



Clinical observations of vancomycin-loaded calcium phosphate cement in the 1-stage treatment of chronic osteomyelitis: a randomized trial

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Background: This study sought to explore the clinical effects of vancomycin-loaded calcium phosphate cement (CPC) in the treatment of chronic osteomyelitis.

Methods: Ninety-eight patients with chronic osteomyelitis, who were treated at our Department from December 1st, 2014 to December 1st, 2015, were randomly allocated into the research group or the control group. Each group comprised 49 patients. Patients in the research group (Group A) received a 1-stage treatment of vancomycin-loaded CPC after debridement, while those in the control group (Group B) received an irrigation and drainage device that administered irrigated antibiotics. The treatment effects, recurrence rates, and safety outcomes of the two groups were observed.

Results: Patients in the two groups were followed up with for a period of 12 months. The control group without recurrence in one case. There was some systemic adverse postoperative effects and safety issues. The X-ray film showed that CPC filling is good and part of the degradation of osteogenesis. Some patients in the research group the CPC particles were absorbed, the bone defect area was healed, after One-year postoperatively. Further, the cure rate was high.

Conclusions: One-stage vancomycin-loaded CPC implantation osteomyelitis lesions fill the die cavity, enable patients to continue to fight infection, induce bone defect osteogenesis, reduce the recurrence of chronic osteomyelitis, and are an effective method for treating chronic osteomyelitis.

Trial registration: Chinese Clinical Trial Registry website (ChiCTR2100044724).

Keywords: Vancomycin; calcium sulphate cement; 1-stage; chronic osteomyelitis

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Introduction

Chronic osteomyelitis is a difficult and complicated disease that is commonly encountered in orthopedics due to its long treatment cycle, high medical costs, poor therapeutic effects, and high recurrence rate. Improper treatment can easily lead to disability, which may have catastrophic effects on patients and families. The conventional treatment for chronic osteomyelitis includes complete lesion removal,

the administration of intravenous antibiotics for 4–6 weeks, local antibiotic irrigation and drainage, and second-stage bone grafting once the infection is under control (1,2). Patients with chronic osteomyelitis develop scars around the lesion, resulting in poor blood supply to tissues and making it difficult for systemic drugs to enter the sclerotic lesion area. During local antibiotic irrigation and drainage, the muscle and fascia often block the drainage or irrigation

Table 1 Comparison of clinical data between the two groups

Group	Gender (M/F)	Age	Course	Sinus formation (%)
A (n=49)	35/14	32.36±3.36	14.25±5.32	22 (44.90)
B (n=49)	38/11	34.51±5.62	11.25±3.47	18 (36.74)
Test statistics	$\chi^2=0.483$	$t=-0.514$	$t=1.209$	$\chi^2=0.676$
P value	0.487	0.608	0.230	0.411

inlets, and body position changes due to poor drainage, resulting in undesirable outcomes. The recurrence or poor control of local lesions results in prolonged times for second-stage bone grafting, and an excessively long treatment cycle that increases the suffering and financial costs of patients (3). Compared with previous reports on vancomycin combined with bone cement in the treatment of chronic osteomyelitis. In this study, a 1-stage implantation of vancomycin-loaded calcium phosphate cement (CPC) after the removal of osteomyelitis lesions was achieved a similar cure rate with fewer surgeries. We present the following article in accordance with the CONSORT reporting checklist (available at <https://dx.doi.org/10.21037/apm-21-1290>).

Methods

General data

All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by Ethics Committee of Sichuan Orthopaedic Hospital and informed consent was taken from all the patients.

A total of 98 patients [69 men and 29 women, aged 7–70 (mean: 33.14±4.12) years] were enrolled in this study. Their disease courses lasted for 4–36 (mean: 13.48±3.37) months. The affected sites included 10 humeri, 4 radius and ulna bones, 6 metacarpal bones, 2 pelvises, 24 femurs, 32 tibias, 16 calcanei, and 4 metatarsal bones. Among the patients, 40 also had sinus formation. To be eligible to participate in this study, patients had to meet the following inclusion criteria: (I) be aged 7–70 years (there were no limits in relation to gender); (II) meet the diagnostic criteria for chronic osteomyelitis in Western medicine; (III) have bacterial cultures that were all sensitive to vancomycin; and (IV) they (or their family members) had to be willing to accept the treatment. Conversely, patients were excluded from the study if they met any of the following exclusion

criteria: (I) had acute osteomyelitis due to various causes; (II) had serious medical or surgical diseases, tuberculosis, tumor, severe diabetes, Parkinson's disease, or rheumatoid arthritis as comorbidities; (III) had surgical contraindications; and/or (IV) they or their family members were unwilling to accept the treatment. The included participants were allocated to a study (Group A) or a control group (Group B) using a random number table. Each group comprised 49 patients. The differences in patients' clinical data were not statistically significant (at $P>0.05$; see *Table 1*).

