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REVIEW ARTICLE

Vehicles for Antibiotic Formulation in Endodontic Treatment: A Narrative Review

Nor Hazwani binti Jamaludin[1], Nurul Ain binti Ramlan[1]*, Afiq Azizi bin Jawami[1], Nurul Aida binti Ngah[2]

[1] Centre of Study for Comprehensive Care, Faculty of Dentistry, Universiti Teknologi MARA Sungai Buloh Campus, Jalan Hospital, 47000 Sungai Buloh, Selangor, Malaysia
[2] Centre of Oral & Maxillofacial Surgery Studies, Faculty of Dentistry, Universiti Teknologi MARA Sungai Buloh Campus, Jalan Hospital, 47000 Sungai Buloh, Selangor, Malaysia

* Corresponding author's email: ainramlan@uitm.edu.my

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ABSTRACT

Triple antibiotic paste (TAP) has been widely utilized in endodontic therapy to treat bacterial infections within the root canal system. The efficacy and biocompatibility of TAP largely depend on the choice of vehicle used for its preparation. This narrative review aims to provide a comprehensive overview of the various vehicles employed in TAP formulations and their impact on clinical outcomes, effective dissolution, uniform distribution within the paste, and long-term stability. Propylene glycol, macrogol (polyethylene glycol), chlorhexidine, and antibiotic-eluting fibers are among the used vehicles for TAP preparation. Each vehicle possesses unique properties affecting the paste's antimicrobial activity, physical characteristics, and biocompatibility. The choice of vehicle in TAP formulations should be guided by considerations such as antimicrobial spectrum requirements, paste consistency preferences, and patient-specific factors. Optimal treatment outcomes with minimal side effects can be achieved when clinicians carefully consider the benefits and drawbacks of each vehicle. Further research exploring the comparative efficacy and safety profiles of different TAP vehicles is warranted to refine clinical guidelines and enhance treatment protocols in endodontic therapy.

INTRODUCTION

TThe microorganisms present in the root canal can potentially invade the surrounding periapical tissue, causing both pulpal and periapical diseases (Kakehashi et al., 1965; Sundqvist, 1993). The affected tooth may require endodontic treatment, which could involve one or more visits depending on criteria such as the complexity of the case and the severity of the infection. The utilization of an intracanal medicament has been shown to significantly improve the process of disinfection after chemomechanical procedures (Alsubait et al., 2020). Intracanal medicament is a chemical agent sealed within the root canal system and used between appointments as an anodyne and/or antimicrobial agent ("Glossary of Endodontic Terms 10th Ed," 2020). Calcium hydroxide, antibiotic paste, and corticosteroid base material are examples of intracanal medicament (Hasselgren et al., 1988; Hoshino et al., 1996; Negm, 2001).

Regenerative endodontic procedures (REP) have shown favorable results in treating an immature tooth diagnosed with pulpal necrosis or apical periodontitis. These procedures have shown potential for increasing root length, root wall thickness, as well as potentially restoring the tooth vitality responses (Hargreaves et al., 2021). REP requires the administration of an intracanal medication that possesses antibacterial qualities (Lovelace et al., 2011; Murray et al., 2007). Subsequently, bleeding is induced to establish a matrix that facilitates the development of new dental-pulpal tissue within the root canal space (Xie et al., 2021). The objective of this review is to analyze and examine the characteristics of vehicles employed in the formulation of triple antibiotic paste (TAP) for intracanal administration.

