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Triple Antibiotic Gel in The Management of Periodontal Disease: A Narrative Review

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Abstract

Periodontal disease is a chronic inflammatory condition caused by bacterial biofilms, leading to progressive destruction of the tooth-supporting structures. Conventional treatments such as scaling and root planing (SRP) are effective but may not completely eradicate pathogenic bacteria, necessitating adjunctive antimicrobial therapies. The use of locally delivered antibiotic gels has emerged as a promising approach to enhance periodontal healing. Triple antibiotic gel formulations, commonly consisting of metronidazole, ciprofloxacin, and minocycline, offer targeted antimicrobial action, reducing bacterial load and inflammation within periodontal pockets. Localized drug delivery minimizes systemic side effects while maintaining therapeutic concentrations at the site of infection. Despite these benefits, concerns remain regarding antibiotic resistance, potential allergic reactions, and long-term efficacy. This review discusses the role of triple antibiotic gel in periodontal therapy, its clinical effectiveness, advantages, limitations, and future research directions. Optimizing antibiotic formulations and developing strategies to mitigate resistance will be essential for ensuring the long-term success of this therapeutic approach in periodontal disease management.

Keywords: Bacteria, Periodontitis, Prevotella Intermedia Vulnerabilities

Introduction

Periodontitis is an infectious disease resulting in inflammation within the supporting tissues of the teeth, progressive attachment loss & bone loss. For optimal growth and proliferation of putative periodontal pathogens periodontal pocket provides an ideal. The worldwide prevalence of periodontal diseases has seen a considerable rise over the past decade. Research findings indicate that the age associated prevalence, incidence was associated with periodontal diseases increased by 7.78% on a world wide scale. periodontal health is sustained by a balanced immune system and a harmonious microbial community. In subgingival biofilms, anaerobic Gram-negative bacteria, characterized by their lipopolysaccharide (LPS)-rich cell walls, play a crucial role in triggering inflammatory responses in the gingival tissues. This activation of inflammation contributes to periodontal tissue breakdown, particularly in individuals who are susceptible to periodontitis.[1]

Periodontitis is linked to a disrupted microbial environment composed of diverse organisms that collectively contribute to harmful inflammation. Certain key pathogens supported by other microbes that assist with nutrient acquisition or colonization are capable of undermining the host's immune defenses. This disruption allows the microbial community to shift into a dysbiotic state, where formerly harmless bacteria become harmful, triggering excessive immune responses and tissue damage. The resulting inflammation can further fuel microbial imbalance by releasing nutrients from degraded tissues, such as collagen fragments and heme compounds, which bacteria can exploit. This creates a self-perpetuating cycle in which inflammation and dysbiosis continuously reinforce each other, potentially explaining the chronic nature of periodontitis. The condition develops in individuals with specific vulnerabilities, and several factors can heighten the risk such as immune system-altering bacteria, systemic diseases, smoking, aging, poor dietary habits, and immune deficiencies. These elements may drive dysbiosis on their own or have an even stronger effect when combined. Even though Subgingival flora contains more than 250 species, potential periodontal pathogens have received the most attention. Of those, Porphyromonas gingivalis, Prevotella intermedia, Aggregatibacter actinomycetemcomitans, and capnocytophaga species are putative pathogens which have a strong association with periodontal disease.[2]

Periodontal infections are a major contributor to tooth loss and can adversely affect overall health. Numerous studies have highlighted a bidirectional relationship between periodontal disease and various systemic conditions, including coronary heart disease, cognitive disorders, diabetes, and other cardiovascular diseases. Due to its detrimental effects, periodontal disease significantly influences both an individual's health status and quality of life.[2]

Various treatment modalities have been tried to combat periodontal diseases. Periodontal therapy encompasses a broad range of treatment modalities, including non-surgical periodontal therapy such as scaling and root planing (SRP), alone or with adjunctive administration of systemic or local antimicrobial agents, and surgical periodontal therapy. subgingival mechanical root debridement effectively reduces or eliminates suspected periodontal pathogens and stimulates an increase in potentially protective systemic antibody levels against these microorganisms.[3]

Over time, and especially when paired with consistent supragingival plaque control, subgingival bacterial communities may slowly repopulate. However, in the absence of proper oral hygiene, harmful subgingival bacteria can return within 42 to 60 days after just one debridement session. Even with repeated subgingival treatments and careful plaque management, certain deep periodontal pockets may show signs of pathogen recolonization within 120 to 240 days. In Addition periodontal pathogens such as Aggregatibacter actinomycetemcomitans and Porphyromonas gingivalis persist after mechanical treatment due to their tissue penetration capability and high affinity to oral mucous tissues. [3]

