The biocompatibility of titanium alloy or stainless steel internal fixation material combined with anti-tuberculosis drug sustained-release carrier

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Abstract. The purpose of this paper is to summarize the treatment of characteristics of bone tuberculosis with titanium alloy or stainless steel internal fixation devices combined with anti-tuberculosis sustained-release materials. A search of literature on the implantation of titanium alloy or stainless steel internal fixation devices combined with anti-tuberculosis sustained-release materials for bone tuberculosis from 1995 to 2019 was performed using PubMed and Web of Science databases. Local sustained-release anti-tuberculosis drugs have been applied in surgical treatment of bone and joint tuberculosis. It can reduce the adverse reactions of systemic administration of a number of anti-tuberculosis drugs in patients with bone tuberculosis and continuously achieve the local effective anti-tuberculosis effect. At present, there are many kinds of materials used in drug sustained-release materials, each of which has its own advantages and disadvantages. It is difficult to achieve the ideal effect of anti-tuberculosis and bone repair. Different materials can be used together to make up the disadvantages for each other. The further progress towards ideal biological materials can be achieved. It may be the developing trend of clinical application of multi-material composite as sustained-release carrier against tuberculosis.

1. Introduction

With the development of internal fixation devices and anti-tuberculosis sustained-release materials, more and more scholars in China and abroad begin to use titanium alloy and stainless steel internal fixation devices combined with anti-tuberculosis sustained-release materials to repair bone tuberculosis. Anti-tuberculosis drug sustained-release carriers have become a new highlight in the treatment of bone and joint tuberculosis in recent years [1]. After being implanted in the bone and joint tuberculosis lesions, the materials can be used as bone substitutes to repair bone defects and release anti-tuberculosis drugs for a long time at the stable concentration [2]. In the past, most clinical internal fixations were made of stainless steel, which is still widely used because of strength and price advantage [3]. Titanium is a safe metal element, very close to the elastic modulus of human bone, so it can produce good compatibility with human body mechanics after implantation. But titanium alloys are expensive, limiting its widespread use [4]. With the development of internal fixation devices and anti-tuberculosis drug sustained-release carriers, more and more domestic and foreign scholars begin
to use titanium alloy or stainless steel internal fixation devices combined with anti-tuberculosis drug sustained-release carriers to repair spinal tuberculosis [5]. In this paper, the characteristics of repairing bone tuberculosis lesions with titanium alloy or stainless steel internal fixation devices combined with anti-tuberculosis drug sustained-release carriers are reviewed.

2. Methods

2.1. Source of data
Articles on titanium alloy or stainless steel internal fixation devices combined with anti-tuberculosis drug sustained-release carriers for bone tuberculosis lesion from January 1995 to February 2019 on PubMed database were indexed by computer for "bone tuberculosis, titanium alloy or stainless steel, fixation, released anti-tuberculosis materials".

2.2. Inclusion and exclusion criteria

2.2.1. Inclusion criteria
Research articles related to the research contents of sustained release drugs against bone tuberculosis. The contents of the literature are representative and the data are reliable.

2.2.2. Exclusion criteria
Poor relevance with the purpose of the study and old, repetitive literature.

3. Results

A total of 129 papers were retrieved, among which 26 literatures with poor correlation with the research purpose and obsolete and repeated contents were excluded, and 103 papers meeting the standards were included for review.

4. Discussion

4.1. Titanium alloy or stainless steel internal fixation materials
In the past, most clinical internal fixations were made of stainless steel. The stainless steel material has good strength, but its elastic modulus is too large to be well matched with the elastic modulus between bones, which may lead to various adverse consequences. Titanium is a safe metal element, very close to the elastic modulus of human bone, so it can produce good compatibility with human body mechanics after implantation. Moreover, titanium alloy has strong inertia and corrosion resistance, not easy to appear a variety of infections. Therefore, titanium alloy is widely used in clinical treatment of various diseases, and play a good role. The experiment compared the effect and biocompatibility of titanium alloy and stainless steel internal fixation material in the treatment of spinal tuberculosis. But stainless steel internal fixation materials due to its price factor is also widely used [6].

4.2. Sustained release carriers of artificial bone drugs
Artificial bone is mainly calcium and phosphorus materials, including hydroxyapatite, tricalcium phosphate, bioglass, calcium phosphate bone cement, calcium sulfate, etc. The chemical composition of such inorganic compounds is similar to that of human bones and can be used as drug sustained-release carriers. In vivo degradable, non-toxic, with good mechanical strength and bone conduction performance. The material has porous structure and can support multiple drugs, bone growth factors and so on. Drug release rate can be controlled by adjusting the pore size of the material itself and the content of additives. The disadvantage of using artificial bone alone is that the PH value of local microenvironment is affected after degradation. The plasticity of ceramic artificial bone is poor, and the degradation speed of artificial bone material is slow, which is not matched with the speed of bone repair. Some scholars developed an implantable sustained-release agent of rifampin-porous hydroxyapatite artificial bone nucleus for the treatment of bone tuberculosis, which was in the shape
of a hollow cylinder [7]. The experiment confirmed that the drug with an effective concentration could be continuously released in the body for at least 27 weeks, and it had an obvious bacteriostatic effect on mycobacterium tuberculosis. Medical calcium sulfate granules containing tobramycin or a mixture of autologous bone and calcium sulfate granules were used for the repair of bone defects after the surgery of bone and joint tuberculosis [8].

