens including Actinomyces, Eubacterium, Fusobacterium, Propionibacterium, Microaerophilic Streptococci, Peptococcus, peptostreptococcus, Veillonella, Prevotella and Porphyromonas. It is specifically an effective invitro against black-pigmented Prevotella and Porphyromonas species [31]. Molander and Dahlen of 2003 investigated the effect of clindamycin on root canal infections and apical periodontitis when placed as an intracanal dressing [32].

The presence and absence of bacteria is determined in samples taken immediately after removal of the dressing. Comparatively, Calcium hydroxide showed more advantage than clindamycin in canal dressing. However, clindamycin was found to be successful in eliminating the bacterial growth in the infected teeth. Lin et al of 2003 compared the antibacterial effect of clindamycin and tetracycline in bovine dentinal tubules model, as well as using agar diffusion test. Their findings showed that clindamycin significantly reduced the amount of viable bacteria in each dentin layer compared with tetracycline [33].

Metronidazole

Metronidazole exhibits a broad spectrum of activity against protozoa and anaerobic bacteria, since it is a metronidazole compound. It is used both systematically and topical due to its effective activity against anaerobic cocci, gram-negative and gram-positive bacteria. Metronidazole readily permeates bacterial cell membranes and then binds to DNA, thereby disrupting its helical structure that leads to rapid cell death [34]. Roche and Yoshimori of 1997 tested the antibacterial activity of metronidazole against clinical isolates from odontogenic abscess in vitro. They showed that metronidazole had excellent activity against anaerobes but it is not effective against aerobes. Metronidazole caused inhibition of growth of all obligate anaerobes tested and was more effective than calcium hydroxide/ calcium hydroxide plus camphorated paramonochlorophenol (CPMC) paste against two of the strains [35]. Lima et al of 2001 evaluated the effectiveness of Chlorhexidine - based or antibiotic - based medications in eliminating *E.faecalis* biofilms [36]. They found that there were significant differences between the formulations that are tested. The association of Clindamycin with Metronidazole significantly reduced the number of cells in one day old biofilms. Wang et al of 2003 evaluated the effect of a metronidazole - Chlorhexidine solution on the treatment of chronic - apical periodontitis and found that 97.6% of the cases healed [37][38]. Yu et al of 2000 evaluated the effect of a paste made of erythromycin succinate, Metronidazole and CPMC to sterilize the root canal system [39]. The clinical observation of 1800 patients with fully developed root apices and acute or chronic apical periodontitis showed that there was no significant differences in root canal disinfection when the erythromycin - ethylsuccinate - metronidazole - CPMC mixture was compared with Formocresol. Therefore, the irritability and toxicity of the treatment could be reduced by using the erythromycin - metronidazole - ethylsuccinate - CPMC mixture. It is said that root canal disinfection with this mixture is a safe and effective method to promote the healing of periapical diseases [40].

Disinfection is more important than cleaning, where irrigants play a very important role [41]. Hoelscher et al of 2006 evaluated the disinfection of dentinal tubules using five antibiotics (Amoxicillin, Penicillin, Clindamycin, Metronidazole, and Doxycycline) added to Kerr pulp Canal sealer against *E.faecalis*. They found that all mentioned antibiotics except for metronidazole, could enhance the antimicrobial efficacy of the sealer [42]. Krithidatta et al of 2007 evaluated the disinfection of dentinal tubules using 2% CHX gel, 2% metronidazole gel, bioactive glass in comparison with Calcium hydroxide. The findings stated that the overall percentage inhibition of bacterial growth was 100% with 2% CHX gel. The inhibition of growth was moderate with 2% metronidazole gel, followed by bioactive glass and calcium hydroxide.

Role of Antibiotics:

a) Ciprofloxacin:

Ciprofloxacin has been used as an antibiotic to eliminate bacteria that are present in the necrotic immature permanent teeth which is prior to regenerative procedures. Kamocki et al of 2015 synthesized scaffolds containing different concentrations of ciprofloxacin to improve the cell viability thereby preserving antimicrobial properties of ciprofloxacin [43].

b) Tetracycline:

Tetracyclines are bacteriostatic agents that are proved to be potential against gram-negative bacteria including putative periodontopathogens namely *Actinobacillus actinomycetemcomitans* (A.a.). The group of tetracyclines are used in the management and treatment of periodontal diseases and also for bone grafting in any periodontal defects [44].

c) Metronidazole:

Metronidazole is found to be effective against anaerobic species. Metronidazole is a group of drugs that includes nimorazole, metronidazole and tinidazole. Metronidazole does not affect the commensal aerobic flora. It is proved to be effective in pericoronitis, acute ulcerative gingivitis, periapical lesions and in osteomyelitis. It can also be used in chronic progressive periodontitis where anaerobic bacteria are present within them [45]

Triple antibiotic paste:

Aerobic and anaerobic bacterial species are responsible for root canal infections. The use of a single antibiotic may not be effective because of the complexity of root canal infections. Hence, a combination of antibiotics are required for the reduction of likelihood of the development of resistant bacterial strains. The combination of Triple Antibiotic Paste is Metronidazole, Ciprofloxacin and Minocycline [46]. Hoshino et al of 1996 evaluated the antibacterial effect of TAP mixture with or without the addition of rifampicin, on the bacteria taken from the dentine of infected root canals. The mixture of antibiotics (TAP) with rifampicin were able to consistently disinfect all the samples [47]. Takushige et al of 2004 tested the potential of a polyantibiotic paste consisting of Ciprofloxacin, Metronidazole and Minocycline, in an clinical outcome of so called - 'Lesion Sterilization and Tissue Repair'

(LSTR) therapy with periradicular lesions compromised primary teeth. They reported that the clinical symptoms such as gingival swelling, sinus tracts, induced dull pain and pain on biting disappeared after the treatment of TAP [48].