Properties of Ideal Intracanal Medicaments in Endodontics

Microorganisms from the root canal space may invade the periapical tissue and progress to pulp and periapical disease (Sundqvist, 1993) and the development and progression of endodontically-induced periapical lesions are associated with the presence of microorganisms in the root canal system (Taneja et al., 2010). Chemomechanical debridement is used to eliminate bacteria from the root canal system. Nevertheless, the utilization of instrumentation and irrigation do not completely eliminate germs from the root canal (Sjögren et al., 1997). The root canal cannot be precisely disinfected by mechanical cleansing alone, as bacteria can conceal themselves in areas that are difficult to access, such as the isthmus, dentinal tubules, and apical delta (Bystrom & Sundqvist, 1985). The usage of interappointment medicament has demonstrated a significant improvement in disinfection following chemomechanical operations (Alsubait et al., 2020). Intracanal medicaments are used for root canal treatment as multiple-visit root canal medication. One of the most often used intracanal drugs is calcium hydroxide (CaOH) (Mohammadi & Dummer, 2011). Hermann introduced the intracanal medicament to dentistry in 1920, and it became popular for root canal therapy in the 1970s and it is today considered one of the first choices for multiple-visit root canal medication (Kumar et al., 2019). An important property of an intracanal medicament is the antimicrobial properties (Doran & Radtke, 1998; Kumar et al., 2019). While the exact modes of action remain unclear, it appears that CaOH raises pH in aquatic environments via the release of hydroxyl ions that lead to harmful effect to most of pathogenic bacteria as they cannot survive this kind of environment. Additionally, CaOH has some protein denaturizing effects that can aid in the dissolution of pulp tissue (Rahimi et al., 2014; Sirén et al., 2004). CaOH requires a carrier substance to achieve the right consistency before being placed into the canal. Normal saline, lidocaine, and chlorhexidine are commonly used for this purpose (Silveira et al., 2011).

Another important property of an

intracanal medicament is the biocompatibility and stability. CaOH has been determined as suitable for use as an intracanal medicament as it is stable for long periods, harmless to the body, and the bactericidal effect only in a limited area. It induces hard tissue formation and is effective for stopping inflammatory exudates (Kawashima et al., 2009).

Apart from CaOH, Grossman first discussed the use of polyantibiotic paste as an intracanal medicament in weeping canals or where there was continuous drain from the pulp space. Mixture of ciprofloxacin, metronidazole and minocycline is useful for sterilization of infected root dentine, at only a low dose of the mixture is required (Sato et al., 1996). The mixed antibacterial drugs are also effective against bacteria in periodontal pockets and dental plaque (Ando & Hoshino, 1990) suggesting that this drug combination may also be useful in the treatment of endodontic-periodontal diseases (Sato et al., 1996).

The intracanal medicaments, such as calcium hydroxide or antibiotic formulation, should possess a consistency that is effective in carrying a maximum number of active component particles (Kumar et al., 2019). For example, when the intracanal medicament is prepared with the usage of gel as the vehicle, it was able to clean the root canal walls and their anatomic complexities effectively due to the viscosity of the gel (International Standard ISO 6876:2001, n.d.). The usage of chlorhexidine gel as the vehicle increases in the viscosity of intracanal medicament, resulting in reduced flowability and may prolonged contacts between particles and the tooth structure, facilitating the antibacterial effect (Al-Sabawi, 2020).

A narrative review on the ideal properties of intracanal medicaments in modern endodontics recommend the following (Kumar et al., 2019):

1. Effective antimicrobial agent
2. Nonirritating to the periradicular tissues
3. Remain stable in solution
4. Prolonged antimicrobial effect
5. Active in the presence of blood, serum, and protein derivatives of tissues
6. Low surface tension
7. Not interfere with the repair of periradicular tissues
8. Not stain tooth structure
9. Not induce a cell-mediated immune response

Thus, to ensure an intracanal medicament exhibits maximum efficacy, it is crucial to prepare it with a suitable vehicle that aligns with its physicochemical properties. Selecting an appropriate vehicle for an intracanal medicament is essential for maximizing its therapeutic properties. The vehicle should be chosen based on the specific needs of the treatment, considering factors such as stability, viscosity, biocompatibility, and antimicrobial activity. By doing so, the effectiveness of the intracanal medicament in disinfecting the root canal system can be significantly enhanced.