4.3. Sustained release materials of polylactones
With polylactic acid (PLA), poly (lactic acid - glycolic acid (PLGA) as the representative of aliphatic polyester synthetic polymer because by chemical synthesis, production, product performance can control, repeatability is good, suitable for the requirement of engineering, but also by changing the structure of the synthesis of polymer, composition to control mechanical properties and biodegradation rate, to meet the needs of different biomedical applications [9]. Them inside the organism and the ester bond rupture due to hydrolysis reaction, degradation, degradation products of lactic acid and glycolic acid but also through the Krebs cycle further isn't toxic metabolic tissue in pairs of carbon dioxide and water, and thus have obtained approval in China and the United States and other countries certification, can be used for the preparation of implanted medical material. After implantation, the material has certain initial mechanical properties. The degradation rate of mechanical properties of degradable materials matched with the rate of bone healing [10]. A series of studies were conducted on the cylindrical PLGA material loaded with isoniazid to study the characteristics of drug release and the repair effect on bone defects. It was indicated that the slow release material system had the ability of local slow release of isoniazid for more than 6 weeks, and the slow release and degradation rate of the material matched the speed of bone repair. However, polylides lack good hydrophilicity, biological activity and sufficient mechanical strength, and generate a large number of low molecular products with carboxyl group after hydrolysis, which can reduce the PH value of the biological internal environment. Low PH value will cause inflammation and damage to the body [11].

4.4. Natural bone materials
The natural bone materials used in clinical practice are mainly produced by the processing of allogeneic bone, including freeze-dried bone, calcified bone matrix, deproteinated bone matrix, acellular bone matrix, etc., with bone conduction and certain bone induction activity [12]. With porous structure and regular pore size, it can load many kinds of drugs. However, as a drug carrier alone, there are still some shortcomings, such as insufficient bone strength, residual immunogenicity, small drug load and poor plasticity [13]. The concentration of anti-tuberculosis drugs plays a vital role in killing mycobacterium tuberculosis. Anti-tuberculosis sustained-release drugs can significantly improve the local drug concentration and enhance the effect of local anti-tuberculosis drugs. Pharmacokinetic studies have proved that maintaining the sustained and stable effective bactericidal concentration around the lesion is the key to killing tuberculosis bacillus. Blood drug concentrations of INH, RFP and PZA almost reach or close to the peak at about 2h after taking the drug, and enter the drug clearance phase at 4-6h. Traditional drug administration makes it difficult for anti-tuberculosis drugs to play a sustained bactericidal role in the local lesion, which is one of the reasons for poor efficacy of spinal tuberculosis and easy to produce drug resistance [14]. Maintaining the local concentration of anti-tuberculosis drugs in the lesion greater than the minimum bactericidal concentration is the key to the treatment of spinal tuberculosis.

4.5. Carriers of multiple materials
Composite material system with single carrier material as joint tuberculosis slow-release drug system used to repair bone defect, and there may be a poor mechanical strength, bone conduction ability only, do not have ability of bone induction, poor plasticity, poor hydrophilicity, microstructure affects cell adhesion, the influence microenvironment PH value, etc, to reach the ideal treatment of joint tuberculosis have ability to repair bone defect [15]. In recent years, the research and application of composite material systems that combine two or more bioactive materials and concentrate the
advantages of different materials into one material have attracted extensive attention from scholars at home and abroad. Therefore, sustained-release materials containing anti-tuberculosis drugs are introduced into the treatment of spinal tuberculosis. Makino et al. embedded the RFP package in the microsphere and found that its release cycle could reach 20 days. Wu et al. developed drug-loaded artificial bone that can carry multiple drugs and has the characteristics of controlled release [16]. The controlled release drug-loaded artificial bone has the characteristics of controlled release and sustained release of drugs. It can achieve the treatment of combined drug therapy and bone defect repair at the same time. However, these studies have shortcomings of single drug delivery or failure to describe in vitro anti-tb performance. Currently, materials for bone defect reconstruction after spinal tuberculosis surgery mainly include autologous bone, allogeneic bone, bone repair materials, etc. [17], among which, autologous bone and allogeneic bone have achieved good results in clinical application [18], but their application is limited due to limited sources and the possible spread of infectious diseases. Bone repair materials shorten the time of bone formation and improve the quality of bone formation, and bone repair materials as the carrier of drug sustained-release system can achieve the dual purpose of bone defect repair and drug treatment.

5. Conclusions
The ideal local sustained-release drug-carrier system for bone and joint tuberculosis should have good biocompatibility, good affinity for cells and high adhesion rate of cells to the material. The materials have bone conductivity and bone inductivity in vivo. It has biodegradable property, high biodegradable matching rate with bone without immunogenicity. The material and its degradation products have no adverse reaction to the body. It has good plasticity, suitable size, porosity and mechanical strength, good physical and chemical properties. It is convenient for medical disinfection. It has the function of slow-release drugs, and there is no adverse interaction between carriers and drugs. The degradation time of sustained-release carriers is long, and the drug effect is maintained for more than 2-3 months. Multiple first-line anti- tuberculosis drugs can be administered together with the carriers, and the concentration of local sustained-release drugs was stable.

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