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Advances in Drug Sustained-Release Carriers for Infectious Bone Defect

Zhang Qian[1], Sun Xinjun[2]

[1]Department of Special Medicine, Basic Medical college ,308 Ningxia Road, Qingdao University, QingDao, China
[2]Traumatology Department of orthopaedics1,The 89th Hospital of PLA(People's Liberation Army), Weifang, China

Abstract: With the development of medicine, more and more sustained-release carriers loaded with antibiotics are used for the treatment of infectious bone defects.On the basis of consulting a large number of literatures, the types of carriers, antibiotics and the preparation methods of sustained-release carriers were analyzed and prospected in this paper.

Keywords: Infectious Bone Defect, Osteomyelitis, Sustained-Release Carriers

Infectious bone defect caused by open fracture is a common refractory disease in the orthopaedics field. The traditional therapies are local lavage and drainage with antibiotics and control infection on the basis of debridement. The residual bone defect needs to be treated by bone grafting or Ilizarov bone transplantation in the second stage after infection control. With the development of medical and health technology, antibiotic-loaded sustained-release carriers are gradually applied to the treatment of infectious bone defects. Compared with traditional treatment methods, the sustained-release carriers have the characteristics of releasing antibiotics and absorbability, avoiding the removal of secondary surgery on the basis of infection control, and do not need to wait for infection control before secondary surgery. In recent years, there have been a lot of studies on sustained-release vectors. This paper summarizes the research progress of sustained-release vectors as follows.

1.Types of sustained-release carriers

At present, the carriers of antibiotic sustained-release system can be divided into two types: non-biodegradable and biodegradable. Non-biodegradable carriers, represented by Polymethylmethacrylate (PMMA), were the first carriers to be used in the treatment of chronic osteomyelitis. Da-hui sun et al. [1] use gentamicin much polymethyl methacrylate (gentamicin - polymethylmethacrylate, G - PM MA) chain bead into 10 patients with the treatment of chronic osteomyelitis, and compared with the lesions clear and local antibiotics lavage fluid drainage treatment of 18 cases of patients with chronic osteomyelitis, the result is G - PMMA group is obviously better than the group of control effect. With the further development, PMMA needs to be removed after infection control because of its non-degradable characteristics. In recent years, researchers at home and abroad are more interested in the research of biodegradable carriers, such as calcium sulfate, calcium phosphate cement, polylactic acid, chitosan and so on. Zhao junqiang et al. [2] conducted a control experiment on 16 rabbit models of tibial osteomyelitis with vancomycin calcium sulfate and vancomycin bone cemen trespectively. According to the comparison of the concentration of vancomycin in drainage fluid and blood after operation, the results showed that the release of vancomycin calcium sulfate in vivo was better than that of vancomycin bone cement.

2. Types of antibiotics loaded

At present, the following consensus has been reached on the choice of topical antibiotics: (1) low allergic reaction rate; (2) good histocompatibility; (3) broad-spectrum, sensitive, low drug resistance; (4) small systemic side effects; (5) no impact on wound healing; (6) good stability of antibiotics (no inactivation due to exposure to biological substances such as blood, pus or cellulose); and (7) high water solubility. Vancomycin is a glycopeptide macromolecule antibiotic with strong potency and is often used when other antibiotics are ineffective against pathogens. Vancomycin has incomparable efficacy in the treatment of Gram-positive cocci. In recent years, more and more vancomycin has been used in the treatment of bone infections. It has excellent antibacterial effects against virtually all pathogens that may cause chronic osteomyelitis, including methicillin-resistant staphylococcus aureus (MRSA). Sun Changgen et al. [3] mixed vancomycin, gentamicin sulphate and cefuroxime sodium with bone cement respectively and placed them in rabbit bone marrow cavity to measure the antibiotic release. The results showed that the method of adding

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Xinjun Sun (Correspondence)
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antibiotics after solid-liquid mixing of bone cement is more conducive to the release of antibiotics, and the release effect of vancomycin was better than other antibiotics.