Triple Antibiotic Paste (TAP)

An intracanal medication with an effective antibacterial action is recommended to predictably eliminate bacteria from the entire root canal system (Chong & Ford, 1992). Since its first use by Hoshino and the team, TAP combination metronidazole, ciprofloxacin, and minocycline (Sato et al., 1996) has been the most widely used intracanal medicament in endodontic regeneration and recommended by American Association of Endodontists (American Association of Endodontists, 2021). TAP showed the antibacterial efficacy on bacteria of carious and endodontic lesions of human deciduous teeth, showing carious and endodontic lesions can be sterilized by the mixed drugs in situ (Sato et al., 1993). In the study, ciprofloxacin, metronidazole, plus a third antibiotic; amoxicillin, cefaclor, cefroxadine, fosfomycin, or rifamycin were used. Later it was reported that ciprofloxacin, metronidazole, and minocycline can inhibit the growth of bacteria in the deep layers of root canal dentine in situ (Sato et al., 1996). High success rates have been observed in regenerative endodontic procedure (REP) with the usage of triple antibiotic paste as the intracanal medicament. TAP containing cefaclor, ciprofloxacin, and metronidazole was used in a clinical study, which included 28 immature permanent teeth with necrotic pulps. The study reported a 100% resolution of periapical radiolucencies, 93% clinical success score and 96.4% survival rate (Chan et al., 2017).

In terms of concentration of triple antibiotic to be used for the treatment, only at concentrations of 0.1-0.01 mg/mL, there was no negative impact on the viability of stem cells from the apical papilla (SCAP) (Ruparel et al., 2012). TAP concentrations of 0.01, 0.1, 1, 10, and 100 mg/mL were applied to SCAP and results indicated that at concentrations of 10-100 mg/mL less than 20% of the stem cells remained viable, at concentrations of 1 mg/mL, 33-56% of the stem cells remained viable when TAP was used. Another concentration study reported that TAP with a concentration of 0.125 mg/ml showed significant antibacterial effects with no cytotoxic effects when it was tested on dental pulp stem cells (DPSCs) (Sabrah et al., 2015).

The usage of the triple antibiotic formulation was shown to have the desired outcome and lesser cytotoxicity when it is prepared with macrogol and propylene glycol (PG) in comparison to water. TAP prepared with water showed to have lower pH and higher toxicity (Faria et al., 2018). The form of antibiotic being used is reported to have different levels of pH and cytotoxicity value, as the United States Pharmacopeia (USP) grade antibiotics showed lower pH and were more toxic in comparison with the tablet/capsule (T/C) type of antibiotic (Faria et al., 2018).

Drug Vehicles

Drug carriers are biocompatible tools for the transport of molecules for pharmaceutical, cosmetic, and nutraceutical applications. The delivery of active pharmaceutical substances to patients is significantly facilitated by the utilization of vehicles, which serve as a vital mechanism for delivering medicine into the body. The choice of vehicles is crucial since it can significantly influence the effectiveness/potency of drug formulation (Allen et al., 2011). A localized medication delivery system is utilized to provide a precise and focused effect, especially in restricted regions. A localized drug delivery system is an approach to administering medication to a targeted site, intending to reduce movement and enhance absorption into the circulatory system (Rolfes et al., 2012). A number of the most popular vehicles are ointments, creams, gels, and lotions (Barnes et al., 2021).

Drug Vehicles in Regenerative Endodontics Procedure (REP)

The use of vehicles in TAP preparation for endodontic therapy is a critical factor that will impact the characteristics and efficacy of the paste. TAP to be used in REP, require the mixing of the antibiotics and a vehicle in which will be mix into a paste form, and later will be placed within the root canal of the tooth. The selection of a vehicle holds significance for multiple reasons, one of which is its biocompatibility. The chosen vehicle must exhibit biocompatibility with pulp tissue, hence avoiding any potential adverse responses or disruptions to the healing process. Another thing to consider is the convenience of handling, as qualities that are easier to handle will facilitate the mixing and delivering of the paste during the treatment procedure. Furthermore, the antibiotic must possess stability and solubility to ensure effective dissolution, uniform distribution within the paste, and long-term stability. Propylene glycol, macrogol (polyethylene glycol), antibiotic-eluting fibers are among the used vehicles for TAP. Each vehicle possesses unique properties affecting the paste's antimicrobial activity, physical characteristics, and biocompatibility.

