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Locally-delivered antibiotics used as adjunctive therapy in periodontitis treatment

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ABSTRACT

Periodontitis is a major public health concern because of its high prevalence and due to the significant impact on the masticatory function and aesthetics. Periodontitis can cause social inequality and greatly reduce quality of life. If a proper periodontal treatment is implemented, effective personal plaque management, and a thorough supportive phase, the majority of patients with periodontitis can preserve their natural teeth for an extended period of time. The subgingival mechanical instrumentation is the gold standard of periodontitis treatment and it determines a significant change in the subgingival microbiota. Due to the fact that in some clinical situations subgingival instrumentation is not totally efficient different locally delivered antibiotics can be used as adjunctive therapies to periodontitis treatment. The present article aims to provide information with respect to some locally delivered antibiotics used as adjunctive therapy in periodontitis treatment.

Keywords: periodontitis, dental biofilm, treatment, locally delivered antibiotics

INTRODUCTION

Periodontitis is a chronic infectious disease produced by the dental biofilm causing irreversible damage to the dento-maxillary apparatus [1]. The primary features of this condition include the loss of periodontal tissue support occurring through clinical attachment loss and alveolar bone loss, the presence of periodontal pockets and gingival bleeding [2].

Periodontitis is a complex disease induced by an imbalanced oral microbiota and the aberrant host immune response. Additional factors, like systemic disorders such as diabetes or poor habits like smoking could worsen the condition [3].

Periodontitis is an important public health concern due to its high prevalence, that impacts chewing function and aesthetics, is a source of social inequality, and significantly decreases the quality of life. Periodontitis is a major cause of edentulism and masticatory dysfunction, has a poor influence on overall health, and results in considerable dental care expenses [4].

Through proper therapy, effective personal plaque management, and a thorough supportive phase, the majority of patients with periodontitis can preserve their natural teeth for an extended period of time. The main goal of periodontitis treatment is to prevent further periodontal destruction as well as the morpho-functional rehabilitation [1].

Researches suggests that combining mechanical periodontal therapy with systemic or locally administered antimicrobial drugs can be an effective treatment strategy for periodontitis [5] and these results were obtained with the use of several locally or systemically administered antibiotics, such as minocycline, doxycycline, or tetracycline [6].

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The aim of the present paper is to provide information with respect to some locally delivered antibiotics used as adjunctive therapy in periodontitis treatment.

PERIODONTITIS – GENERAL FEATURES

Periodontitis is a complex polymicrobial disease in which numerous host variables play an important role in determining the individual susceptibility to disease [7]. It is well known that the relationship between periodontal microbiota and the host is generally benign, but when the specific bacterial species overgrow in the subgingival areas, this will cause periodontal inflammation and destruction [8]. Periodontal inflammation may occur as a result of immune system dysregulation, leading to the further induction of microbial dysbiosis [9]. New developments in periodontal research suggest a different pathogenesis model for periodontitis, where a dysbiotic and synergistic microbial population initiates the disease rather than specific periodontopathogens. In this polymicrobial synergy, different members or specific gene combinations within the community fulfill distinct roles that converge to shape and stabilize a disease-provoking microbiota [10]. One of the primary conditions for the emergence of a potentially pathogenic community is the ability of certain species, known as "keystone pathogens", to modify the host response in ways that alters the immune surveillance and tip the balance from homeostasis to dysbiosis. Through interactive contact with accessory pathogens, keystone pathogens increase the pathogenicity of the entire microbial population [10].

Interleukin (IL)-6 is one of the key host inflammatory mediators engaged during the inflammatory response, that along with other inflammatory mediators implicated, decreases the progression of periodontitis and periodontal tissue deterioration. Unbalanced IL-6 levels may be more accurate than other periodontal pathogens in biofilms in predicting the early emergence of periodontitis, and serum IL-6 levels may be useful in determining the degree of periodontitis [11]. Periodontitis patients had greater salivary IL-6 levels than individuals in good health, and a proportional increase in salivary IL-6 was connected with the severity of periodontitis and tooth loss [11].

Inflammatory periodontitis is treated primarily by supra and subgingival debridement of affected tooth surfaces. Mechanical instrumentation and surgical treatment combined with proper oral hygiene measures can arrest or prevent further periodontal attachment loss in most individuals. Despite diligent periodontal treatment, some individuals continue to experience periodontal breakdown, may be due to the ability of major periodontal pathogens, like *Aggregatibacter actinomycetemcomitans, Porphyromonas gingivalis, Fusobacterium nucleatum* or *Treponema denticola,* to invade periodontal tissues or the furcations area or other tooth structures outside the reach of periodontal instruments or due to poor host defense mechanisms [8].

