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Review Article

Intracanal medicaments: A review

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ABSTRACT:

The crucial goal for an endodontic treatment to be successful is absolute eradicationof microorganisms and to prevent reinfection. The disinfection protocol depends on the ample usage of irrigants and intracanal medicaments. Intracanalmedicaments arechemical agents sealed within the root canal system; used between appointments as an anodyne and/ or antimicrobial agent. Hence, it is essentialfor clinicians to understand the action and effects of intracanal medicamentand incorporate them into the disinfectionstrategy to maximize the chances of healing.The current review was performed to check for various intracanal medicaments available and their effect.

Keywords: Antimicrobial Peptides, Calcium hydroxide,Intracanal medicament,Natural intracanal medicaments, Triple Antibiotic Paste.

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INTRODUCTION

Apical inflammatory lesions are caused by microorganisms, and the aim of endodontic treatment is to prevent and control pulpal and periradicular infections. To decrease the amount of bacteria in the root canal system, a number of strategies have been implemented, such as different mechanical instrumentation techniques, irrigation regimes, and intracanal medications.[1]

Disinfection of pulp space is an important step during and after cleaning and shaping.It mostly entails preparing and cleaning the root canal space using irrigantsin addition to endodontic instruments.Nonetheless, in some clinical scenarios, the polymicrobial character of the endodontic infection necessitates the administration of an intracanal medication in conjunction with the irrigants.

Intracanal medicaments are used for root canal disinfection as part of controlled asepsis in an infected root canal and their role is secondary to shaping and cleaning of the root canal.[2]It is defined as a chemical agent sealed within the root canal system; used between appointments as an anodyne and/ or antimicrobial agent.(American Association Of Endodontics 2020)

RATIONALE

The rationale behind intracanal antiseptic medication is to eliminate bacteria from the root canal and prevent reinfection.It is possible for residual bacteria in an obturated root canal to either survive and eventually multiply or to be denied access to nutrition and perish.

Even though chemical mechanical preparation has a significant cleansing impact, not all of the bacteria that are housed in dentinal tubules within the root can be eliminated by this method.

If a disinfectant is not applied to the canal in between visits, the residual bacteria may continue to grow and sometimes reach the same concentration as at the beginning of the previous session.

As a result, using an efficient intracanal medicament is necessary to disinfect the root canal.[3]

Intracanal medicaments can be used in various endodontic conditions including multiple visit endodontics after trauma or in regenerative endodontics. These medicaments can be applied for different periods varying from 1 week to several

months.The American Association of Endodontists recommends the application of intracanal medicament for a minimum of 1 week for clinical regenerative procedures.[4]

Ideal requirements of Intracanal Medicaments

1. It should be an effective antimicrobial agent.
2. It should be nonirritating to the periradicular tissues.
3. It should remain stable in solution.
4. It should have a prolonged antimicrobial effect.
5. It should be active in the presence of blood, serum, and protein derivatives of tissue.
6. It should have low surface tension.
7. It should not interfere with the repair of periradicular tissues.
8. It should not stain tooth structure.
9. It should not induce a cell-mediated immune response.[2]

Classification Of Intracanal Medicaments [5]

TABLE: 1

GROSSMAN'S CLASSIFICATION	
ESSENTIAL OILS	Eugenol
PHENOLIC COMPOUNDS	Para ChloroPhenol Camphorated Parachloro phenol (CMPP) Formocresol Glutaraldehyde Cresatin
HALOGENS	Sodium hypochlorite Iodide
QUATERNARYAMMONIUMCOMPOUNDS	Aminoacridine

TABLE: 2

GENERAL CLASSIFICATION	
ESSENTIAL OILS	Eugenol
PHENOLIC COMPOUNDS	Phenol Camphorated Monochloro phenol(CMCP) Camphorated Parachloro phenol (CMPP) Camphorated chloroxylenol(ED84) Cresol Creosote(beech wood) Thymol
ALDEHYDES	Formocresol Glutaraldehyde Paraformaldehyde
HALOGENS	Sodium hypochlorite Chloramine T Iodine
QUATERNARYAMMONIUMCOMPOUNDS	Aminoacridine
ANTIBIOTICS	Triple Antibiotic paste (ciprofloxacin, metronidazole, minocycline Grossman paste Cortico steroids(ledermix) LSTR
CALCIUM HYDROXIDE	

