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Treatment of Chronic Osteomyelitis Using Vancomycin-Impregnated Calcium Sulphate Cement

Deng Lei, Ma Zhanzhong, Yang Huaikuo, Xue Lei, Yang Gongbo
*Orthopedic Department of Beijing XiYuan Hospital,
China Academy of Chinese Medical Science,
China*

1. Introduction

In the treatment of chronic osteomyelitis, the common methods in primary stage are debriding, draining and lavaging, but the clinical outcomes are not always satisfactory. Autogenous bone grafting in a second stage procedure has been the gold standard for this type of treatment, but its quantity is limited. In addition the autogenous bone graft will be absorbed or become sequestrum if the inflammation control is not sufficient [1][2]. Allogeneic bone, although solving the problem of limited supply, is likely to cause or increase the immune response and infection [3][4]. The availability of antibiotic loaded polymethylmethacrylate (PMMA) bone cement, particularly the antibiotic bead chain, provides a new direction for the treatment of osteomyelitis. However, antibiotic impregnated bone cements are non-absorbing, can support a biofilm and become a foreign body and nidus for infection at the implant site. They must be removed in a further surgical procedure if bone graft implantation is required.

In recent years, surgeons have paid increasing attention to calcium sulphate and calcium phosphate bone cements because of their biocompatibility, they are biodegradable, injectable and can be impregnated with antibiotics or other therapeutics. These advantages are more attractive for their use in infection cases. This study is based on the routine primary treatment of infection, and applies vancomycin-impregnated calcium sulphate cement to fill the focus cavity in a second stage procedure. The clinical results were satisfactory. The case reports are as follows.

2. Materials and methods

2.1 Materials and patient selection

There were 20 cases of chronic osteomyelitis in the patient group, 18 males and 2 females. Aged from 16 to 60 years old, the mean age was 41 years old. Classifying the cases according to the focus site, 1 case was in iliac, 4 cases were in femur, 5 cases were in the lower tibia and 10 cases were in calcaneus. All 20 cases suffered traumatic injury and initially had internal fixation. Although these patients had anti-infective treatment regimen immediately after

surgery, all developed chronic osteomyelitis. The time to presentation with osteomyelitis was a minimum of 6 months and a maximum of 25 years (femoral and calcaneal osteomyelitis recurrent attack) after the index procedure. All patients had routine anti-infective treatment in the primary stage procedure and later were treated with implantation of vancomycin-impregnated calcium sulphate cement (Stimulan Kit). The details of information are in the table below.

| case | Focus site | Surgical method | | Result of treatment |
|------|-------------------|--|---|---|
| | | I stage Primary treatment | II stage Further treatment Stimulan+vancomycin | |
| 1 | Calcaneus (right) | Debriding, draining | After debridement again, fill vancomycin-impregnated calcium sulphate cement into the focus site 5cc calcium sulphate cement + 0.8g vancomycin | Wound Closed in primary stage, drainage occurred one week after surgery, treated and healed by changing dressings |
| 2 | Calcaneus (right) | Debriding, antibiotics chain, draining | 10cc calcium sulphate cement + 1.6g vancomycin | Healed |
| 3 | Calcaneus (left) | Debriding, draining | 10cc calcium sulphate cement + 1.6g vancomycin | Healed |
| 4 | Calcaneus (left) | Debriding, draining, antibiotics chain | 5cc calcium sulphate cement + 0.8g vancomycin | Healed |
| 5 | Calcaneus (left) | Debriding, antibiotics chain | 5cc calcium sulphate cement + 0.8g vancomycin | Healed |
| 6 | Calcaneus (left) | Debriding, antibiotics chain | 5cc calcium sulphate cement + 0.8g vancomycin | Healed |
| 7 | Calcaneus (left) | Debriding, antibiotics chain | 5cc calcium sulphate cement + 0.8g vancomycin | Healed |
| 8 | Calcaneus (left) | Debriding, antibiotics chain | 5cc calcium sulphate cement + 0.8g vancomycin | Healed |
| 9 | Calcaneus (left) | Debriding, antibiotics chain | 5cc calcium sulphate cement + 0.8g vancomycin | Healed |