Antimicrobial agents can reach the periodontal pocket through both systemic and local delivery methods. Systemic antimicrobials enter the pocket after being absorbed in the intestines and distributed through the bloodstream into oral tissues, gingival crevicular fluid, and saliva. While this approach ensures that all periodontal sites are exposed to the antimicrobial agent, it also carries the risk of side effects affecting other parts of the body. In contrast, local antimicrobial therapy for periodontitis involves directly applying antimicrobial agents to subgingival areas. This targeted approach helps limit the effects on other body systems while concentrating the treatment where it is needed most. For this reason, in adjunctive to supra and subgingival instrumentation Drug Delivery Systems were introduced for an effective treatment strategy. The effectiveness of locally administered antimicrobial agents in treating periodontitis relies on several factors. These include ensuring proper delivery of the agent into subgingival areas, maintaining sufficient contact time between the antimicrobial and the targeted microorganisms, and reaching an optimal concentration of the agent for maximum efficacy.[4]

Local drug delivery offers a more effective alternative by directly applying antimicrobials to the affected area, ensuring sustained drug presence at the infection site. Compared to systemic therapy, local administration reduces systemic side effects, maintains consistent drug levels, and minimizes the risk of antibiotic resistance in non-oral regions. Studies have shown that local drug delivery can achieve up to 100 times higher antimicrobial concentrations in subgingival areas compared to systemic administration. Dated back to 1913 introducing antimicrobial agents into periodontal pockets concept was introduced where sodium hypochlorite (antiformin) was used for pocket epithelium removal. J. Max Goodson in 1970 devised the modern framework for local drug delivery in periodontal treatment was established. Since then, numerous antimicrobial agents and local delivery systems have been developed to complement conventional periodontal therapy.

Drug delivery systems (DDS) have become an essential component in the treatment of infectious diseases, offering a controlled and targeted approach to medication administration. These systems, which include pharmaceutical formulations and medical devices, are designed to transport therapeutic agents such as antibiotics, herbal, enzymes to specific sites within the body. By ensuring a controlled release over a predetermined period, DDS enhance treatment efficacy while minimizing adverse effects. They are classified based on factors such as their physical form, site of action, route of administration, and drug release mechanism.[5]

Over the years, various forms of drug delivery systems have been developed, including fibers, gels, strips, films,

biodegradable gels, solutions, vesicular systems, microparticles, and nanoparticles. The success of these delivery systems is largely influenced by the biological environment, as well as the properties of both the polymer and the drug being administered.[6]

A wide range of antimicrobial agents have been incorporated into these systems. Earlier drug delivery devices were nonbiodegradable, requiring their removal after completing treatment. However, biodegradable alternatives have since been developed, offering the advantage of eliminating the need for device retrieval, thus improving patient convenience. Naturally occurring polymers such as chitosan, cellulose, and alginate, along with synthetic polymers like poly(ε-caprolactone) (PCL), poly (d, l-lactide) (PLA), poly(d,l-lactide-co-glycolide) (PLGA), poly(vinylpyrrolidone) (PVP), and poly(vinyl alcohol) (PVAL), have been extensively studied for their role in controlled drug release.[7]

The release of drugs from these systems occurs through multiple mechanisms, including solute diffusion, polymer swelling, degradation, and erosion. Drug release is generally regulated by diffusion, solvent activation, and chemical reactions, ensuring sustained antimicrobial effects within periodontal pockets. In early 1950 s integration of drugs into solid polymers for controlled release were used initially for, originally for agricultural applications before expanding into medical use in the mid1960s. In periodontal therapy, antimicrobial treatments are commonly used alongside mechanical debridement to manage infections. [8]Terminology related to local drug delivery has evolved over time. Kornman introduced terms such as "local delivery," "site-specific delivery," and "targeted delivery" to describe precision-based drug administration. Additional concepts include "controlled-release" and "sustained-release" drug delivery, which define the duration and consistency of therapeutic agent release at the treatment site. While topical drug application generally refers to localized treatment, "local delivery" implies a more precise and direct approach. Subgingival drug delivery is categorized based on its duration of action. "Non-sustained release" delivers the drug for a short period, whereas "sustained release" maintains drug presence for less than 24 hours. "Controlled release" extends drug delivery beyond 24 hours, ensuring prolonged therapeutic effects. More recently, Tan et al. refined these classifications to accommodate the growing use of adjunctive agents and advanced medical devices in periodontal treatment.[9]

