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Research progress of local sustained-release drug delivery system in the treatment of peri-implantitis

Yijing Cao[1], Wenjie Zhang[1], Suiyan Wei[1], Guoqiang Xu[1,*]

[1]The First Affiliated Hospital of Xinjiang Medical University (Affiliated Stomatological Hospital), Urumqi, Xinjiang Uygur Autonomous Region, 830054, China
[*]Corresponding author: dentist1980@163.com

Abstract: *With the increasing demand for oral implants, the incidence of peri-implantitis is also increasing year by year, and serious cases may even lead to implant loss. Studies have shown that the clinical treatment of peri-implantitis is divided into resection and regenerative surgery, and conventional drug treatment is divided into systemic and local administration. Compared with systemic administration, the local sustained-release system can not only reduce the adverse reactions and drug resistance of systemic administration, but also achieve a high concentration of drugs that can continuously kill bacteria in the periodontal pocket. Therefore, the treatment of peri-implantitis with local sustained-release system has become a research hotspot at home and abroad. This article reviews the research progress of local sustained-release system in the treatment of peri-implantitis in recent years.*

Keywords: *material, peri-implantitis, local drug-loaded sustained-release materials*

1. Introduction

Studies have shown that the 10-year success rate of dental implants can reach 94.6 % [1].With the increase of implant cases, the incidence of peri-implantitis is about 3 % -47 % [2-3].When the plaque biofilm is formed between the implant and the osseointegration interface, the osseointegration and soft tissue closure will be destroyed by inflammation and difficult to regenerate, eventually leading to the failure of implantation [4]. At present, the main treatment methods for peri-implantitis include laser therapy, radiofrequency ablation, antibiotic drug therapy and photodynamic therapy[5]. Although there are many treatments for peri-implantitis in clinical practice, it is found that adjuvant antibiotic therapy can significantly benefit the treatment process. However, traditional methods such as oral or topical use cannot maximize the efficacy of drugs, and require long-term use by patients, causing many inconveniences to patients. Therefore, local application of antibiotics is an indispensable treatment for peri-implantitis.The local sustained-release system can release drugs in a long-term manner. When it is loaded with antibacterial drugs for the treatment of peri-implantitis, it can not only have a long-term antibacterial effect, but also create a microenvironment conducive to late osteogenesis.

The sustained-release drug delivery system is a pharmaceutical preparation that prolongs the release rate of therapeutic drugs in a controlled manner within a specified time. Why do we need to control drug release from the carrier? By far, the biggest advantage of local drug delivery systems is to extend the duration of the drug at the desired site (such as periodontal pockets). Sustained-release drug administration, that is, prolonging the release rate of the drug from the matrix, means that the release rate and release amount of the drug can be controlled over time [6].

When the local drug delivery system is used for peri-implantitis, the local drug delivery system can be used in various ways for its treatment. For example, the sustained-release material is injected into the periodontal pocket of the patient by in-situ injection to achieve antibacterial effect. It is also possible to combine the local drug sustained-release material with 3D printing technology to personalize the bone graft substitute material according to the bone defect morphology of the implant area and implant it simultaneously with the implant. Surface modification technology can also be used to prepare drug coatings on peri-implantitis to prevent and treat peri-implantitis. However, the above should be used based on the good biocompatibility of local drug sustained release carrier materials. Here we will explain the common materials used in local sustained release system in recent years:

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2. Classification of drug carrier materials

2.1 Bioceramic materials

Bioceramics refer to materials including alumina, zirconia, bioactive glass, glass ceramics, hydroxyapatite, and absorbable calcium phosphate [7]. Because of their biocompatibility and excellent physical and chemical properties, a large number of bioceramic materials are used in dental treatment and can be classified as bioinert, bioactive and biodegradable ceramic materials. They have specific features designed together to implement their functions. They can be used as root canal sealers, adhesives, root canal repair or filling materials. Bioceramic materials can be used as direct pulp capping materials for pulp exposure caused by trauma, dental caries or other mechanical reasons[8].