3. Preparation of sustained-release carrier

3.1 Artificially Prepared Sustained Release Carriers

Qiu Yi-yan et al. [4] conducted an experimental study on the biocompatibility and safety of the two kind of self-made calcium sulfate products which are placed in the bone:calcium sulphate loaded with vancomycin and calcium sulfate loaded with gentamicin. It was found that the two products both had good biocompatibility and safety,which are ideal replacement materials for bone repair in bone defect repair and are worthy to be tested and applied in clinical practice. PENG Zhi et al. [5] analyzed the 62 patients with bone defects treated with vancomycin sulfate artificially mixed granules filling and found that 8 months after the operation, all patients had a good absorption of calcium sulfate granules, and the medullary cavity was recanalized. From 4 to 6 months after operation, 62 patients with bone defect achieved clinical healing, which also showed that calcium sulfate loaded with drugs had a good clinical effect on the treatment of bone defect. Zhang zhan et al. [6] mixed medical calcium sulfate and vancomycin into patients with traumatic osteomyelitis, and measured the release characteristics of antibiotics in local area and blood. The results showed that vancomycin calcium sulfate artificial bone could release high concentration of vancomycin locally, while the whole body concentration was low, the safety was high, and it had bone-guiding effect. Its sustained release rule in human body is consistent with the treatment of osteomyelitis, and it fully meets the requirements of osteomyelitis treatment. At present, there is no uniform method for the preparation of antibiotic sustained-release carriers in clinic. The relationship between the preparation of sustained-release carriers and the shape and size of the carriers and the release of antibiotics needs to be further studied.

3.2 Sustained-release Carriers Prepared by 3D Printing

As a manufacturing technology, 3D printing has developed rapidly in many fields. The principle of its printing carrier is to print layer by layer, stack layer by layer, and each layer or part can be set by computer. Therefore, it can realize arbitrary moulding of the carrier and fixed-point addition of drugs. Because of its simple operation, good flexibility, high repeatability and wide adaptability, now it is widely used in immediate released tablet, sustained-release preparations, compound preparations , control-released carriers and other aspects for research and application [7]. Compared with traditional drug delivery systems which has the disadvantage of difficult to regulate the internal structure,3D printing has a series of merit including specific drug delivery, fewer untoward effects, fewer times of usage and so on [8]. Therefore, the use of 3D printing technology can not only control the external shape of the carrier, make it to the greatest extent consistent with the patient's drug delivery site, but also control the internal structure of the preparation, so that it can be released in patients at a constant rate or at a fixed time.

Zang Xiao-long et al. [9] use 3D biologic printing technology to prepare polylactic acid hydroxy acetic acid / nano hydroxyapatite scaffold material, testing its porosity, pore size, slow release performance, degradation rate, mechanical strength and so on, which conform to construct tissue engineering bone biological requirement. Weigang Wu et al. [10] apply three dimensional printing technology, according to the production principle as "layers of print, layered overlay", assembling the carrier material (levorotatory polylactic acid powder) and active pharmaceutical (levofloxacin and tobramycin) into a concentric cylinder structure with four layers from the center to the periphery, where levofloxacin and tobramycin are arranged from inner to outer layer by layer. In vitro drug release experiments showed that the two drugs were released sequentially from the inside to the outside, thus realizing the controllability of drug release. Three-dimensional printing technology has unique advantages for controlled-release artificial bone with complex spatial structure and multi-drug distribution. 3d printing technology has unique advantages for controlled release drug loading artificial bone with multiple drug distribution and complex spatial structure. It is characterized byaccurate, convenient and controllable drug loading, individualized preparation, and high computer control automation in the preparation process.

4. expectation

At present, there are a lot of experimental and clinical studies on antibiotic carriers for infectious bone defect caused by chronic osteomyelitis, but most of them are manually prepared, which have the shortcomings of poor accuracy, uneven mixing and uncontrollable release of antibiotics. With the increasing application of 3D printing technology, a new method for the preparation of this sustained-release carrier has been proposed, which is hopefully beneficial to us. A personalized sustained-release carrier was prepared by using 3D printing technology according to the patient's imageen Q, Zheng Q, Vancomycin release of vancomycin-calcium sulfate and vancomycin polymethylmethacrylate in animal

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examination data. The carrier will have controlled absorption, controlled sustained-release, and controlled shape and structure, so that it can cooperate with Ilizarov bone transplantation and be implanted in one stage. With the continuous degradation of sustained-release carrier and the continuous release of antibiotics during bone migration, the goal of one-stage healing of infectious bone defects was achieved.

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