PERIODONTITIS TREATMENT – A BRIEF OVERVIEW

The European Federation of Periodontology S3 level Clinical Practice Guideline recommends a stepwise treatment approach applicable for all periodontitis cases consisting of the supragingival plaque control plus the management of patients' susceptibility and professional subgingival mechanical instrumentation that eliminates subgingival calculus and biofilm deposits [1].

The first step of therapy aims to provide to the periodontitis patient the adequate preventive and health promotion tools to facilitate compliance with the prescribed therapy and the assurance of adequate outcomes. This step not only includes the implementation of patient's motivation and behavioral changes to achieve adequate self-performed oral hygiene practices but also the control of local and systemic modifiable risk factors that significantly influence the disease progression. While this initial stage of therapy may not fully address the needs of a periodontitis patient, it serves as the basis for achieving the best possible treatment outcomes and long-term stability [1].

The removal of the supragingival dental biofilm and calculus deposits is considered an essential component in the primary [12] and secondary [13] prevention of periodontitis as well [14].

The second step of therapy, subgingival mechanical instrumentation aims to eliminate of the subgingival biofilm and calculus [15].

The first and second-step therapies reduce dysbiosis and suppress local inflammation [16], improving clinical parameters, and remains the gold standard of periodontitis treatment, but sometimes has a limited efficiency in eliminating subgingival deposits and periodontal pockets [17]. Different adjunctive therapeutical strategies have been suggested to improve the effectiveness of subgingival mechanical instrumentation, especially in severe and high-risk cases, although some locally delivered antimicrobials used in conjunction with subgingival mechanical instrumentation have been shown to determine a significantly greater reduction of periodontal pockets as compared to subgingival instrumentation alone [17].

After active periodontal therapy, if the endpoint of the treatment: pocket closure, defined by probing pocket depth (PPD) ≤4 mm and absence of bleeding on probing (BOP) are obtained, regular supportive periodontal care through combined preventive and

therapeutical approaches maintains periodontal stability over time [1].

ADJUNCTIVE ANTIMICROBIAL THERAPY IN PERIODONTITIS TREATMENT

Periodontal treatment aims to eradicate periodontal pathogens. Through subgingival mechanical instrumentation are eliminated hard and soft deposits from the tooth surface and inflammation is suppressed, but therapy has significant limitations due to the difficulty of addressing to deep periodontal pockets where may persist the periodontal pathogens, such as *Aggregatibacter actinomycetemcomitans* and *Porphyromonas gingivalis* after instrumentation and this might result in microbial recolonization [18-21].

With respect to this issue, adjunctive systemic and localized antibiotics have been applied to compensate for the limitations of mechanical therapy.

Systemic antibiotics have been shown to considerably enhance the results of mechanical periodontal treatment. A mean attachment gain of 0.3-0.4 mm, was reported by Herrera et al. and Haffajee et al., when systemically administrated antibiotics were used adjunctive to subgingival mechanical instrumentation, comparative with subgingival instrumentation alone [22,23].

All the antibiotics used in periodontal therapy inhibit the growth of the major periodontal pathogens such as *Porphyromonas gingivalis*, *Campylobacter rectus* and *Capnocytophaga*. In contrast, none are particularly effective in the inhibition of Eikenella corrodens (minocycline and doxycycline being best). Minocycline appears to be the most effective antibiotic, which achieves levels that should be completely inhibitory (antibiotic activity = 600%) to most of the periodontal pathogens but may inhibit the growth of beneficial species as well [24]. Amoxicillin appears almost as effective as minocycline. Tetracycline, the most commonly used antibiotic but appears to be relatively ineffective against *Aggregatibacter actinomycetemcomitans*, for which it has been used most commonly. Erythromycin appears to be a poor choice for any oral infection. Metronidazole is uniquely effective in treating *Selenomonas sputigena* and *Peptostreptococcus infections* and equal to minocycline in treating *Fusobacterium infections* [24].

