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Triple Antibiotic Paste: Current Evidence, Clinical Applications and Future Perspectives

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ABSTRACT

Triple antibiotic paste (TAP) is among the most important intracanal medicaments currently used in modern endodontics, being endowed not only with an extensive antimicrobial spectrum but also with the potential for use in regenerative endodontics. Containing metronidazole, ciprofloxacin, and minocycline as active ingredients, TAP has demonstrated sufficient antibacterial activity against a wide range of endodontic pathogens and microorganisms associated with persistent infections and apical periodontitis. The ability of the paste to penetrate into the dentinal tubules and reduce the overall microbial load in the root canal have contributed to its extensive use as an antimicrobial agent in endodontic disinfection. Apart from standard root canal therapy, TAP has found its way into regenerative endodontics and is used for immature permanent teeth with necrotic pulp. The review covers TAP's antimicrobial properties, mechanisms of action, indications, and applications in clinical dentistry. At the same time, some drawbacks of using TAP are discussed, including possible dentin discoloration, development of antibiotic resistance, and impact on stem cells' viability and differentiation. Multiple modifications of TAP, double antibiotic paste, modified TAP, and other intracanal medicaments were introduced and analyzed.

INTRODUCTION

Endodontic infections are usually polymicrobial and consist of a mixture of bacteria and fungi, primarily obligate and facultative anaerobes that colonize dentinal tubules, root canal irregularities, and biofilms [1]. The most prevalent persistent endodontic infection is caused by Enterococcus faecalis, which is frequently connected to treatment failures due to its ability to thrive in adverse environments and resist to antimicrobial agents. Moreover, Candida albicans was detected in chronic endodontic infections because of its adhesion to dentin and invasion of dentinal tubules. Microbial biodiversity in infected root canals may present insurmountable difficulties in attempts to eradicate the infection [2].

Therefore, combination antibiotics have been considered as potential intracanal medicaments for treating endodontic infections. TAP is regarded as the safest and most effective method for managing the microbiota of the root canal system. It comprises three antibiotics with various mechanisms of action. They are capable of inhibiting DNA replication, protein synthesis, and

DNA helix formation in bacteria [3].

TAP has been integrated into the modern endodontic treatment strategy for intracanal disinfection and regenerative endodontics. Its antimicrobial properties have drawn researchers' attention, who have investigated how it can help manage persistent endodontic infections. Nevertheless, there are a few drawbacks to TAP, including minocycline-induced tooth staining, concentration-dependent cytotoxicity, suppression of stem cells, and antibiotic resistance development. Thus, modified TAP, double antibiotic paste, or other intracanal medicaments have been introduced to address these undesirable side effects [4].

The current study aimed to provide insight into the composition, mechanism of action, antimicrobial efficacy, and application of TAP. At the same time, the article discusses the molecular mechanisms of TAP's biological limitations and safety concerns and thoroughly analyzes recent developments and future prospects of TAP in endodontics

TYPE OF REVIEW AND METHODOLOGY

The manuscript is a narrative review of the composition, antimicrobial efficacy, clinical applications, biological effects, safety, limitations, and future prospects of triple antibiotic paste (TAP). The review aimed to present an overview of the evidence related to TAP in endodontics with a focus on its application in endodontic disinfection, regenerative endodontics, LSTR, and development of modified antibiotic formulation rather than quantitative synthesis of the evidence.

PubMed/MEDLINE, Scopus, Embase, Web of Science, and Google Scholar databases were searched for relevant literature published from inception through September 2026. The search strategy comprised terms related to the composition and application of TAP, its antimicrobial efficacy, and clinical applications such as "triple antibiotic paste," "intracanal medicament," "endodontic infection," "antimicrobial efficacy," "regenerative endodontics," "revascularization," "lesion sterilization and tissue repair," "double antibiotic paste," "modified triple antibiotic paste," "cytotoxicity," "stem cell survival," "tooth discoloration," and "antibiotic resistance." Boolean operators (AND and OR) were used to combine the search terms.

The inclusion criteria comprised original research articles, in vitro and in vivo studies, randomized controlled trials, clinical studies, case reports, systematic reviews, and relevant narrative reviews on the composition, mechanism of action, antimicrobial effectiveness, clinical applications, biocompatibility, limitations, and modification of TAP. The articles investigating the alternative combinations of antibiotics and herbal or organic intracanal medicaments were included if they addressed the objectives of the review. Publications unrelated to TAP or its clinical and biological applications in endodontics, duplicate records, and articles lacking relevant information were excluded from the study.