2.2 Organic polymer materials

With the continuous development of science and technology, a single material cannot be full. In order to meet the needs of the current rapid development of technology, people are committed to developing various new composite materials.In recent years, a large number of natural and synthetic organic polymer materials have attracted attention due to their good degradation rate and excellent biocompatibility. Natural polymers such as chitosan, hyaluronic acid, silk fibroin and gelatin are often used to construct drug coatings, which can construct porous structures. Most of the surfaces are positively charged, which can interact with negatively charged bacterial surfaces, destroy cell membranes, release intracellular components, and play a role in sterilization and inhibition of biofilm formation [9-1].

2.3 Functional nanomaterials

Nanomaterials are materials composed of individual units between 1 and 100 nanometers. Due to the special physical and chemical properties generated by their high specific surface area and nanometer size, they have great potential in many fields, including pharmaceuticals and biomedicine. Intelligent engineering of nanostructures through appropriate surface or bulk functionalization gives them multifunctional capabilities, opening up new possibilities for biomedical fields such as biosensors, drug delivery, imaging, medical implantation, cancer treatment, and tissue engineering [11]. In recent years, carbon nanomaterials have been used as drug carriers to accurately and timely release drugs because of their good mechanical properties, antibacterial properties and biological properties. Among them, the carbon nanomaterial coating based on graphene and its derivatives as a drug sustained release system can deliver drugs to surgical wounds, prevent infection, promote wound healing and implant osseointegration[12-13].

3. Local drug delivery system for the treatment of peri-implantitis

3.1 Hydrogel sustained-release system

A hydrogel is a group of materials with a three-dimensional polymer network that can hold a large amount of water. Because of its good biocompatibility, stable degradation rate and excellent mechanical properties, it has become an excellent material for biomedical applications. In 2019, CHEN [14] et al,used a thermosensitive micelle hydrogel to encapsulate ibuprofen fibroblast growth factor to study its feasibility as an early local treatment for peri-implantitis. It can promote soft tissue healing after implant surgery and has good anti-inflammatory effect. It is an ideal local sustained-release drug delivery system. In 2020, Huang Pingping[15] et al,injected nano-zinc oxide particles wrapped in chitosan / β-glycerophosphate composite thermosensitive hydrogel into periodontal pockets. The study found that it has good physical and chemical properties, biocompatibility and antibacterial properties. It is expected to become an auxiliary material for the prevention and treatment of peri-implantitis. In 2022,Zhou[16]et al,developed a dexamethasone-hyaluronic acid-chitosan composite hydrogel to treat peri-implantitis. The results showed that the prepared multifunctional hydrogel achieved sustained release and promoted the growth of fibroblasts.

3.2 Coating material slow release system

Surface modification is beneficial to increase the physical and chemical properties, bone induction and antibacterial properties of the material, inhibit the initial colonization of bacteria, reducethe

