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Research progress in topical antibiotic prophylaxis in the treatment of peri-implant diseases

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Abstract: *At present, implant restoration is one of the repair methods of dentition defects and dentition loss, and peri-implant diseases are the main causes of implant failure, so the prevention and treatment of peri-implant diseases has become a research hotspot. Antibiotics are commonly used to prevent early postoperative infection and treat peri-implantitis, and the application methods are divided into systemic application and topical application, this article reviews the strategies of topical antibiotic prevention and treatment from three aspects: prevention of early postoperative implant infection, reversal of early peri-implantitis and treatment of peri-implantitis.*

Keywords: *Peri-implantitis, Antibiotic, Drug release, Antibacterial*

1. Introduction

With the aging of China's population, the number of patients with dentition loss or dentition defect is increasing year by year, and the highly advantageous implant restoration has become the preferred treatment method for more and more patients, and at the same time, the prevalence of its main complication, that is, peri-implant diseases, is also increasing. One long-term follow-up study showed that half of the patients developed peri-implant disease after implantation, with the prevalence of peri-implant mucositis being 22.1% and peri-implant inflammation 22.3% [1].so the prevention and treatment of peri-implant diseases has become a research hotspot.

Implants are made of biocompatible materials that can be fixed directly to the jaw and are called "osseointegration". Peri-implant disease (PI) is an infectious disease caused by bacteria in peri-implant tissues, and its lesions are present in soft tissues, i.e. peri-implant mucositis, and if it affects the supporting bone tissue around the implant, i.e. peri-implantitis, it is the main cause of implant failure. Peri-implantal mucositis refers to a reversible inflammatory process in soft and connective tissues near the implant. Peri-implantitis is a progressive and irreversible peri-implant soft and hard tissue disease with progressive bone loss, bone resorption, decreased osseointegration, increased pocket formation, and purulence.

At the 6th European Symposium on Periodontology in 2008 [2], it was emphasized that plaque biofilm is an important causative factor of PI, and it is necessary to thoroughly and effectively remove plaque biofilm through anti-infection measures to control inflammation around the implant.

This article will explain the application of local antibiotic strategies in three aspects: prevention of early infection after implant surgery, reversal of early peri-implantitis, and treatment of peri-implantitis.

2. Antibiotics to prevent early infection after implant surgery

The formation of bacterial biofilm is a continuous process, which is mainly divided into four stages: the colonization stage of reversible adhesion of bacteria, the agglomeration stage of irreversible adhesion, the maturity stage of biofilm and the shedding and recolonization stage of bacteria. It is difficult to remove the biofilm after it has matured, so in order to prevent peri-implant diseases, scientists intervene before the biofilm forms. At present, most implants are made of pure titanium or titanium alloy, but this material itself does not have antibacterial ability, giving the implant or the surrounding environment antibacterial properties is the key to prevention. In the early stage of implantation, through the local

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antibiotic sustained release system, it is slowly released in the surrounding local tissues, which has a long-term bacteriostatic effect, such as coating, microparticles, membrane, hydrogel, etc. can improve the implantation environment, thereby preventing the occurrence of the disease and improving the success rate of implantation.

2.1 Coating

In recent years, a large number of studies have been devoted to loading antibiotics on the surface of implants/abutments to prepare antimicrobial coatings and achieve local release of antimicrobial drugs. Some researchers [3] constructed a graphene oxide coating on the surface of the titanium abutment, and the graphene oxide coating was loaded with minocycline hydrochloride to achieve the effect of preventing peri-implantitis. Studies have shown [4] that in order to prevent implant-related infections and avoid the harmful effects of high concentrations of antibiotics in implants on local cells (including primary human adibris-derived stem cells (ADSC)), a drug sustained-release coating was prepared with coral-derived hydroxyapatite and a biodegradable polylactic acid (PLA) film as the substrate to deliver gentamicin and attach to the surface of the titanium alloy implant, which inhibited the value-added of Staphylococcus aureus biofilm and had no adverse effect on local cells.