The reference list of the included articles was screened for additional relevant publications. The collected literature was thematically grouped according to the composition and pharmacological properties of TAP, its antimicrobial efficacy, clinical applications, preparation, factors influencing its effectiveness, biological and safety concerns, modified antibiotic formulations, and emerging alternatives. The findings of the included literature were synthesized narratively to present an overview of the evidence, clinical implications, limitations, and future research directions. The quantitative data pooling and meta-analysis were not performed since the review aimed to provide a descriptive analysis of the evidence

Rationale for the use of triple antibiotic paste in endodontics

The main justification for using TAP in endodontics lies in the medication's nature and mechanism of action. The paste contains metronidazole, ciprofloxacin, and minocycline which act in different manners to ensure the destruction of a large variety of bacteria present in the root canals. It may be hypothesized that the triple action of the antibiotics helps to reduce the number of pathogens inside the root canals and dentinal tubules and eliminate the infection source. The reduction of the affected area is crucial in the case of endodontic infection since it allows decreasing the degree of inflammation around the periapical region. Moreover, TAP has been shown to be relevant in regenerative endodontics since it ensures optimal conditions for the stem cells present in the root canals. Nevertheless, it should be noted that the discussed benefits of TAP are offset by several disadvantages related to its negative impact on the tissues and potential bacterial resistance to antibiotics [4].

Composition and pharmacological properties of triple antibiotic paste

TAP consists of three antibiotics, namely metronidazole, ciprofloxacin, and minocycline, used in the treatment of endodontic infections. Metronidazole is a type of nitroimidazole antibiotic that is primarily active against obligate anaerobic bacteria. Its mode

of action involves the reduction of nitro groups by bacterial enzymes leading to the formation of reactive intermediates that interfere with DNA replication and transcription process in the targeted bacteria. Ciprofloxacin is a fluoroquinolone antibiotic with an enhanced activity against gram-negative organisms. It inhibits DNA-dependent RNA polymerase thus preventing DNA replication. The combination of metronidazole and ciprofloxacin is effective against various types of bacteria causing endodontic infections. Minocycline is a semisynthetic tetracycline antibiotic with a broad spectrum of activity against both gram-positive and gram-negative organisms. It acts by inhibiting the protein synthesis in bacteria which prevents their proliferation. However, minocycline has a major disadvantage of causing tooth discoloration thus its use is limited. In addition to the three antibiotics, the antibiotic paste also includes a vehicle that facilitate easy usage and proper consistency of the antibiotic inside the root canals. The most common vehicles used are propylene glycol, polyethylene glycol, and water. Together with the three antibiotics, the vehicle enhances the effectiveness of the antibiotic paste and improves its overall performance during the treatment of endodontic infections [5].

Clinical applications of triple antibiotic paste

TAP has several applications in endodontics, primarily as an intracanal medicament. It is widely used in regenerative endodontic procedures and revascularization protocols to disinfect the root canal system and create a favorable environment for tissue repair. It has also been investigated for the management of periapical lesions, external inflammatory root resorption, and horizontal root fractures. In primary teeth, TAP has been explored in the lesion sterilization and tissue repair (LSTR) technique, in which the antibiotic mixture is placed in the pulp chamber to control infection and promote healing without conventional extensive root canal instrumentation. The described approach is aimed at eliminating clinical manifestations and facilitating the healing of the affected sites. Nevertheless, the accurate choice of the cases, proper coronal sealing, and consistent clinical and radiographic follow-up are of utmost importance. Additionally, TAP has been investigated for controlling interappointment endodontic flare-ups and as an additive to root canal sealers and gutta-percha points to enhance antimicrobial activity and potentially reduce reinfection. Another emerging application involves incorporating TAP into scaffolds for localized antibiotic delivery during regenerative procedures. Nevertheless, further clinical research is required to establish the long-term effectiveness and safety of these applications [6].

Preparation of triple antibiotic paste

TAP can be prepared by first pulverizing the individual components of antibiotics and then combining them with an appropriate solvent to form a paste. The commercially available antibiotics are placed separately in clean dappen dishes. The enteric coating of the tablets is removed by scraping with a sterile blade, while the outer material of the capsules is removed appropriately. The individual antibiotics are then pulverized separately in a clean and dry mortar and pestle to avoid contamination and exposure to moisture. If storing, the powdered components should be stored separately in tightly closed porcelain containers away from light and humidity. They can be stored in a dark and dry place or under refrigeration.

After pulverizing, the individual components of antibiotics are transferred onto a clean glass slab or mixing pad. The appropriate solvent is dispensed separately. To prepare a good mixture, it is advisable to divide the powders into seven portions and use one part of the solvent for every seven parts of a mixture of the powder. Each portion of the powder is added to the appropriate solvent and mixed well to make a good consistency mixture.

The mixture should ideally be a soft cohesive mass with a ball like consistency with a diameter of about 1 mm. If the mixture is too soft, more of the antibiotic powder can be added. However, if the mixture is too dry, flaky, or too hard, a few drops of the solvent can be added. The opaque mixture is then stored in an airtight container. if the mixture becomes translucent, it should be discarded [7,8].