Systemic antibiotics, on the other hand, reach all oral surfaces as well as having the ability to reach periodontal bacteria that eventually penetrate the host's tissues [25,26]. The disadvantages of systemic antibiotics over locally applied antibiotics include adverse effects [27], uncertain patient compliance [28] and lower concentration of the drug at subgingival sites [29]. The use of systemic antibiotics rises a serious concern due to the possibility of bacterial resistance development.

As opposed to oral administration, local administration of anti-infective agents, offers the ability to reach higher concentrations of drug directly to the affected region while reducing potential systemic adverse effects [30]. Drugs such as minocycline or doxycycline have been researched, marketed, and approved for local-delivery within the pocket and some clinical researches has shown that these anti-infective agents show a statistically and clinically significant decrease of the PPD and increases of the clinical attachment level in periodontitis patients [31].

The main advantage of this method is that it avoids the negative effects of systemically administered pharmaceuticals and reduces the possibility of bacterial resistance development to the therapies. As a result, various studies have been conducted to evaluate the efficacy of locally applied antiseptics and antibiotics as adjuncts to periodontal treatment [32,33]. The overall outcomes of these treatments were not particularly promising [34-36], which might be partially explained by some of the ecological concepts, such as the notion of periodontits as an infection that affects the entire oral cavity. As a result, it was recognized that the use of localized therapies restricted to a subset of deep subgingival sites is particularly limited, and local antimicrobial therapy has more commonly been used during the supportive periodontal care, for treating residual and isolated active pockets [37,38].

LOCALLY DELIVERED ANTIBIOTICS IN PERIODONTITIS TREATMENT – TYPES AND CLINICAL OUTCOMES

Minocycline

Minocycline has anti-inflammatory properties and for example, has been found to reduce the inflammatory response in LPS-challenged monocytes [39], inhibit matrix metalloproteinase and pro-inflammatory cytokines, [40], and limit bone resorption by directly acting on osteoclast precursors [41]. Many studies have shown that minocycline can lower inflammatory indicators and enhance clinical results in short-term assessments as well as after the first and second steps of periodontitis treatment [42-46]. There has been a paucity of research into the use of locally administered minocycline microspheres in longer-term supportive treatment in periodontitis patients and to determine their impact on inflammatory markers. Meinberg et al. reported that using subgingival mechanical instrumentation in combination with minocycline microspheres resulted in lower PPD and less frequent bone height loss than standard periodontal care [47]. Since the clinical efficacy of minocycline microspheres used

in conjunction with subgingival mechanical instrumentation has been demonstrated in active therapy protocols [44,48], this drug has become a common treatment for residual pockets during routine supportive periodontal care, since these areas are more likely to deteriorate [49].

Several short-term studies have been conducted to investigate the effect of subgingival mechanical instrumentation combined with minocycline microspheres during periodontitis therapy. After 30 days, the study conducted by Goodson et al., that followed 127 patients, divided in 2 groups, in which one of the group received only subgingival mechanical instrumentation and the other group received subgingival mechanical instrumentation + minocycline microspheres, the authors observed a 25% reduction in bleeding on probing in the subgingival mechanical instrumentation + minocycline microspheres group, compared to 13.8% in the subgingival mechanical instrumentation alone group. The researchers also observed a clinical attachment gain of 1.2 mm in the subgingival mechanical instrumentation + minocycline microspheres group after 1 month, compared to 0.8 mm in the subgingival mechanical instrumentation alone [45].

Williams et al. observed, in the study that compared the subgingival mechanical instrumentation to subgingival mechanical instrumentation + minocycline microspheres, in 748 patients, a 1.32 mm reduction in PD in the subgingival mechanical instrumentation + minocycline microspheres sites after 9 months, whereas the subgingival mechanical instrumentation alone sites shown a 1.08 mm reduction in PD. BOP decrease in moderate pockets was comparable among treatment groups [50].

Paquette et al. also reported, after following 271 smokers patients at 1, 3 and 9 months, that adding minocycline microspheres to subgingival mechanical instrumentation reduced the initial probing pocket depth with 1.19 mm [51].

According to Killeen et al., PD was reduced with 17% (0.9 mm) and 19% (1.0 mm) when the patients received subgingival mechanical instrumentation + minocycline microspheres after 6 and 12 months, respectively [31].

Commercial examples of products based on Minocycline:

- ARESTIN® - minocycline hydrochloride, 1 mg, OraPharma, Inc.,
- SUNSTAR Periocline® 2% gel, Dental Ointment.