In addition, the preparation of multilayer film by layer self-assembly technology is also a mature control drug release. The controlled release of drugs can be realized and the time of drug release can be prolonged by deposition of two substances with opposite charge layer by layer by electrostatic adsorption. Researchers [5] prepared vancomycin multilayer sustained-release coating, which showed high bactericidal activity and good biocompatibility in animal models of bone infection, which provided a new strategy for the treatment of bone infection. To improve osseointegration and reduce bacterial colonization at the surgical site.

2.2 Titanium nanotube

Because the titanium nanotube structure has a nano-shaped surface with anti-adhesion properties and a tubular structure with a controllable volume, it can prevent bacterial adhesion and does not affect cell growth, and its tubular structure has the ability to surface load, store and release fungicides, so it is used as a substrate for local drug delivery systems.

In order to improve the antibacterial efficiency of titanium nanotubes, extend the drug release time, and reduce the drug release, researchers modified titanium nanotubes. The release time is extended by controlling its diameter, length and ratio. Some researchers [6] made the upper 35 and 70 nm diameter tubes as nanocaps, respectively, and the lower 140 nm diameter tubes as titanium nanotubes in the reservoir chamber for loading antimicrobial peptides, which effectively slowed down the rate of drug release.

Another approach is that the nanopores formed by surface modification can be loaded with drugs and then covered with polymer coatings of different thicknesses that act as physical barriers, thus slowing the rate at which drugs are released from the aperture. The nanopores formed by surface modification can be loaded with antibiotic drugs and then covered with polymer films of different thicknesses to act as a physical barrier, thereby slowing the rate of antibiotic release from the pore size. Some researchers [7] formed a titanate nanolayer on the surface of titanium through alkalizing water heat treatment, which was covered with polymer PVA film after loading metronidazole, which improved the wettability and biological activity of the implant surface and had bacteriostatic effect.

However, some studies believe that polymer membrane-sealed antibiotic-loaded nanotubes will affect their initial antibacterial activity, so some scholars [8] use antibiotic-containing chitosan mixed membrane-sealed drug-loaded nanotubes, and the release kinetics confirm that the sustained release of drugs can be controlled through the film. In addition, due to its powerful antimicrobial properties, this film not only inhibits initial bacterial adhesion, but also enhances cell viability. This antibiotic sustained-release system has considerable potential as a biomaterial for the prevention of initial release and peri-implant infection.

However, after the long-term release of the drug, the drug reserve will still be insufficient. Therefore, some scholars have designed a trigger response coating on this basis to play an antibacterial role only in the case of bacterial invasion. In general, bacterial infections in surrounding tissues are accompanied by changes in the local microenvironment or an increase in certain bacterial biomolecules. These changes can be used as switches that trigger the antibacterial effects of the coating. The coating of this design improves the antibacterial efficiency.

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Some researchers have applied PH-sensitive acetal connectors to load AgNPs onto titanium nanotubes to prepare antibacterial coatings for delivering AgNPs. The coating can store AgNPs at physiological pH, releasing only a small amount of AgNPs, and then quickly releasing a high dose of AgNPs when the pH is reduced to 5.5 [9].

Li et al. prepared a heat-sensitive hydrogel layer in an animal model of subcutaneous infection and verified that a layer that releases glycerol when triggered by a temperature increase has good antibacterial effects. In addition to changes in the concentration of biomolecules during bacterial infection, some biomolecules, such as bacterial hyaluronidase secreted by bacteria, can act as triggers [10].

Yuan et al. used LBL technology to functionalize hyaluronic acid and chitosan based on catechol-coated multilayer TNT loaded with vancomycin. During a bacterial infection, bacterial hyaluronidase degrades layers based on hyaluronic acid, leading to the release of vancomycin in loaded titanium nanotubes which ultimately kills the bacteria [11].