TABLE: 3

INGLE'S CONVENTIONAL ANTISEPTICS AS INTRACANAL MEDICAMENTS	
PHENOLIC COMPOUNDS	Eugenol Camphorated monoparachlorophenol (CMCP) Parachlorophenol (PCP) Camphorated parachlorophenol (CPC) Metacresylacetate (Cresatin) Cresol Creosote (Beechwood) Thymol
ALCOHOLS	Ethyl alcohol Isopropyl alcohol
HEAVY METAL SALTS	Salts of silver, mercury, copper
HALIDES	Sodium hypochlorite Iodine- Potassium iodide
CATIONIC DETERGENTS	Quaternary ammonium compounds

A. Phenol and phenol derivatives: Chemicals of the phenol group such as phenol, formocresol, cresatin, parachlorophenol (monoparachlorophenol), camphorated phenol, and camphorated parachlorophenol (CMCP) have a long history in endodontics as locally used root canal disinfecting agents.

Using varying amounts of the phenol component, they have either been introduced into the pulp chamber using a moist cotton pellet (vapor action) or by filling the canal with liquid. It was thought that because of their volatile properties, it could penetrate dentinal tubules and anatomical irregularities.

However, it was later demonstrated that these compounds have a short life and their volatility can diffuse through the temporary fillings and also through the periapical tissue causing toxicity.[6]

B. EUGENOL: Eugenol is a volatile phenolic constituent of clove essential oil obtained from *Eugenia caryophyllata* buds and leaves. Its derivatives have been used in medicine as a local antiseptic and anesthetic. The wide range of eugenol activities includes antimicrobial, anti-inflammatory, analgesic and antioxidant. [7]

Eugenolhas Antiseptic and anodyne effect.It inhibits intradental nerve impulses.It has a well-documented, but limited antimicrobial effect and is applied primarily for its pain- relieving effect.It is now considered as a periradicular tissue toxin and its use is no longer recommended.[2]

C. HALOGENS: Halogens include chlorine, iodine and Sodium hypochloriteused in various formulations in endodontics. They are potent oxidizing agents with rapid bacterial effects. [3]

Chlorinated solutions have been used for many years to irrigate root canals. They are also used as intracanal dressings in the form of chloramine-T, an N-chloro-tosylamide sodium salt. Iodine, in the form of Iodine potassium iodide (IKI), is a very effective antiseptic solution with low tissue toxicity.

IKI is an effective disinfectant for infected dentin and can kill bacteria in infected dentin in 5 minutes in vitro. It releases vapors with a durable antimicrobial effect.The solution can be prepared by mixing 2 g of iodine in 4 g of potassium iodide; this mixture then is dissolved in 94 mL of distilled water. [5]

Sodium hypochlorite

Hypochlorite was first used by Semmelweis in 1847 as a hand disinfectant. This initial use of potassium hypochlorite was substituted by sodium hypochlorite by carrel and Dakin for wound disinfection. [6]

Tissue proteins react with hypochlorite to produce nitrogen, formaldehyde, and acetaldehyde. The proteins disintegrate as a result of the peptide linkages being disrupted. This process results in the formation of chloramine, which is crucial to the antibacterial activity of amino groups because it replaces the hydrogen in the amino groups (-HN-) with chlorine (-NCl-). As a result, pus and necrotic tissue disintegrate, making it easier for the antimicrobial agent to penetrate and disinfect the affected areas.

Dakin suggested a 0.5% solution (Dakin‟s Solution). At this concentration toxicity is low and it affects only necrotic tissue. A 1% sodium hypochlorite solution,however, is more potent and provides an increased antimicrobial effect.