| case | Focus site | Surgical method | | Result of treatment |
|------|-----------------------|---|--|--|
| | | I stage Primary treatment | II stage Further treatment Stimulan+vancomycin | |
| 10 | Calcaneus (bilateral) | Debriding, antibiotics chain | 15cc calcium sulphate cement + 2.4g vancomycin | Closed wound in the primary stage, drainage occurred one week after surgery, treated and healed by changing dressings |
| 11 | Iliac (right) | Debriding and simultaneous removal of internal fixation, draining, lavaging | After debridement again, focus site filled with vancomycin-impregnated calcium sulphate cement 25cc calcium sulphate cement + 4.0g vancomycin | Healed |
| 12 | Middle femur (right) | Debriding, draining, lavaging, antibiotics chain | After debriding again, focus site filled with vancomycin-impregnated calcium sulphate cement 30cc calcium sulphate cement + 4.8g vancomycin | Healed |
| 13 | Middle femur (right) | Draining, lavaging, antibiotics chain | After debriding again, focus site filled with vancomycin-impregnated calcium sulphate cement 20cc calcium sulphate cement + 3.2g vancomycin | Healed |
| 14 | Middle femur (right) | Draining, lavaging, antibiotics chain | After debriding again, focus site filled with vancomycin-impregnated calcium sulphate cement 20cc calcium sulphate cement + 3.2g vancomycin | Healed |
| 15 | Middle femur (left) | Debriding, draining, lavaging | After debriding again, focus site filled with vancomycin-impregnated calcium sulphate cement 20cc calcium sulphate cement + 3.2g vancomycin | Focus site filled with vancomycin-impregnated calcium sulphate cement into the focus site 2 times Eventually healed |

| case | Focus site | Surgical method | | Result of treatment |
|------|---------------------|--|--|---|
| | | I stage Primary treatment | II stage Further treatment Stimulan+vancomycin | |
| 16 | Lower tibia (left) | Debriding, draining, lavaging, antibiotics bone cement | After debriding again, focus site filled with vancomycin-impregnated calcium sulphate cement 25cc calcium sulphate cement + 4.0g vancomycin | Drainage occurred 3 weeks after surgery, treated and healed by changing dressings |
| 17 | Lower tibia (right) | Debriding, draining, lavaging, antibiotics chain | After debriding again, focus site filled with vancomycin-impregnated calcium sulphate cement 20cc calcium sulphate cement + 3.2g vancomycin | Healed |
| 18 | Lower tibia (right) | Draining, lavaging, antibiotics chain | After debriding again, focus site filled with vancomycin-impregnated calcium sulphate cement 20cc calcium sulphate cement + 3.2g vancomycin | Healed |
| 19 | Lower tibia (right) | Draining, lavaging, antibiotics chain | After debriding again, focus site filled with vancomycin-impregnated calcium sulphate cement 30cc calcium sulphate cement + 4.8g vancomycin | Healed |
| 20 | Lower tibia (left) | Draining, lavaging, antibiotics chain | After debriding again, focus site filled with vancomycin-impregnated calcium sulphate cement 15cc calcium sulphate cement + 2.4g vancomycin | Healed |

2.2 Methods for treatment

Primary stage treatment: Routine treatment of chronic osteomyelitis includes resection of soft tissue focus, removal of sequestrum, fenestration drainage of bone lesions (ilium, calcaneus), lavaging (tibia, femur) and polishing the surface of sclerotic bone with a burr. In addition to the methods above, for long bone with a closed marrow cavity, firstly add antibiotic bead chain or antibiotic bone cement as the anti-inflammatory transitional stage when drilling medullary cavity and lavage at the same time. The cement is then removed in

the revision surgery 4 to 6 weeks later. The bacterial culture and sensitivity tests are carried out as routine preoperative examination before the surgery. Only 1 case of femoral osteomyelitis in this group was staphylococcus aureus positive, other cases were all negative.

Second stage treatment: 4-6 weeks after all the patients had primary routine treatment, and local infected sites had shown no irritation, pain or purulent exudates. Surgical sites were then filled with vancomycin-impregnated calcium sulphate cement and the wound closed immediately. The common dosage of antibiotics was 1g vancomycin in 5cc calcium sulphate cement. Depending on different sizes of the focus, the volume of calcium sulphate cement used ranged from 5cc- 30cc (case 1, 2). The author has found that the calcaneal osteomyelitis may have high recurrent risk due to the infected area having more cancellous bone. Therefore we pay more attention when performing second stage treatment. Before the second stage treatment is carried out, a negative bacteria culture must be achieved and second time debridement must be carried out before the use of the vancomycin-impregnated cement. In addition, the sclerotic bone needs to be trimmed and the sequestrum space needs to be debrided and cleaned completely. The infected cavities should be filled as tightly as possible without leaving dead space in order to maximize the treatment with antibiotics.

