The sustained-release effect of triple anti-tuberculosis drugs carried by calcium sulfate/poly-amino acid compound materials in bone tuberculosis lesion

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Abstract. This article is to review the research progress of the sustained-release effect of triple anti-tuberculosis drugs carried by calcium sulfate/poly-amino acid compound in bone tuberculosis lesion, and to investigate the biocompatibility, sustained-release and anti-tuberculosis properties of calcium sulfate/poly-amino acid compound materials from the aspects of tissue engineering modification. Papers from January 2000 to February 2019 are retrieved in PubMed database and Web of Science database. Searching words are "bone tuberculosis, biocompatibility, sustained release, anti-tuberculosis, calcium sulfate/poly-amino acid". A total number of 26 articles were included. After the artificial sustained release system of calcium sulfate/poly-amino acid containing triple anti-tuberculosis drugs was put into the bone tuberculosis lesion, the anti-tuberculosis drugs could be released slowly and continuously for up to three months according to results of the related papers. This locally sustained release effect is caused by the direct diffusion of anti-tuberculosis drugs from the carriers and the dispersion of drugs caused by the exposure of drug groups between calcium sulfate crystals after the degradation of the artificial material. The drug concentrations of the three anti-tuberculosis drugs in the bone and lumbago major muscle tissues at each detection time point were higher than those in venous blood. Three anti-tuberculosis drugs carried by calcium sulfate/poly-amino acid compound can be simultaneously released and sustained-released into the bone lesion. It is more efficient and faster to kill tuberculosis bacillus than the single-drug slow-release material which was previously studied, and consistent with the principle of using anti-tuberculosis drugs.

1. Introduction
In view of the barrier effect of the lesion wall, it is difficult to reach the effective drug concentration in the local lesion of spinal tuberculosis through oral and intravenous administration, which often leads to the uncured or recurrent treatment of spinal tuberculosis. How to improve the concentration of local anti-tuberculosis drugs in the lesion is of great significance for improving the efficacy of spinal tuberculosis [1]. Drug release system implantation is the focus of current spinal tuberculosis research, and many studies have confirmed that calcium sulfate/poly-amino acid can be used as bone repair materials. The material after implantation, except with filling and osteogenesis effect for composite
degradation process in absorption phase is different, the artificial materials so the load of drugs can be sustained, effective slow release, in order to improve the lesion partial effective anti-tb drug concentration, reduce drug adverse reaction, reduce the emergence of resistant strains, make further shortened the chemotherapy treatment, improve curative effect [2]. The physical and chemical properties, in vitro and in vivo sustained release properties and other aspects of the artificial sustained release materials of calcium sulfate/poly-amino acid containing triple antituberculosis drugs have been deeply studied, and its good local sustained release properties have been verified [3].

2. Methods

2.1. Source of data
Articles on the sustained-release effect of triple anti-tuberculosis drugs carried by calcium sulfate/poly-amino acid compound in bone tuberculosis lesion from January 2000 to February 2019 on PubMed and Web of Science database were indexed by computer for "bone tuberculosis, biocompatibility, sustained release, anti-tuberculosis, calcium sulfate/poly-amino acid".

2.2. Inclusion and exclusion criteria

2.2.1. Inclusion criteria
The sustained-release materials of calcium sulphate-polyamino acid containing triple antituberculosis drugs and the study on treatment of bone tuberculosis lesion were retained and summarized.

2.2.2. Exclusion criteria
The articles with poor correlation with the research objective and outdate and repeated contents were excluded.

3. Results
A total of 39 papers were retrieved, among which 13 literatures with poor correlation with the research purpose and obsolete and repeated contents were excluded, and 26 papers meeting the standards were included for review. After the artificial sustained release system of calcium sulfate/poly-amino acid containing triple anti-tuberculosis drugs was put into the bone tuberculosis lesion, the anti-tuberculosis drugs could be released slowly and continuously for up to three months according to results of the related papers. This locally sustained release effect is caused by the direct diffusion of antituberculosis drugs from the carriers and the dispersion of drugs caused by the exposure of drug groups between calcium sulfate crystals after the degradation of the artificial material. The drug concentrations of the three anti-tuberculosis drugs in the bone and lumbago major muscle tissues at each detection time point were higher than those in venous blood.

4. Discussion

4.1. Preparation and implantation of the sustained-release material
According to the literature, calcium sulfate, amino acids, isoniazid, pyrazinamide and rifampicin in 9:1:0.3:0.3:1.2 the proportion of mixed, preparation of carrying the joint the chemotherapy medicine calcium sulphate/poly (amino acid material of artificial bone, are preparing to grow 5 mm, 3.5 mm wide, 3.5 mm high rule of bone, using electronic balance measured containing triple the chemotherapy medicine calcium sulphate/poly (amino acid artificial slow-release materials of bone quality is 144.24 mg, pyrazinamide contained, isoniazid and rifampicin respectively is 14.67, the quality of 3.67, 3.67 mg. Artificial bone materials without calcium sulfate/poly-amino acid were prepared by the same method, and no anti-tuberculosis drugs were added. The implantation of sustained-release materials: after the tuberculosis lesion was cleared, the bone groove was implanted with the artificial bone
sustained-release materials containing calcium sulfate/poly-amino acid, a triple anti-tuberculosis drug [4-6].