Greater concentrations of NaOCl (2.5 and 5%) attack living tissue without making a major therapeutic difference (i.e., increase in antibiotic activity).

Bystrom and Sundqvist have shown that using a 0.5% or 5% concentration of Na OCl did not affect the rate of root canal disinfection. Although NaOCl's activity is intense, it is transient. Therefore, it is best to apply the chemical to the root canal every other day.[5,8]

D. Formaldehyde: Formaldehyde, used as formocresol (19% formaldehyde, 35% cresol, 15% glycerol and 31% water-buckley'sformocresol) is highly toxic, mutagenic, and carcinogenic. Historically, it has been used extensively in endodontic therapy.
It is volatile and releases antimicrobial vapors when applied to a cotton pellet for pulp chamber disinfection.All formaldehyde preparations are potent toxins with antimicrobial effectiveness much lower than their toxicity.[6]

E. Steroids: Steroids have been used locally, within the root canal system to reduce pain and inflammation.Medications such as Ledermixpaste(Lederle Pharmaceuticals,Wolfratshausen, Germany) has been advocated as an initial dressing, particularly if the patient presents with endodontic symptoms. Ledermix paste contains anti-inflammatory corticoid 1% triamcinolone acetonide in combination with the broad-spectrum antibiotic demeclocycline.It is a nonsetting, water-soluble paste material for use as root canal medicament or as a direct or indirect pulp capping agent.
Clinical effect is a rapid relief of pain associated with acute inflammatory conditions of the pulp and periodontium.[9]

F. POLYANTIBIOTIC PASTE: Grossman mentioned about the utilization of polyantibiotic paste as an intracanal medicament in weeping canals or where there was a continuous seepage from the pulp space.PBSC containing penicillin, bacitracin, and streptomycin with cryolite as a vehicle. PBSCN combination was also advocated with N standing for neomycin as an antifungal agent. [2]

G. Calcium hydroxide: Calcium hydroxide is the most popular intracanal medication in use. It was introduced by Hermann in 1920. [10]
It is a white odourless powder with the chemical formula $Ca(OH)_2$ and a molecular weight of 74.08 (Farhad&Mohammadi 2005).[12] It has low solubility in water (around 1.2 g L^{-1} at 25 °C), which decreases with a rise in temperature (Siqueira& Lopes 1999).[13] It has been demonstrated that the dissociation coefficient of $Ca(OH)_2$ (0.17) controls the slow release of both calcium and hydroxyl ions (Rehman *et al.* 1996).[14] This low solubility is a useful clinical characteristic as an extended period is necessary before it becomes solubilized when in direct contact with fluids from vital tissues (Spångberg&Haapasalo 2002).[15]

Mechanism of action

1. Antimicrobial activity of calcium hydroxide is related to the release of hydroxyl ions in an aqueous environment. Hydroxyl ions are highly oxidant free radicals that show extreme reactivity, reacting with several biomolecule.

They destroy bacteria by:

- Damaging the cytoplasmic membrane
- Protein denaturation
- Damaging bacterial DNA [5,11]

Effect of liquid vehicle - The vehicles mixed with $Ca(OH)_2$ powder play an important role in the overall dissociation process because they determine the velocity of ionic dissociation causing the paste to be solubilized and resorbed at various rates by the periapical tissues and from within the root canal. The lower the viscosity, the higher will be the ionic dissociation.[16]

2. Antifungal activity-While fungi are more frequently discovered in filled root canals of teeth that have gotten infected after treatment or in teeth that have not responded to treatment, they have also been discovered in initial root canal infections on occasion. Fungi often range in frequency from 1% to 17% in infected root canals. Numerous other yeast species, such as Saccharomyces species, Candida glabrata, Candida guilliermondii, Candida parapsilosis, Candida krusei, Candida inconspicua, Candida dubliniensis, and Candida tropicalis, have also been identified from the oral cavity.