3. Result

Stitches were removed 3 weeks after surgery. 17 cases showed stage I wound healing. 2 cases in the calcaneus and 1 case in the tibia showed site drainage after surgery, but no purulent secretions were found and the bacterial cultures were negative. The wound gradually healed after changing dressings. No recurrences of infection or pathological fractures were found after 10 to 30 months follow-up. The antibiotic-impregnated cement was completely absorbed within 3 months and ossification in the bone defect was 100%. No systemic abnormal reactions were found.

4. Discussion

4.1

The treatment of chronic osteomyelitis has become a difficult problem in orthopaedics as it is difficult to eradicate. Due to the availability of new materials and methods, many new concepts and technologies have been developed for treatment of chronic osteomyelitis on the basis of regular treatment. The uses of non-absorbable antibiotic-impregnated bone cement and absorbable biological bone cement to treat the infection have been reported recently subsequent to routine antibiotics chains being used. Non-absorbable bone cement needs to be removed after the antibiotics has released and the local concentration of antibiotics released in soft tissue, bones and joints is lower than levels delivered by antibiotic-impregnated absorbable biological cement [5]. The commonly used antibiotics for impregnation today are Gentamycin, Kanamycin, Tobramycin, and Rifampin. Quinolones have also been reported such as Moxifloxacin [6]; the common drug carriers include medical grade calcium phosphate cement (CPC) [7] [8] [9], Hydroxyapatite [10] [11] and PMMA bone cement. However the reported use of vancomycin-impregnated calcium sulphate cement (CSC) is less common. In the application of antibiotic-impregnated biological cement, it is

necessary to choose not only the effective antibiotics but also the carriers. The carriers must have same crystal structure in terms same size and shape in order to encourage the osteogenesis. If a carrier is absorbed too fast, it will decrease the function of osteoconductivity, while if a carrier is absorbed too slow, it will inhibit new bone formation. Pharmaceutical grade calcium sulphate cement, Stimulan Kit, is synthetically produced from high purity reagents. It has a physiologic pH and a higher purity compared to calcium sulphate prepared from gypsum rock. Stability and the absorption speed are close to new bone formation speed. So we believe that the calcium sulphate is an ideal antibiotic carrier. We used self-made vancomycin-impregnated calcium sulphate cement in all cases. 17 cases showed wound healing in first stage and the other 3 cases gradually healing after changing dressings.

Tomoyuki et al reported that the concentration level of antibiotics releasing in vancomycin-impregnated calcium sulphate cement was 50 times and 13 times that of PMMA bone cement at 1 and 2 weeks after use, which greatly enhanced the efficacy in local focus. Kyriaki et al carried out a comparison study of vancomycin-impregnated calcium sulphate cement and PMMA bone cement and reported that the concentration level of local antibiotics releasing in former was much higher than the latter. Many experimental studies have confirmed that the level of antibiotics released by vancomycin-impregnated calcium sulphate cement is higher than PMMA bone cement. In addition, vancomycin-impregnated calcium sulphate cement produces no heat of polymerization, is completely absorbed and releases all of the antibiotic load. It also will not affect the osteogenesis in focus site.

4.2

Complete primary first stage treatment is an essential step for antibiotics-impregnated calcium sulphate cement filling. Since systemic antibiotic treatment is less effective in the treatment of chronic osteomyelitis, focus site treatment become critical. The bacterial culture in chronic osteomyelitis is often gram negative, which is considered to be related to long term antibiotic use and low grade toxicity of the bacteria. In this study, all cases took secretion culture and drug susceptibility tests before and after surgery. Only one case in femoral focus cultured positive for staphylococcus aureus, the others were all clear. Treatment methods included debriding thoroughly, polishing the surface of sclerotic bone with a burr, and adequate drainage. One case of iliac bone and 10 cases of calcaneus osteomyelitis carried out debridement and drainage until the drain was clear, then filled the antibiotic-impregnated calcium sulphate cement; 5 cases of tibial and 4 cases of femoral osteomyelitis had debridement and catheter flushing first. At the same time the canal was drilled and filled with self-made antibiotics chain or antibiotic bone cement. On removing the chain or antibiotic bone cement surgical sites were filled with vancomycin-impregnated calcium sulfate cement when lavaging fluid is clean after 4-6 weeks. After use of antibiotics chain, a drainage strip was placed. Although some antibiotic will be lost through the drain, a higher rate of wound healing was evident. Yang Xingguang ^[12] et al also reported that the drainage or lavage may be reduce the concentration of antibiotics, but it is important for the healing of soft tissue.