Factors influencing the action of triple antibiotic paste

The effectiveness of triple antibiotic paste is affected by a range of factors, including the concentration and quantity of antibiotics, microbial diversity, penetration into dentinal tubules, smear layer, biocompatibility, and the potential for tooth discoloration. An adequate quantity and concentration of the antibiotics are required to facilitate sufficient diffusion throughout the root canal system and achieve effective antimicrobial activity. Since endodontic infections are usually caused by various aerobic and anaerobic bacteria, multiple antibiotics offer more antimicrobial coverage than a single antibiotic and may reduce the risk of developing resistant organisms [9]

The choice of antibiotics also requires consideration

of their impact on host tissues. The early polyantibiotic preparations containing penicillin were associated with sensitization and superinfection; therefore, an ideal intracanal medicament should be broad-spectrum antimicrobial, minimally cytotoxic, irritant, and hypersensitivity-inducing, and possess biocompatibility [9].

The smear layer can reduce the penetration of TAP into the dentinal tubules, and its removal allows achieving a better disinfection effect. Various methods can be used to remove the smear layer, including chelating solutions, such as EDTA, and ultrasonic irrigation, or a combination of these techniques [9].

Minocycline, an antibiotic included in the composition of TAP, has a negative impact on the color of the tooth, especially if it penetrates the dentinal tubules. There are several recommendations to prevent discoloration, among which is a technique described by Reynolds et al. The researchers suggest using dentin bonding agents on the middle third of the root canal to prevent staining, although it cannot be prevented entirely [10].

According to Banchs and Trope, applying a protective barrier of flowable composite resin over the canal orifice is a better option to avoid minocycline contact with dentin. This technique is recommended because it prevents the antibiotic from penetrating the dentinal tubules, thus reducing the risk of staining, although it does not eliminate it altogether [11].

Modified triple antibiotic paste

The problems associated with conventional triple antibiotic paste (TAP) such as minocycline-induced tooth discoloration, cytotoxicity, and antibiotic resistance have necessitated the modification of the conventional TAP. Modifications include the substitution or elimination of minocycline, the alteration in the proportion of the various antibiotics, and changes in the vehicle in which the antibiotics are delivered into the canal. The main aim of the modifications is to produce an antimicrobial agent that is devoid of adverse effects.

A modified version of the triple antibiotic paste is the 3C antibiotic paste made up of ciprofloxacin, clindamycin, and cefaclor. Chandra and Thosar compared the antimicrobial efficacy of the 3C and the conventional TAP. They evaluated the activity of the antibiotic pastes against Enterococcus faecalis and Candida albicans which are frequently implicated in endodontic infections. The comparison was done by determining the zones of inhibition of the growth of the bacteria and fungus after 24 and 72 hours of exposure. The 3C is a minocycline-free antibiotic formulation with broad antimicrobial activity. The results of the study show that 3C has the potential to be used as an alternative to the conventional triple antibiotic paste. This is because it has been found to be more effective than the conventional triple antibiotic paste. These results are significant in the search for modified TAPs that can be used in human primary teeth [12].

Double antibiotic paste (DAP) is a modified form of the conventional triple antibiotic paste. This modification was done to overcome the problem of minocycline-induced discoloration associated with the triple antibiotic paste. Double antibiotic paste consists of metronidazole, ciprofloxacin only without minocycline. Whereas the conventional TAP consists of metronidazole, ciprofloxacin, and minocycline.

The removal of minocycline is intended to reduce the risk of antibiotic-associated tooth discoloration while retaining broad antimicrobial activity through the complementary actions of the remaining antibiotics.

Double antibiotic past has become a subject of particular interest in regenerative endodontic procedures. Its use requires a balance between the need to remove intracanal microorganisms and the possible negative effects of intracanal medicaments on stem cells survival [13,14]. Nevertheless, the omission of minocycline from intracanal medicaments does not necessarily eliminate all limitations associated with the use of antibiotic pastes. The antimicrobial spectrum of DAP may differ from that of traditional TAP, and antibiotic concentration, vehicle, dentinal penetration, and exposure time may affect its antimicrobial efficiency and biological effect. Hence, DAP has been investigated as an alternative intracanal medicament, especially in esthetic indications or when the possible biological consequences of TAP are of concern [13].

Akcay et al. assessed the discoloration potential of different antibiotic pastes used in regenerative endodontic procedures, including double antibiotic paste and traditional TAP containing minocycline, doxycycline, amoxicillin or cefaclor. An in-vitro experiment on extracted bovine incisors evaluated the crown color changes after 3-week incubation using spectrophotometry. The DAP group showed no color changes greater than the clinically perceptible threshold while TAP with minocycline, doxycycline or cefaclor significantly greater coronal discoloration than the control group. So, the use of DAP can be a more esthetic option if antibiotic-based intracanal medicaments are used in the anterior region during regenerative endodontic procedures [15].