All Candida species (C. albicans, C. glabrata, C. guilliermondii, C. krusei, and C. tropicalis) have been shown to have either an equal or greater resistance to aqueous calcium hydroxide than did E. faecalis. Additionally, it has been shown that C. albicans cells have a high level of resistance to Ca(OH)2. It's possible that C. albicans is unaffected by the alkalinity of saturated Ca(OH)2 solution because the fungus can thrive at a variety of pH levels. Furthermore, Ca(OH)2 pastes might supply the Ca2+ ions required for Candida proliferation and morphogenesis. The lack of effectiveness of Ca(OH)2 against Candida albicans may be explained by these processes.

3. Anti-inflammatory action- The elevated pH of Ca(OH) 2 inhibits the substrate adherence capacity of macrophages and decreases or eliminates the amount of MMP-8, improving tissue circulation and controlling exudation as immunomodulatory effect. Endogenous inflammatory mediators like Interleukin- 1α and TNF-α play a role in regulation of inflammation, tissue destruction and denaturation of proinflammatory cytokines.[17]

Vehicles can be classified as follows-

a. Aqueous- sterile water, normal saline.

b. Viscous- glycerine, polyethylene glycol, propylene glycol.
c. Oil-based vehicles such as olive oil, silicone oil, camphor (the oil of camphorated parachlorophenol), some fatty acids (including oleic, linoleic, and isostearic acids), eugenol and metacresylacetate (Fava & Saunders 1999).[18]

Commercially, calcium hydroxide for intracanal disinfection is available as a nonsettable form which can be removed with minimum instrumentation. [2]

Limitations of Calcium Hydroxide

The handling and proper placement of Ca(OH)2 present a challenge to the average clinician. The removal of Ca(OH)2 is frequently incomplete, resultingin a residue covering 20% to 45% of the canal wall surfaces, even after copious irrigation with saline, NaOCl, or EDTA.

Endodontic sealers based on zinc oxide and eugenol may set faster with residual Ca(OH)2. Specifically, it could impede the root filling's seal and lower the treatment's quality. The ineffectiveness of Ca(OH)2 against a number of endodontic infections, including as E. faecalis and C. albicans, is another cause for concern.[6]

H. CHLORHEXIDINE: Chlorhexidine (CHX) is a wide-spectrum antimicrobial agent, active against gram positive, gram-negative bacteria and yeasts.It is recommended both as a root canal irrigantand as an intracanal medicament. Its pH is between 5.5 and 7. As a medicament, it can be used as: 2% CHX gel or Mixture of CHX and Ca(OH)2. [6]

Mechanism of action- CHX is a positively charged hydrophobic and lipophilic molecule that interacts with phospholipids and lipopolysaccharides on the cell membrane of bacteria.

Its effectiveness stems from the way the negatively charged phosphate groups on the microbial cell walls interact with the positively charged molecule, changing the osmotic balance of the cells. This makes the cell wall more permeable, enabling the CHX molecule to enter the bacteria.[19]

CHX has been shown to be effective against both E. faecalis and Candida albicans. [6]

Triple antibiotic paste: It takes more than one antibiotic to eradicate harmful flora, hence a cocktail of medications known as "triple antibiotic paste" (TAP) is advised. It combines minocycline, ciprofloxacin, and metronidazole in a specific ratio of 1:1:1.

TAP's efficacy against dentin infected with Escherichia coli was initially evaluated in vitro. Its ability to kill bacteria from carious dentin and diseased pulp was also evaluated.It was found that the mixture of antibiotics is sufficiently potent to eradicate the bacteria.[20]

TAP is used in the cases of periapical lesions, external inflammatory root resorption, root fracture, and treatment flareups, which is a common complication of endodontic treatment

Composition and preparation -According to Hoshino *et al.* - Antibiotic 3 mix—ratio is 1:1:1 ;Ciprofloxacin 200mg, metronidazole 400mg, and minocycline 100 mg

Carrier (MP)—ratio 1:1; Macrogol ointment and propylene glycol.