Advantages of Triple Antibiotic Paste:

Triple Antibiotic Paste is used for any lesion sterilization and for tissue therapy since they require a combination of antibacterial drugs for complete disinfection of any pulpal lesions or non carious cervical lesion [49][50]. A combination of metronidazole, ciprofloxacin and minocycline are available as 3MIX MP and was first used by Sato et al [51]. The use of TAP contains metronidazole of 500mg, ciprofloxacin of 200mg and minocycline of 100mg in the ratio of 1:1:1 as recommended by Hoshino et al. propylene glycol and macrogol ointment are recommended as a carrier for TAP mixed at as ratio of 1:1 [47]. Takushige et al modified the formulation and recommended a 3:3:1 ratio of metronidazole, minocycline and ciprofloxacin. This can be mixed and used as root canal sealers, which is currently not recommended [48]. The use of TAP as an intracanal medicament for more than 5 weeks resulted in excellent infection control and continuous osseous healing of the periapical lesion and root apex formation [52][39].

Role of TAP in revascularisation/ regeneration:

Proper disinfection of root canal results in reverse inflammation and tissue proliferation. Disinfection of root canal, placement of matrix and bacterial tight seal of access opening are important steps for revascularization of teeth [53]. Since, the infection is due to polymicrobial agents, TAP is used. During infectious conditions the level of matrix metalloproteinases 9 increases that is used as a marker [54]. Triple Antibiotic Paste showed the highest percentage increase in dentin wall thickness when compared with Calcium hydroxide and Formocresol [55]. A necrotic bicuspid has achieved revascularization by using TAP due to the presence of both bactericidal and bacteriostatic agents within them that allows successful revascularization [56].

Disadvantages of Triple Antibiotic Paste:

The only disadvantage of using TAP is discoloration of the tooth. The presence of minocycline causes discoloration since it binds with the calcium of dentin forming insoluble complexes that results in discoloration. Extended use of Triple Antibiotic Paste for a longer time produces extensive discoloration [57][5] [50] [51]. The carrier, propylene glycol might be difficult to remove from the dentin surface and reopening of tooth to remove TAP introduces risk of contamination.

Antibiotic containing scaffolds:

Antibiotics **containing** scaffolds are introduced to overcome the drawbacks of TAP. Biologically safe antibiotic drug delivery system is achieved by using polymer-based antibiotic-containing electrospun scaffolds that are used in regenerative endodontics, similar to Novamin that consists of calcium, sodium and phosphosilicate which helps in bone regeneration [58]. This enhances the drug delivery due to its higher surface fibres that are arranged in an interconnecting structure. Hence, it improves drug adaptation to canal walls

[59]. Scaffolds degrade over time but removal of scaffolds is not necessary since it reduces the risk of contamination [60]. The drug release system is classified as rapid, intermediate and delayed, based on the polymer that is used. Root maturogenesis and regeneration of pulp-dentine complex can be achieved by using electrospun nanocomposite fibrous material, recommended by Bottino MC et al [61]. Dental erosion is treated by using Grape seed extract and cranberry which are natural products containing polyphenols [62]

Antibiotic compound	Antibiotic present	Usage
PBSC	Penicillin, Bacitracin, Streptomycin and Caprolate sodium	antibiotic
PBSN	Penicillin, Bacitracin, Streptomycin and Nystatin	antibiotic
Ledermix paste	Demethylchlortetracycline	Pulp capping agent
Septomixine forte	Neomycin Polymixine B Sulphate	Intracanal medicament
Clindamycin	clindamycin	Intracanal medicament and dressing
Metronidazole	Metronidazole	antibiotic
Triple Antibiotic Paste	Metronidazole, Ciprofloxacin and Minocycline	Canal disinfection and pulp revascularization
Antibiotic-containing scaffolds	Metronidazole or Ciprofloxacin	Canal disinfection and pulp revascularization

Side effects

The most common side effects of antibiotics in endodontics infections are hypersensitivity reactions and drug fevers to penicillin and other beta lactam antibiotics. They may cause nausea, vomiting, and gastrointestinal distress that are found in common with macrolides and photosensitivity in tetracycline, clarithromycin and azithromycin are associated with less gastrointestinal irritations when compared with erythromycin [57].

CONCLUSION

Antibiotic application for the root canal system is more effective when given locally than systematically. Ledermix has anti-inflammatory, antibacterial antiresorptive activities that helps to reduce the periapical inflammatory reaction including clastic cell mediated resorption. Clindamycin can reduce the bacterial load inside the root canal system significantly. A Triple Antibiotic Paste is found to be very effective in the disinfection of the root canal system. Among the documented side effects, the most common effects are hypersensitivity and drug fever reactions.

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