4.3

The main disadvantage for using PMMA bone cement is that it will become a foreign body after drug release. The authors found that bone cement, as a drug carrier, had not only a

limited drug release, but was also associated with necrosis between the surface of cement and the surrounding tissue. It confirms the poor compatibility of bone cement in inflammatory tissue or it may be related with the elevated temperature effects during polymerization. It should therefore be removed. Some research has also confirmed adhesion of bacteria on the bone cement surface after using the antibiotic chain, speculating that this is one of the factors of recurrence of inflammation. As antibiotics-impregnated calcium sulphate cement is absorbable and demonstrates simultaneous absorption and osteogenesis, it will not result in necrosis adjacent to the material and will eliminate the focus infection. The X-ray follow up also demonstrated and confirmed the absorption of calcium sulphate cement was matched with the speed of osteogenesis. The X-rays were taken in all cases and osteogenesis was found in all at 3 to 4 weeks after surgery with partial absorption of the calcium sulphate. The calcium sulphate cement was fully absorbed after 3 months and the local new bone formed well.

4.4

The clinical efficacy of absorbable bone cement, as a drug carrier, will be influenced by the setting time, strength, the level of concentration, the antibiotic elution rate and the porosity of the set cement. In order to ensure the releasing concentration of vancomycin did not affect the calcium sulfate bone cement's strength after solidification in this study, the ratio of vancomycin and cement was 0.8g vancomycin/5cc calcium sulphate. The setting time and strength of calcium sulphate did not change in the surgery. Osamu's tests showed that when using PMMA as the antibiotic carrier, the effective drug release is not as high as the absorbable antibiotic-impregnated cement. Michal et al used injectable antibiotic-impregnated cement to treat chronic osteomyelitis, the preliminary tests also showing positive results.

The authors believe that vancomycin-impregnated calcium sulfate cement performs the function of filling bone voids and dead space and maintaining effective release of antibiotics. The local concentration of antibiotics releasing in calcium sulphate is higher than observed with antibiotic loaded PMMA bead chains or antibiotic loaded PMMA bone cement, and can be many times the minimum inhibitory concentration (MIC) for the involved pathogen. Treatment of chronic osteomyelitis using self-made vancomycin-impregnated calcium sulfate cement has achieved a satisfactory therapeutic effect. Therefore the authors recommend it as a method to treat chronic osteomyelitis.

5. Case accessories

Case 1: Male, 40 years old. Patient sustained left distal tibia and fibula fractures (Pilon fracture) caused by traffic accident. Infection appeared after wire fixation and developed osteomyelitis. Infection invaded to the ankle joint and the talus just three months after the first operation. Although patient had kept the wound clean, and changed dressing, the wound remained unhealed. The patient was transferred to our unit 8 months after initial trauma. Patient was twice cleared and underwent debridement. Antibiotic PMMA bone cement was used to fill the bone marrow cavity of tibia and ankle, with a drain present. 6 weeks later, the bone cement was removed and the void filled with self-made vancomycin-impregnated calcium sulfate cement. The osteomyelitis of the tibia and talus was eradicated 6 weeks after using vancomycin-impregnated calcium sulfate cement. The calcium sulfate cement began to be absorbed, and callus began to grow at 10 weeks (Fig. 1, 2).