Preparation-*3Mix MP*: It is prepared using metronidazole 33%, minocycline 34%, and ciprofloxacin 33% with a macrogol and propylene glycol (MP) paste.[21]

Objective behind combining the antibiotics- Conventional antibiotics, when used individually, are unable to generate a "bacteria-free zone" in the canal due to the involvement of diverse microbiota in tooth infection.

Additionally, antibiotic medication may also eliminate the native bacterial flora in the canal, resulting in a more aggressive infection. As a result, to avoid microbial resistance, all endodontic illnesses must be treated with a mix of antibiotics.[20]

The most important drawback is the tooth discoloration after treatment studies, which indicated that TAP was associated with the highest amount of discoloration as compared to other medicaments and control group, which was related to of minocycline. Different medicament replacements, such as amoxicillin and Cefaclor (a member of the second-generation cephalosporins), have been used to prevent the problem.In addition to avoid the discoloration dentin bonding agent (resin) is used to avoid penetration of minocycline and to avoid discoloration, tooth bleaching procedure is used to reverse the discoloration.[21]

Frequency of medication

According to the general principles of root canal management, disinfectant dressings should preferably be renewed in a week and not longer than 2 weeks because dressings become diluted by periapical exudate and are decomposed by interaction with the microorganisms.[5]

I. NATURAL INTRACANAL MEDICAMENTS

Propolis

Propolis is a natural resinous mixture, which is produced by honeybees. The raw propolis is composed of basically 50% resins, 30% waxes, 10% essential oils, 5% pollen, and 5% various organic compounds. It consists of highly active bioflavonoids which have antimicrobial, antioxidant, and antiinflammatory properties. The antioxidant property of propolis is attributed to its radical scavenging ability, which was better than vitamin C and that the antiinflammatory property is due to the presence of

caffeic acid phenethyl ester.It has been proved to be a less irritating solution and were effective in eliminating *Enterococcus faecalis.*Propolis was also found to induce the production of high-quality tubular dentin. Propolis has been known to be a potent sensitizer, is allergenic, and may lead to eczematous contact dermatitis in some cases.[22]

Curcumin(Haridra - Turmeric)
Active constituents of turmeric are the flavonoid curcumindiferuloylmethane- the main yellow bioactive component of turmeric has a wide spectrum of biological actions, including antimicrobial, anti-inflammatory and antioxidant activities.Curcumin has significant antibacterial activity maybe attributed to its ability to eliminate the extracellular polysaccharide matrix of E.faecalisand thus can be used in endodontics for root canal failures.[23]

Aloe barbadensis Miller (Kumari - Aloe)
Aloe vera is used in cases of apthous ulcers, lichen planus, alveolar osteitis.*A. vera* gel has inhibitory effectson *Streptococcuspyogens* and *E. faecalis* because of anthraquinone.However, its bactericidal activity is found to be less than Ca $(OH)_2$.

Acacia nilotica Linn. (Babool - Indian gun Arabic)
Babool has been proved as an effective medicine in the treatment of malaria, sore throat (aerial part) and toothache (bark).It has shown to possess antibacterial activity against *Streptococcus mutans* and *E. faecalis*. Antimicrobial function is believed to be due to tannins, phenolic compounds, essential oil, and flavonoids.[24]

Morindacitrifolia Linn. (Ashyuka - Indian mulberry)
It has been demonstrated that morinda inhibits the growth of pathogenic bacterial strains, including Shigela, P. aeruginosa, Staphylococcus aureus, Bacillissubtilis, E. coli, and Salmonella.Antibacterial, anti-inflammatory, antiviral, anticancer, antihelmenthic, analgesic, hypotensive, and immune-boosting properties are only a few of the many medicinal benefits of its juice. On E. faecalis-infected root canal dentin, the antibacterial efficacy of 2% CHX gel, propolis, Morindacitrifolia juice, and Ca (OH)2 has been compared. Propolis and M. citrifolia were found to be efficacious against E. faecalis in the dentin of removed teeth.[24]

Cinnamon
Cinnamon also known as C. zeylanicum belongs to the Lauraceaefamily.Extracts for the same is obtained from the leaf, bark, fruit and flowers.The antibacterial activity exhibited by cinnamon is due to the presenceof vanillic, caffeic, gallic, protocatechuic, p-coumaric, and ferulicacidsin the extracts. Cinnamon extract has better antibacterial effectiveness against E. faecalis compared to calcium hydroxide agents.[25]

Citrus limonum *Risso. (*Nimbuka - Lemon)
Fresh lemon solution is used as root canal medicament due to its wide antibacterial efficiency including *E. faecalis*. Oil of lemon is topically used for the treatment of oral thrush and stomatitis.