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formation of plaque biofilm, improve the state of tissue inflammation, and form a soft tissue and bone tissue barrier against bacterial infection by promoting cell adhesion, proliferation and differentiation, thereby preventing the occurrence of peri-implantitis. The drug coating can not only give the implant / abutment surface antibacterial, promote osseointegration and soft tissue closure, but also reduce the systemic toxic and side effects, which can greatly reduce the medical cost and improve the comfort of patients[9-10]. In 2017, GEULI[17]et al. deposited drug-loaded HAp nanoparticles (NPs) on the surface of titanium implants by electrophoretic deposition. The drug-loaded HAp nanoparticles (NPs) were loaded with 12.5 % gentamicin sulfate (Gs) and 12.8 % ciprofloxacin (Cip) to prepare hydroxyapatite coatings loaded with gentamicin sulfate or ciprofloxacin. Nano-hydroxyapatite coating extended the release time of gentamicin sulfate and ciprofloxacin to 10 d and 25 d, respectively, and effectively inhibited Pseudomonas aeruginosa. The study found that the nano-hydroxyapatite coating obtained by nanotechnology is more conducive to drug loading and sustained release.In 2017, WANG[18]et al.successfully prepared a silica-gentamicin-gelatin coating by one-pot method. It was found that the coating had good compatibility with gingival fibroblasts. In the first 8 hours, high concentration of gentamicin was rapidly released during the decomposition of silica, and then slowly released withthe gradual degradation of gelatin. The coating effectively inhibits the growth of S.aureus. The coating makes it possible for the stable storage and controlled release of gentamicin, has good antibacterial properties and biocompatibility, and has the potential to prevent peri-implantitis.In 2020, WEI[19]et al,loaded aspirin into polylactic acid-glycolic acid copolymer by electrospinning technology, constructed a nanofiber coating on the surface of titanium (Ti), and modified it with dopamine to ensure the adhesion between the two. The study found that the drug in the coating could be continuously and stably released for 60 days, and could promote the osseointegration of the implant, inhibit osteolysis and improve inflammation. In 2021, SUCH[20]et al,prepared a vancomycin-loaded hydroxyapatite implant coating, and found that the coating can be used to prevent bone destruction caused by infection and promote osseointegration, and has the potential to prevent peri-implantitis. In 2021, DINDELEGAN [21]et al, proposed porous titanium as a substrate to coat a composite coating material composed of chitosan membranes loaded with growth factors such as BMP2 and IGF1 engulfing microspheres on its surface. Microspheres were obtained by depositing double-layer calcium crosslinked pectin-chitosan / pectin polyelectrolyte on BSA (bovine serum albumin) gel core. The multilayer is envisioned to behave like a third-generation biomaterial, by slowly delivering viable growth factors around the implant and assisting in the healing of implanted wounds and the development of new important bones. The biological effects of growth factor delivery were studied on MSC-CD1 mesenchymal stem cells in vitro and CD1 mice in vivo. Growth factors promote cell proliferation and differentiation, especially IGF1 and BMP2. It was found that the coating could slowly release two growth factors, which played a role in promoting cell proliferation of IGF1 and promoting cell differentiation of BMP2.This coating could promote wound healing and new bone formation to prevent peri-implantitis.

3.3 Composite bone tissue engineering material sustained release system

Bone tissue engineering has always been closely related to 3D printing. It uses rapid prototyping technology to print personalized bone scaffolds suitable for different people according to the shape of bone defects as bone substitute materials to promote bone repair and regeneration. When it is loaded with different drugs, drugs can directly intervene in the lesion site by direct contact [22]. In 2021, Ahlfeld[23]et al,used 3D printing technology to combine calcium phosphate cement and fibrin gel to form a new biphasic bone structure, and loaded bone marrow mesenchymal stem cells in fibrin gel. The study found that the combination of the delivery system and MSC can create a new regenerative implant for the treatment of alveolar bone defects, which is conducive to promoting osseointegration regeneration. In 2020, Liu[24]et al,created an innovative silk fibroin/collagen/hydroxyapatite biological scaffold through low-temperature 3D printing technology, and loaded recombinant human erythropoietin for bone defect reconstruction. In vivo experiments found that with the degradation of the composite scaffold, it promoted the aggregation and proliferation of osteoblasts and the formation of collagen fibers, which could significantly promote the reconstruction of alveolar bone defects.

4. Outlook

Local drug delivery system is currently a research hotspot in the treatment of various diseases. It has excellent physical and chemical properties, good biocompatibility, long-term drug release time, and controllable degradation rate. It is a better medical biological substitute material. However, its deficiency is that for the carrier material, whether it can bring convenience to patients, whether the price is affordable,

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whether the concentration of the drug is controllable after loading, and whether the degradation of the carrier material will affect the formation of bone and whether it needs to be taken out again ? Although there are many studies, it has not been fully used in clinical practice, and its clinical efficacy needs to be further verified.

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