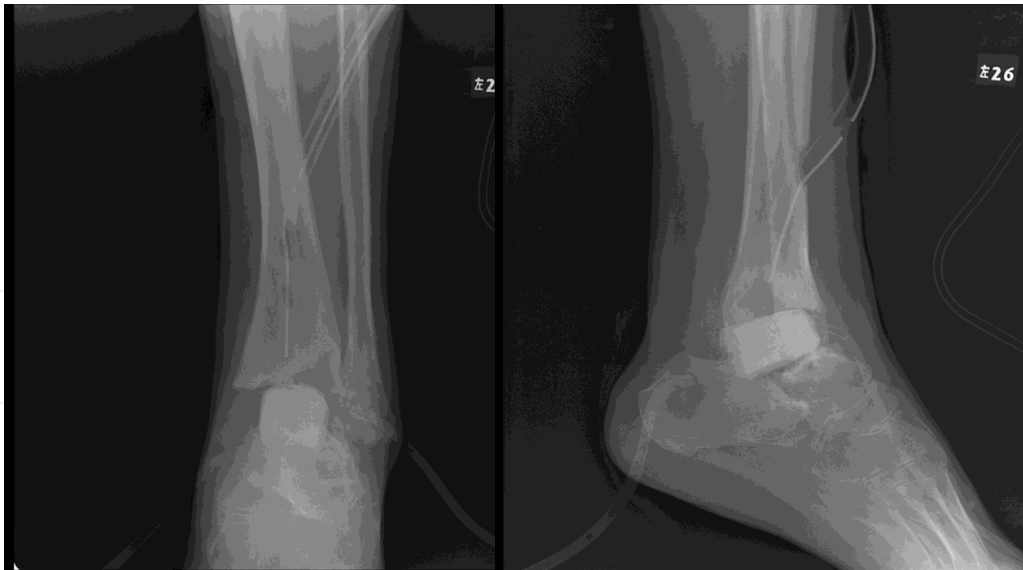


Fig. 1. After debridement, antibiotics bone cement was implanted and catheter drainage was placed.



Fig. 2. The calcium sulfate cement began to be absorbed, and callus began to grow at 10 weeks.

Case 2: Female, 50 years old. Patient suffered chronic osteomyelitis after calcaneus fracture surgery. Patient underwent debridement treatment and initial fixation plates were removed. Antibiotic loaded PMMA bone cement was implanted in the cavity. Patient underwent secondary debridement treatment 8 weeks later and vancomycin-impregnated calcium sulphate cement was placed. The wound healed three weeks later and the stitches were removed. CT follow up show vancomycin-impregnated calcium sulphate cement was partially absorbed and callus appeared at the fracture defect two months after placing the vancomycin-impregnated calcium sulphate cement.



Fig. 3. Infection and persistent sinus occurred after calcaneus fracture surgery and the wound was not healed. The patient was transferred to our unit and debridement treatment was given and antibiotic loaded PMMA cement chain was placed until the sinus was clean, free of leakage with no bacterial growth.

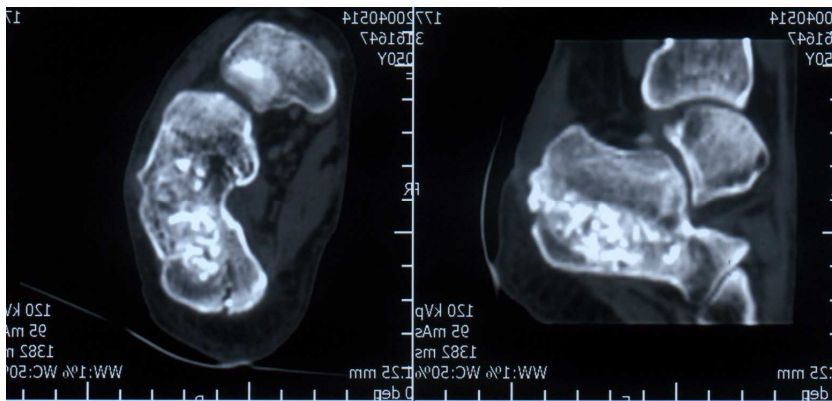


Fig. 4. Patient had secondary surgery and antibiotics-impregnated calcium sulphate cement was placed. CT showed that the antibiotics-impregnated calcium sulphate cement in the calcaneus was partially absorbed.

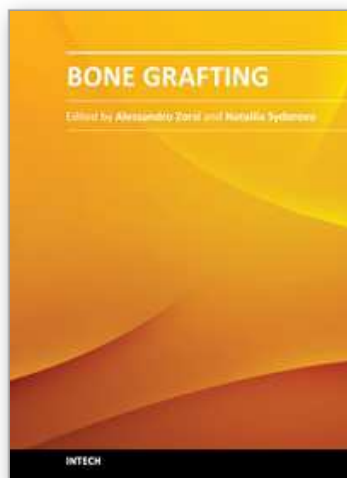


Fig. 5. The wound healed fully and patient was able to perform weight-bearing exercises.

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Bone Grafting

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Bone grafting is the surgical procedure in which new bone (bone graft) or a replacement material (graft substitute), is placed into bone fractures or bone defects to aid in healing. Bone grafting is in the field of interest of many surgical specialties, such as: orthopedics, neurosurgery, dentistry, plastic surgery, head and neck surgery, otolaryngology and others. In common, all these specialties have to handle problems concerning the lack of bone tissue or impaired fracture healing. There is a myriad of surgical techniques nowadays involving some kind of bone graft or bone graft substitute. This book gathers authors from different continents, with different points of view and different experiences with bone grafting. Leading researchers of Asia, America and Europe have contributed as authors. In this book, the reader can find chapters from the ones on basic principles, devoted to students, to the ones on research results and description of new techniques, experts will find very beneficial.

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University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
Fax: +385 (51) 686 166
www.intechopen.com

InTech China

Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821

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