AzadirachtaIndica
Commonly known as neem. It has an excellent and wide range of antimicrobial and antifungal activity. The most important active constituents that contribute to the wide range of antimicrobial activity are azadirachtin, nimbolinin, nimbin, nimbidin. Intracanal medicaments and irrigants that contained neem have been tried and tested over time.

Eucalyptus Oil
It is an essential oil, obtained from the leaf of Eucalyptus with anti-inflammatory and antibacterial activities. It has a wide spectrum of antimicrobial action and its potential use as a vehicle for calcium hydroxide has indicated towards its use as being an effective intracanal medicament.

Uncaria Tomentosa
An Amazonian herb possessing anti-inflammatory, antiviral, antibacterial, and antioxidant activities. It consists of oxindole alkaloids, triterpenes, vegetal steroids, phenolic compounds, glycosides, tannin and flavonoids which contribute to its antimicrobial activity. It can be used as an intracanal medicament.

Ocimum Sanctum
Widely known as Tulsi, it belongs to the Labiateae family and exhibits antibacterial, antifungal and antiviral properties. Ocimum sanctum's essential oil extract has excellent antibacterial effect which increases with increase in concentration.

Allium Sativum
Also referred to as Garlic. With both bacteriostatic and bactericidal actions, it possesses a wide range of antimicrobial qualities. Its capacity to prevent the synthesis of toxins and the expression of pathogenic enzymes accounts for its antibacterial efficacy.

Cumimum Cynimum
Commonly known as cumin, it has been reported to have excellent antioxidant, antibacterial, antifungal and analgesic properties. Activity against E. Faecalis tested and presents with good biocompatibility, effective to be used as an intracanal medicament.

Glycyrrhizaglabra
Liquorice is known for anti-inflammatory, antiviral and anticarcinogenic properties. Among various active ingredients is Glycyrrhizin, a triterpenoid compound which is active against different strains of S. Mutans. It has greater biocompatibility when compared to calcium hydroxide.[24,26]

Recent Advancements InIntracanal Medicaments
Antimicrobial peptides (AMPs)

The majority of AMPs are cationic oligopeptides that are either artificially created or obtained from natural sources, such as bacteria, fungus, plants, and animals. They are viable substitutes that have limited bacterial resistance, strong antibacterial potency, and good biocompatibility.

There is ongoing discussion over the mechanism by which AMPs eradicate bacteria (Bechinger&Gorr 2017).[27]Compared to traditional antibiotics, it is more difficult for bacteria to become resistant to AMPs on a large scale because they lack specific protein targets in bacteria. More knowledge of AMPs' antibacterial actions could aid in the development of more targeted and potent AMPs for intracanal use as drugs.[26]

Nanoparticles

Nanoparticles, including metal, polymeric and ceramic are commonly mixed in the calcium hydroxide paste as additives to enhance the antimicrobial potency of calcium hydroxide (SyAgossa et al., 2021).[28]

Due to its broad-spectrum antibacterial action and straightforward production methods, silver nanoparticles (AgNP) are among the most researched metal nanoparticles against E. faecalis (Halkai et al., 2018).[29]The future of intracanal medications may lie in the combination of antibacterial medicines with various delivery systems. When compared to either single AMP or single AgNP, the antibacterial activity of the AMP-AgNPnanocomposites was much higher (Ye et al., 2022).[30] This could be explained by the synergistic effect that AMPs produce when they induce the creation of bacterial transmembrane pores, which allow AgNPs to reach internal targets.[26]

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