2.3 Periodontal pockets carry medication

Sustained release of periodontal pockets to effectively improve the peri-implant inflammatory environment and prevent early postoperative implant infection. Liu [12] et al. compared the effect of minocycline hydrochloride ointment with oral antibiotics and gargle, and showed through clinical parameters that topical application of minocycline hydrochloride can prevent the formation of dental plaque, thereby reducing the incidence of peri-implantitis and achieving the purpose of prevention.

3. Antibiotics reverse early peri-implant mucositis

Since peri-implant mucositis may progress to peri-implant inflammation, its prevention or treatment will be the most effective way to prevent progressive peri-implant bone loss. In the early stage of peri-implant mucositis, removal of plaque biofilm can effectively reverse its occurrence. This goal can be achieved through professional mechanical therapy and regular supportive therapy, in addition to the combination of antibiotic assisted therapy to further control the plaque biofilm. After systemic antibiotics combined with mechanical debridement, gingival bleeding index and probing depth were significantly reduced at 0-3 months and 0-6 months [13].

Topical use of antibiotics is more effective than systemic use. In the early stages of peri-implantal mucositis, topical antibiotic sustained release is effective in reversing its occurrence. Some scholars [14] compared the therapeutic effect of topical minocycline hydrochloride ointment and oral ornidazole, and the clinical parameters indicated that the former was more effective. Minocycline hydrochloride ointment in combination with other antibiotics reduces the degree of inflammation, reduces periodontal tissue destruction, improves clinical efficacy. One randomized controlled [15] study showed that minocycline hydrochloride ointment in combination with metronidazole sustained-release membrane significantly reduced levels of inflammatory factors in gingival sulcus fluid compared with minocycline ointment alone.

4. Antibiotics for peri-implantitis

Plaque biofilm is the main cause of the development of peri-implant inflammation. Therefore, the treatment should minimize the production of plaque biofilms, remove microorganisms from the implant surface, and eliminate tissue inflammation around the implant. This method is essential for protecting bone tissue around the implant and for regenerating bone lost when disease occurs. Non-surgical treatment, including mechanical debridement and oral health instruction, has been shown to be effective in alleviating symptoms, but this approach alone may not be effective. The success rate of direct removal of the implant biofilm and curettage of the granulation tissue was low. Increased use of adjuvant means can enhance the effectiveness of surgical and non-surgical treatment. AIDS usually include chemical agents, such as chlorhexidine and sodium hypochlorite; Mechanical debridement rinsing agent, such as normal saline and hydrogen peroxide, etc. Antibiotics such as tetracycline and amoxicillin. Among them, in the course of surgical treatment and non-surgical treatment, the combined use of local antibiotics as an adjuvant treatment can significantly improve clinical periimplantitis, and can improve the success rate of surgery.

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4.1 Non-surgical treatment

Mechanical debridement is a common treatment method for early peri-implantitis, but due to the complex structure of the implant, the influence of the location and accessibility of bacterial biofilms, it is difficult to completely remove the microbial film of plaque on the surface of the implant by mechanical debridement alone, and this method is somewhat traumatic and easy to cause other complications, so it is necessary to combine antibiotic treatment methods on this basis to improve the plaque index and gingival groove bleeding index at the same time, improve the depth of exploration index, promote the regression of plaque, control inflammatory factors, and have few adverse reactions. High security, worthy of choice. The application of antibiotics can be divided into systemic use and local use. Oral antibiotics have the disadvantages of small drug concentration in the local area, long-term drug resistance, damage to multiple target organs, poor patient compliance and so on. Therefore, the local use of antibiotics has become the main method.

The recent use of antibiotics in periodontal pockets is a new treatment for peri-implantitis. In a randomized controlled trial [16], Butcher et al. compared Atrigox™, a single mechanical debridement, with a combined topical application that produced a sustained slow release of doxycycline. The results showed that the periodontal attachment level of the patients treated with doxycycline sustained release system was significantly increased, the depth of probe was significantly reduced, and the therapeutic effect was better than that of mechanical debridement alone. Local use of antibiotics can not only alleviate the clinical symptoms of peri-implant inflammation, but also effectively reduce the bacteria around the implant.