4.2. Selection of anti-tuberculosis drugs in the sustained-release implantation system
Clinical anti-tuberculosis drugs include streptomycin, rifampicin, isoniazid, ethylamine butanol, pyrazinamide, etc., and streptomycin is the most commonly used drug for the traditional focus after the elimination of bone and joint tuberculosis. Although streptomycin is broad-spectrum antibiotic, but in vivo it is difficult to achieve bactericidal effect, mainly play a role in bacteriostasis. It is not easy to enter the cell membrane and cheese tissue, poor effect on bone tuberculosis, fibrous cavity type tuberculosis [7]. And because of the serious consequence of streptomycin allergy, it has certain limitation in clinical use. Pyrazinamide is an effective oral anti-tuberculosis drug, which has a special killing effect on the mycobacterium tuberculosis in the cell or in the static state. It has enhanced antibacterial effect in the acidic environment, but it is more toxic. At present, rifampicin and isoniazid are often selected in the study of sustained release of anti-tuberculosis drugs. The reproduction of bacteria has bactericidal effect [8]. To the tuberculosis bacilli of quiescent period, raise medicaments concentration or prolonging contact time also can have antiseptic effect, and have coequal to the tuberculosis bacilli inside and outside the cell kill [9].

4.3. Requirement of the drugs and carriers for bone tuberculosis lesion
Tuberculosis focal tissue of bone and joint includes caseous necrotic material, dead bone, cold abscess, tuberculosis granulation tissue, and mycobacterium tuberculosis flora. In non-sclerosing lesions, the periphery is surrounded by fibrous connective tissue. In sclerosing lesions (approximately 70% of spinal tuberculosis), the periphery of the lesion is a sclerotic wall, namely sclerotic bone [10]. In non-sclerosing lesions, the concentration of first-line anti-tb drugs can reach above the minimum inhibitory concentration. However, in the sclerosing type, the sclerosed bone limited the development of the lesion, but there was almost no blood supply [11]. The anti-tuberculosis drugs in the sclerosed bone were only at the minimum inhibitory concentration, which could not reach the bactericidal concentration, and formed a barrier to prevent the drugs from entering the lesion. However, the bacteria hiding in necrosis and caseous lesions were only sensitive to rifampicin and pyrazinamide. Extremely low drug concentration, relatively closed environment of the lesion, hypoxia and other complex factors make it difficult to kill the bacteria in sclerosed osteonecrosis and caseous lesions, which become potential factors for tuberculosis recurrence [12]. Therefore, the drug is directly placed in the lesion through local drug delivery, and anti-tuberculosis drugs are locally released, which is conducive to the treatment of tuberculosis. The advantage of the local drug sustained-release system for bone and joint tuberculosis lies in that it can achieve a higher local bactericidal concentration, which is conducive to killing or inhibiting the growth and reproduction of mycobacterium tuberculosis and reducing drug resistance caused by low local drug concentration. Blood drug concentration is low, systemic adverse reaction is small [13]. To avoid the scar tissue and bone sclerosis caused by surgery to prevent the anti-tuberculosis drugs from reaching the focus. After the implantation of the lesion, the drug carrier material will be gradually degraded by the body and the drug will be released and eventually replaced by bone tissue [14].

After the artificial sustained release material of calcium sulfate/poly-amino acid containing triple anti-tuberculosis drugs was put into the bone lesion defect of the spinal tuberculosis model, the anti-tuberculosis drugs could be released slowly and continuously for up to three months. Locally released drugs not only enter the bone and the lumbar maximus tissue on its surface, but also part of them can be absorbed into the blood circulation of the whole body [15]. This locally sustained release effect is caused by the direct diffusion of anti-tuberculosis drugs from the surface of the artificial material and the dispersion of drugs caused by the exposure of drug groups between calcium sulfate crystals after the degradation of the artificial material. The drug concentrations of the three anti-tuberculosis drugs in the bone and lumbago major muscle tissues at each detection time point were higher than those in venous blood. Three anti-tuberculosis drugs can simultaneously be released from the slow-release
material and enter the local lesion site. Compared with the single-drug slow-release material previously studied, it can kill tuberculosis bacillus more efficiently and rapidly, which is more consistent with the principle of using anti-tuberculosis drugs.

5. Conclusions
It is believed that calcium sulfate/poly-amino acid sustained-release materials containing triple anti-tuberculosis drugs can be directly implanted into the bone tuberculosis lesions, which can effectively improve the concentration of local anti-tuberculosis drugs, significantly improve the antibactericidal efficiency, shorten the treatment cycle, significantly improve the curative effect, and enable patients to recover at an early date. However, the material still has problems such as insufficient compressive strength and rapid drug release. With the effective solution of these problems, the artificial sustained-release materials will have a broader application prospect in clinical practice.

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