Doxycycline

Doxycycline (DOX) inhibits Gram-positive and Gram-negative bacteria as well as particular periodontal pathogens [52]. Its primary antibacterial therapeutical action is protein synthesis inhibition [53] and it has anti-inflammatory characteristics due to the direct suppression of the activity of matrix metalloproteinase, which is involved in periodontal tissue destruction [54], and also, is believed to be the most effective anti-collagenase agent [55]. DOX also has an osteogenic effect, promoting bone tissue creation by activating osteoblasts and inhibiting bone resorption [56]. At sub-therapeutic levels, DOX has beneficial effects on bone tissue repair processes and modulation of the host response [53]. DOX's non-antimicrobial properties, may thus contribute to its efficacy in the treatment of periodontitis [57]. The use of a gel to apply a drug in the periodontal pocket ensures longer retention of the drug in place, which prolongs its effects [58]. The inflammatory process in periodontitis, on the other hand, enhances the renewal rate of gingival crevicular fluid, resulting in faster drug diffusion from the delivery device [59]. Thus, an important goal in the development of drug delivery systems is to maximize adhesiveness [60]. DOX gel 10% has been used in the treatment of periodontitis and has been shown to more successfully in reducing PPD and increase clinical attachment level when compared to subgingival mechanical instrumentation alone, thus raising the quality of life of people affected by periodontitis [61]. However, Garrett et al. reported that the treatment of moderate to severe periodontitis with 10% DOX was only as effective as subgingival mechanical instrumentation [62].

Thus, to improve treatment efficacy and prevent physicochemical and biological degradation of drugs, molecular inclusion strategies, including those employing cyclodextrins, have been investigated. The benefits of beta-cyclodextrin include its use in drug carrier systems, enhanced solubility, bioavailability, the capacity to offer aqueous stability for lipophilic drugs, and control over the release patterns of water-soluble drugs such as DOX [61].

These advantages serve to increase therapeutic efficacy and reduce local and systemic adverse effects [61].

Commercial examples of products based on Doxycycline:

- ATRIDOX® (doxycycline hyclate) 10%, TOLMAR Inc.,
- Ligosan® Slow Release, Kulzer.

Tetracycline

The tetracycline groups of drug are among the most often used agents to treat periodontitis. Tetracycline can be used systemic, but also as a local drug delivery agent which, have the advantage of avoiding the harmful effect of systemic administration including the development of resistant flora, suppression of normal flora and poor patient compliance [63].

Locally delivered antibacterial agents into periodontal pockets have been extensively studied since 1979 and this mode of drug delivery avoids most of the problems associated with systemic therapy, limiting the drug to its target site, and hence achieving a much higher concentration [64]. These locally administrated drugs, used in periodontology have gained recognition and appeal over systemic treatments due to a lower likelihood of resistant flora development, opportunist infection, and adverse effects [65].

Tetracycline, in various forms, has considerable promise for managing the course of periodontitis due to its capacity to reduce microbial load, limit collagenase activity, and possibly inhibit bone loss [66,67]. A meta-analysis published in 2003 reported a significant mean reduction in probing depth in favor of local tetracycline therapy and suggested more advantage with fibers compared to other devices [33]. In contrast to these findings, Matesanz-Perez P et al. found that there is no meaningful improvement and advised using this data with care due to the high degree of heterogeneity and risk of bias in the included studies [68].

Commercial examples of products based on Tetracycline:

– Periodontal Plus AB™, Advanced Biotech Products (P) Ltd.

Regarding the products available on the European market, the systematic review, conducted by Herrera et al., revealed statistically significantly improved PPD reduction of locally applied antibiotics as an adjunct to subgingival debridement on short-term follow-up (6–9 months) for Atridox® [69]. On short-term follow-up (6–9 months), Ligosan® showed statistically significant improved clinical attachment level when was used as adjunct to subgingival debridement. Long-term data did not show significant improvement of clinical attachment level for any product. Data on BOP and pocket closure were insufficient and the estimated effect size indicated an increased effect of 10%–30% in PPD reduction [69].

In **conclusion**, the European Federation of Periodontology S3 level Clinical Practice Guideline, based on the current evidence regarding the use of locally delivered antibiotics as adjunctive to subgingival mechanical instrumentation, through evidenced based recommendations, suggest to practitioners that may consider the use of locally antibiotics in specific clinical situations [1].

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