Macrogol and Propylene Glycol

Macrogols, also known as polyethylene glycols (PEG) and propylene glycol (PG) are synthetic substances that are used as vehicles in a variety of cosmetic and medical products. Macrogol is commonly used in the treatment of constipation, particularly when first-line treatments such as education and lifestyle modifications do not yield the desired results. In regenerative endodontics procedure (REP), PEG is the most widely used as it is antimicrobial effective and easily manipulated. PEG is a polyether compound derived from petroleum with many applications, from industrial manufacturing to medicine. PEG, often referred to as polyethylene oxide (PEO) or polyoxyethylene (POE), is named differently based on its molecular weight. It is readily soluble in water, ethanol, acetone, glycols, and chloroform. PEGs that present mostly as hydrophilic, they are favorably used as penetration enhancers, example in topical dermatological preparations (Becker et al., 2017).

PG is a clear, colorless, viscous, practically odorless liquid with a density of 1.038 g/cm^3 at 20°C and a molecular weight of 76.095. It is an alcohol that is soluble in water and is a well-known pharmaceutical excipient that is used for several purposes in a wide range of pharmaceutical dosage forms. For example, 15% of the PG been used as humectant in topicals, 15 to 30% as a preservative in solutions, 10–25% as a co-solvent in aerosols, and 5 to 80% in topicals application (European Medicines Agency, 2017). PG is mainly used in medication formulation to increase the solubility of hydrophobic compounds (Co & Gunnerson, 2019).

Both PEG and PG are considered biologically inert and safe by the United States Food and Drug Administration (US FDA). However, the toxicity linked to PG arises from its metabolism by alcohol and aldehyde dehydrogenase in the liver, resulting in the production of lactic and pyruvic acids. This can cause different levels of anion gap metabolic acidosis and impairment of liver function. PG is excreted in the urine without undergoing any changes, which can worsen toxicity in patients with acute renal injury due to the accumulation of the substance (Lim et al., 2014). Research has suggested that propylene glycol is likely to be toxic at concentrations exceeding 25 mg/dL (Barnes et al., 2006). There is increasing data indicating that over 72% of the population, who have never been treated with PEGylated medications, have measurable levels of anti-PEG antibodies (Yang et al., 2016). The identification of an allergy to PEG typically occurs after a diagnosis of an allergy to a growing array of apparently unrelated goods, such as processed foods, cosmetics, medications, and other substances that either include PEG or were produced using PEG (Wenande & Garvey, 2016).

In dentistry, PEG have been used to address periodontitis by encapsulating stem cells in the gel, which promotes healing in the gums. The gel with encapsulated stem cells was to be injected into the site of disease and crosslinked to create the microenvironment required for the stem cells to function (Ma et al., 2017). In REPs, both PEG and PG play roles in facilitating the disinfection of the root canal space, delivering medicaments to promote tissue regeneration, and creating an environment conducive for healing. In a study, the utilization of carriers such as PEG and PG has been proposed as a means to enhance the permeation of antibiotics and facilitate their transportation into the dentinal tubules. In turn, it contributes to the efficient elimination of microbial burden (Cruz et al., 2002) a critical factor in the treatment of REPs. Moreover, preparing this TAP with PEG and PG has been demonstrated to yield the desired outcome with less cytotoxicity, in comparison when the TAP was prepared with water, it was demonstrated to have a lower pH and greater toxicity (Faria et al., 2018).

Antibiotic-Eluting Fibers

As technology continues to evolve, the integration of TAP components into electrospun small-sized biodegradable polymeric fibers has been suggested as a potentially more cellular-friendly methodology on account of the significantly reduced antibiotic content (Karczewski et al., 2018). Antibiotic-eluting fibers are a type of biomaterial designed to release antibiotics gradually over time. These fibers are typically made from biocompatible polymers that can be impregnated or coated with antibiotics. Study reported that the use of TAP-eluting nanofibers for the disinfection of biofilm-infected dentin samples showed similar antimicrobial activity as compared to TAP (Albuquerque et al., 2017). Apart from that, the use of TAP-eluting nanofibers resulted in less tooth discoloration compared to the use of TAP, indicating a lower concentration of antibiotics in the TAP-eluting nanofibers (Albuquerque et al., 2017). These antibiotic-eluting fibers represent a valuable strategy for localized drug delivery in medical and dental practice, offering controlled release of antibiotics to effectively manage infections and promote tissue healing.