Park et al. compared the effectiveness of mechanical debridement, mechanical debridement combined with minocycline ointment, or combined with minocycline - metronidazole ointment in a randomized double-blind, three-arm clinical trial. After 4 months, the periodontal pocket depth and periodontal probing index in the antibiotic group were significantly lower than those in the mechanical debridement group alone. The bacterial counts of P. gingivalis, P. intermedia, T. denticola, T. forsythia, C. rectus, and F. nucleatum were significantly reduced in the antibiotic group. In the mechanical debridement group, only P. gingivalis was significantly reduced [17].

In adjuvant therapy, antibiotics may be more effective than chemical agents. Topical minocycline microspheres improved the treatment of early or intermediate peri-implantitis more than topical submucosal administration of 0.1 mL chlorhexidine gel 1%, while the additional efficacy of topical minocycline in deep (>5 mm) peri-implant pockets was unclear, and there was no significant difference in the average total number of bacteria between the two groups. Topical antibiotics are more effective than oral antibiotics [18].

In one clinical trial [19], investigators compared the clinical effects of oral antibiotics with topical minocycline hydrochloride ointment. The results showed that the treatment effect of early peri-implantitis in the observation group was significantly higher than that in the control group, indicating that the effect of topical minocycline hydrochloride in the treatment of early peri-implantitis was accurate, which could effectively improve periodontal index, shorten the treatment time and accelerate the resolution of symptoms.

In the sustained-release system of antibiotics, membrane preparation is superior to ointment preparation. In a case study, Lin [20] et al. used ornidazole sustained-release membrane for peri-implantitis, and the results showed that the extended-release film dosage form has high adsorption in periodontal pockets due to the ointment dosage form, and can slowly release the drug over time, maintaining a relatively stable drug concentration environment before and after treatment, while the ointment is more likely to be weakened due to the loss of unconscious tissue movement from the periodontal pocket of the implant due to food chewing in the mouth.

Besides, microsphere preparations can also be used as antibiotic drug carriers for periodontal pocket treatment PI, and some researchers [21] assisted the use of minocycline microspheres into periodontal pockets on the basis of mechanical therapy, and the results indicate that the microsphere group effectively improves the depth of exploration and can last for 6 months, but must be repeated.

4.2 Surgical treatment

If peri-implantitis cannot be completely treated with basic therapy, further surgical treatment is required. Combination with topical antibiotics in surgical treatment improves the success of treatment.

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Studies have shown [22] that repeated topical minocycline combined with surgery improves clinical parameters and radiological bone fill, and leads to higher treatment success rates in short healing periods. In one case report [23], investigators mechanically cleaned the implant surface and applied tetracycline along with bone grafts to the defect area. During follow-up, treatment of peri-implantitis with tetracycline showed improved clinical outcomes.

Antibiotics can also be added to implants during bone reconstruction surgery. Some scholars [24] evaluated the clinical and radiographic outcomes of regenerative treatment of periimplantitis with vancomycin and tobramycin impregnated allografts (VTAs) after 12 months. Topical delivery of antibiotics used with bone grafting can reduce adverse effects and the risk of resistance associated with systemic administration. Depending on the results obtained, these graft materials may provide new therapeutic strategies for the surgical regenerative treatment of peri-implantitis.

5. Conclusions

Topical antibiotic anti-infection strategies are an effective way to treat and prevent peri-implant disease. In the pre-implantation stage, local antibiotic sustained release systems such as coatings, particles, membranes, hydrogels, etc. can improve the implantation environment, thereby preventing the occurrence of the disease and improving the success rate of implantation. In the early stages of peri-implant mucositis, this strategy can effectively reverse its occurrence; In the setting of peri-implantitis, topical antibiotics can be used as adjuncts to both non-surgical and surgical treatment with good results. At present, a variety of drug carriers are used for local sustained release, and it is promising to carry out new topical drug sustained release systems with certain biological properties in the future to carry antibiotics for the treatment of peri-implant diseases.

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