However, the esthetic benefit of using DAP should be weighed against its antimicrobial and biological effects. The omission of minocycline may affect the antimicrobial spectrum of the paste as compared to the conventional TAP. Therefore, its antimicrobial efficacy, optimal concentration, cytotoxicity, dentinal penetration, and effects on stem-cell survival and differentiation should be examined when choosing an intracanal medicament.

The single antibiotic paste (SAP) is a modified intracanal medicament that utilizes a single antimicrobial substance instead of two or three antibiotics present in TAP or DAP. The idea of using SAP is based on the reduced amount of antibiotics compared to TAP/DAP, with the intent to decrease the negative side effects of poly-pharmacy while maintaining the high standards of microbial reduction. Nitrofurantoin is a synthetic antimicrobial substance from the family of nitrofurans that has shown a broad range of activity against Gram-positive and Gram-negative bacteria. This antibiotic has demonstrated its antimicrobial activity in vivo and in vitro; thus, it has drawn attention to replace a combination of antibiotics in TAP/DAP with a single nitrofurantoin-containing SAP. Mali et al. evaluated the antibiotic efficacy of the modified TAP (M-TAP), DAP, and nitrofurantoin-based SAP. The researchers have tested the antimicrobial activity of the pastes against the strains of Staphylococcus aureus, Streptococcus viridans, and Streptococcus pyogenes using an ex-vivo agar well diffusion model. The results of the study showed that SAP had the highest zone of inhibition among the tested materials for all of the three bacterial species. Moreover, the researchers have found the antimicrobial activity of SAP to be considerably higher compared to DAP and M-TAP. Although the findings of the article suggest that the nitrofurantoin-based SAP can become a viable alternative to the antibiotic pastes used for intracanal debridement, additional clinical trials are needed to confirm this theory [16].

An emerging approach to overcome the limitation of conventional TAP is the use of natural or organic antimicrobial combinations. Kotha et al. tested triple organic paste formulations prepared using neem leaves, turmeric rhizomes, ginger rhizomes, garlic bulbs, bitter gourd seeds and Triphala for their antibacterial efficacy against Enterococcus faecalis, Streptococcus mutans and Candida albicans and compared them with TAP. It was found that most of the organic formulations showed considerable antimicrobial activity with few formulations demonstrating larger zones of inhibition than TAP. Thus, these natural product based formulations could potentially be good alternatives to conventional antibiotic pastes; however, there is a need for in vivo and clinical studies to evaluate the efficacy and safety.

Further evidence of alternate therapy was provided by Tawde et al. who evaluated the efficacy of an herbal combination of tulsi oil, turmeric oil and aloe vera gel as intracanal medicament compared to TAP and camphorated monochlorophenol (CMCP) in deciduous molars. All the three medicaments resulted in significant reduction of Enterococcus faecalis count following 48 h of application with no statistically significant difference between the groups [18]. This herbal combination could be a potential alternative to the commonly used medicaments; however, extensive clinical trials are needed to confirm its clinical effectiveness and safety

Emerging approaches and future perspectives

The drawback of a conventional triple antibiotic paste such as tooth discoloration, cytotoxicity, and possible development of bacterial resistance, prompts the need to investigate other modified and alternative antimicrobial pastes. The modified TAPs included double and single antibiotic pastes, dilution of antibiotics in TAP, use of herbal antimicrobial agents, nanoparticle carriers and approaches to sustained release of active ingredients. Future studies on antimicrobial pastes should be directed towards the concept of targeted antimicrobial therapy. Moreover, there is a need to develop specific protocols for the management of various microbial infections including the selection of an appropriate antimicrobial agent, its concentration and method of placement during root canal treatment. Further studies, preferably clinical trials with long-term follow-up, are necessary to verify the effectiveness of these modified pastes and to evaluate their impact on the physiologic healing of a root canal system and the entire tooth structure.

CONCLUSION

TAP is regarded as an important intracanal medicament due to its broad-spectrum antimicrobial properties and its established role in endodontic disinfection and regenerative procedures. However, concerns regarding tooth discoloration, cytotoxicity, antibiotic resistance and their effects on regenerative cells prompted the development of its modified, double and single antibiotic analogs. Emerging alternatives seek to preserve antimicrobial efficacy while improving biological and esthetic performance. Future research should address standardized formulation approaches,

targeted antimicrobial delivery, antibiotic stewardship and well-designed clinical studies to confirm the long-term safety and efficacy of these approaches.

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