Hydrogels

Hydrogels are the material that provides a three-dimensional (3-D) scaffold that mimics extracellular matrix. Examples of these materials are chitosan, gelatin, and hyaluronic acid. These hydrogels are important components in drug delivery as they can control the release of drugs over time and deliver them in a targeted manner, enhancing the effectiveness of treatments while minimizing side effects. The bioactive components of the drug delivery have the capacity to interact with biological systems, including the living tissues (Leveque et al., 2023). A variety of bioactive materials were already designed and proposed to improve interactions between cells and tissues, triggering processes such as cell adhesion, proliferation, differentiation, and the promotion of tissue regeneration. In endodontics, the bioactive components are incorporated into this hydrogel such as antibiotics, peptides, or nanoparticles thus making them bioactive (Ribeiro et al., 2022). Bioactive endodontic hydrogels could be considered as advanced and innovative materials for REPs that were specifically designed to promote and enhance dental pulp regeneration.

Most of the hydrogel used in endodontic is in injectable forms as it is more convenient to the operator (Leveque et al., 2023). Several parameters such as porosity, mechanical strength, or biocompatibility of the hydrogel could strongly promote or reduce its properties and changes in the endodontic environment may result in the ability of the hydrogel to change in its shape, its degradation over time, the efficiency of active components, and variations when in contact with fluids (Leveque et al., 2023). As in periapical environments, inflammation of the tissue potentially influences the local pH and therefore the ionization state of bioactive molecules, thus modifying the solubility, resulting in the release of bioactive materials in hydrogels.

White Petrolatum

White petrolatum, also known as white soft paraffin and petroleum jelly, is a semisolid mixture of hydrocarbons that is composed of a white to yellowish color and is dewaxed from paraffinic residual oil. The carbon numbers of the hydrocarbons are primarily greater than C25 (Bao et al., 2020). The major constituents inside the white petrolatum are n-paraffin, iso-paraffin, and naphthene (Barry & Grace, 1971). White petrolatum differs from petrolatum as it is the purified form of petrolatum or petroleum jelly, and it is highly refined. It is commonly used in cosmetic and pharmaceutical applications, including skincare products, ointments, and lip balms. In comparison, petrolatum is the original, unrefined form of petrolatum and it is used mainly in industrial applications and certain less refined products. It has properties of the present in semi-solid consistency at room temperature, melting point ranges from 36-60°C therefore the ointment viscosity will decrease following application (Greaves et al., 1993) hydrophobic, colorless, translucent (Bao et al., 2017), inert and non-reactive with other substances. A randomized control trial reported that white petrolatum is safe and effective wound care ointment, and it possesses an equally low infection rate and minimal risk of induction allergy (Smack, 1996). White petrolatum has been used in the medical field for many functions one of which is as a moisturizer (Purnamawati et al., 2017). In addition, white petrolatum is much utilized as an eye ointment, serving as an excipient/vehicle in the formulation (Bao et al., 2017; Bao et al., 2020). The advantages of this material are ease of application and ease of manipulation. This material has been used in the field of dentistry as a vehicle in which in the year 1990, white petrolatum has been used as a vehicle in preparation with tetracycline to be used in the treatment of periodontal disease (Eckles et al., 1990). Besides, a study reported that white petrolatum does not show direct relation with antimicrobial effect, which is it only modulates the antimicrobial effect in topical application usage for the prevention of skin infection (Czarnowicki et al., 2016). This is an important property as when the white petrolatum is used as a vehicle with triple antibiotic, the antibacterial effect is modulated by the antibiotic itself. This potentiates white petrolatum to be used as a vehicle in the preparation of triple antibiotic paste for regenerative endodontic procedures.

CONCLUSION

In conclusion, the choice of vehicle for TAP formulations in endodontic therapy plays a crucial role in determining the treatment's efficacy, safety, and clinical outcomes. While this narrative review provides valuable insights into the properties and applications of different TAP and intracanal medicaments vehicles, further research is needed to address the remaining gaps in knowledge. Comparative studies evaluating the efficacy and safety profiles of various TAP formulations could enhance our understanding, and white petrolatum is a potential vehicle for use in the preparation of TAP for regenerative endodontic procedures following the guide in evidence-based clinical practice.

CONFLICT OF INTEREST

The authors affirm that they have no conflicts of interest, whether financial or of any other nature..

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