Biodegradable and injectable therapeutic agents in gel and semisolid forms have long been utilized for the localized delivery of antimicrobials into periodontal pockets. Gel-based systems offer several advantages over other delivery methods. Their production is relatively straightforward, and they are easy to apply. Additionally, they provide dimensional stability while remaining adaptable to the complex three-dimensional structure of periodontal pockets. Being minimally invasive, they enhance patient compliance and reduce discomfort. Furthermore, these gels are rapidly broken down and eliminated from the application site through natural metabolic processes and fluid movement, minimizing irritation and ensuring efficient drug clearance. Various gel formulations have been created, incorporating different concentrations of antibiotics from multiple classes, such as nitroimidazoles, tetracyclines, macrolides, lincosamides, quinolones, and ureidopenicillins, along with antimicrobial agents like bisbiguanides. Various natural and synthetic substances, available in gel or injectable formulations, have been evaluated for their potential in improving periodontal disease management. These include propolis extract,

green tea catechins, alendronate, simvastatin, taurolidine, probiotic bacterial strains, quorum sensing inhibitors, silver nanoparticles, quercetin, hyaluronan, and amino acid-buffered sodium hypochlorite.[10]

Various species of bacteria were present in periodontal pockets, single empirical antibiotic does not seem to be enough in disinfecting a periodontal pocket. A non-specific antibiotic therapy will only result in suppressing the natural microbial flora, and an opportunity for the persistent, virulent residual bacteria to repopulate the periodontal pockets. Therefore, in order to eliminate the pathogens thoroughly and break the resistance of the virulent bacteria, using a combination of antibiotics is necessary. When combined with mechanical biofilm disruption in periodontal treatment, antibiotics help slow microbial recolonization and enhance clinical results. Triple antibiotic gel comprises of Metronidazole, Minocycline and ciprofloxacin in 1:1:1 concentration to counteract against wide variety of periodontal pathogens.[11]

Metronidazole

- Metronidazole, a nitroimidazole compound, possesses a broad spectrum of activity against protozoa and anaerobic bacteria. Renowned for its potent antimicrobial effects against anaerobic cocci, as well as both Gram-negative and Gram-positive bacilli, it has been extensively utilized in periodontology in both systemic and localized treatments. Its effectiveness against obligate anaerobes, along with a relatively low incidence of side effects, makes it a preferred choice for managing periodontitis. Unlike tetracyclines, it poses a lower risk of selecting for multidrug-resistant bacteria and has minimal impact on the body's normal microbiota, making it a safer option for periodontal therapy.
- Metronidazole is effective against anaerobes such as Porphyromonas gingivalis and Prevotella intermedia.[12]

Tetracycline

- Tetracyclines, such as tetracycline-HCl, minocycline, and doxycycline, are broad-spectrum antibiotics known for their effectiveness against a diverse range of microorganisms. Beyond their antimicrobial properties, tetracyclines also inhibit collagenases, helping to prevent tissue breakdown, and suppress clastic cell activity, contributing to their anti-resorptive effects.
- Minocycline is effective against a broad spectrum of microorganisms. Minocycline is a broad-spectrum antibiotic within the tetracycline class, exhibiting greater efficacy against a wide range of microorganisms linked to periodontal disease compared to other antibiotics in its group. It is known for its strong substantivity and enhanced lipid solubility making it particularly effective in periodontal therapy Minocycline demonstrates strong activity against periodontal pathogens, including enteric rods, Pseudomonas, and other invasive bacteria. Its effectiveness stems from its ability to penetrate cells, enabling it to exert potent bactericidal effects against a wide range of harmful microorganisms.[13]

Ciprofloxacin

Ciprofloxacin is a second-generation fluoroquinolone antibiotic known for its rapid bactericidal effect. It demonstrates strong antimicrobial activity against Gram-negative bacteria, while its effectiveness against Gram-positive bacteria is more limited. ciprofloxacin is the only antibiotic in periodontal therapy to which all strains of A. actinomycetemcomitans are susceptible.[14]

Conclusion

Periodontal disease is a prevalent condition that significantly impacts oral and overall health. The use of triple antibiotic gel, consisting of metronidazole, ciprofloxacin, and minocycline, may emerge as an effective adjunct to conventional periodontal therapy (scaling and root planing). This localized drug delivery system may offer targeted antimicrobial action, reducing bacterial load, improving clinical parameters, and minimizing systemic side effects with effective long term maintenance of periodontal health.

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