Methods

Preoperative procedures

Patients in both groups underwent three-dimensional computed tomography of the lesion, and the scope of the lesion was measured. In patients with sinus formation, deep secretions were taken through the sinus preoperatively for bacterial culture testing. Based on the drug susceptibility results, the systemic infusion of sensitive antibiotics was administered as an anti-infection treatment 3–5 days preoperatively as necessary.

Intraoperative procedures

Infected necrotic tissues (including bone tissues without blood supply, purulent necrosis of fascia and muscle tissues, and open-closed medullary cavities) were completely removed, and the surgical cavity was then rinsed 3 times with a large solution of normal saline (3–6 L), povidone-iodine solution, and hydrogen peroxide. A curette was used to scrape the walls of the wound cavity until fresh blood oozing was visible. In Group A, antibiotic CPC was prepared after drying the wound cavity with sterile gauze. To prepare the antibiotic CPC, a sufficient amount of self-setting CPC powder was fully mixed with a matching vancomycin powder (in the proportion of 50,000 units of vancomycin powder injection per 100 g of self-setting CPC). The mixed self-setting CPC powder and the curing

liquid were mixed at a weight/volume ratio of 2.5–3:1, and an appropriate amount of self-setting CPC and curing liquid was added for blending (4). The blending duration generally did not exceed 5 min (5). Once a thin slurry mixture was achieved, it was poured into a special mold to solidify into particles of 5 mm or 3 mm in diameter for 10–20 min. Next, CPC particles were extracted to fill the lesion bone defect until it became level with the bone cortex (6). A tube was placed into the wound cavity for drainage.

In Group B, after the complete removal of the lesion, two drainage tubes were placed in the medullary cavity of the lesion for irrigation and drainage. Sensitive antibiotics were applied with normal saline for continuous irrigation and drainage. In both groups, the incisions were sutured directly or with reduced tension, any soft tissue defect was repaired with the flap technique (7), any entire bone defect was fixed with external fixation, and any focal defect was fixed with a plaster.

Postoperative treatment plan

In Group A, the drainage tube was removed when drainage flow was <4 mL. The placement duration ranged from 7–14 (mean: 10) days (8). In Group B, 0.9% normal saline (6–9 L daily) was continuously flushed via the irrigation tube for 24 h. Additionally, the drainage tube was kept unobstructed and was removed approximately 7–10 days when the drainage flow was <4 mL after rinsing. Based on the results of intraoperative secretion cultures, patients in the two groups received a system infusion of antibiotics for 2–3 weeks, which was then changed to oral administration for 4–6 weeks.

Outcome

Patients in both groups were followed up with for 12 months to monitor for recurrence.

Microbiological indicators

Drainage fluids or secretions were obtained for 3 consecutive days (i.e., days 7, 8, and 9) postoperatively for bacterial cultures to observe whether the local infection was controlled.

Safety indicators

Liver and kidney functions were re-examined at 1, 2, and 4 weeks postoperatively, and the results were compared with

the preoperative measurements.

Inflammation indicators

The blood routine, C-reactive protein (CRP), and erythrocyte sedimentation rate were rechecked at 1, 2, and 4 weeks postoperatively, and the results were compared with the preoperative measurements.

Imaging examination

According to intraoperative findings, the placement of CPC was recorded. X-rays were re-examined at 1 week, and 1, 3, 6, and 12 months postoperatively to observe lesion packing and osteogenesis.

Efficacy evaluation

The criteria were based on the standard of the chronic osteomyelitis curative effect established by “*Huang Jiasi Surgery*” in 2008. Under this standard, patients may be classified as “healed”, “improved”, or “unhealed”.

Healed

Patients are classified as “healed” if their systemic and local symptoms and signs disappear, inflammatory indicators are completely normal, the function of the affected limb has returned to normal, the sinus and wound are completely healed, X-ray scans show that the bone density is uniform, no sequestrum or cavity is observed at the original lesion, and the disease does not recur during the 1-year follow-up period.

Improved

Patients are classified as “improved” if their systemic and local symptoms and signs have improved, some inflammatory indicators have returned to normal, the function of the affected limb is partially restored, the sinus and wound have healed well, X-ray scans show that the bone is partially repaired, the lesion has improved, no residual sequestrum is observed, and the disease does not recur during the 1-year follow-up period.

Unhealed

Patients are classified as “unhealed” if their systemic and local symptoms and signs have not changed significantly or have even worsened, their inflammatory indicators are abnormal, X-ray scans show that the lesion is unstable

Table 2 Comparison of treatment effects between the two groups

Group	Efficacy, n (%)				Recurrence, n (%)
	Healed	Improved	Unhealed	Total effective	
A (n=49)	30 (61.22)	16 (32.65)	3 (6.12)	46 (93.87)	0 (0.00)
B (n=49)	16 (32.65)	20 (40.82)	13 (26.53)	36 (73.47)	11 (22.49)
χ^2	Z=-3.227		$\chi^2=7.470$		$\chi^2=12.391$
P value	0.001		0.006		0.000

and continuing to develop, and sequestra and cavities are observed.

Statistical analysis

The statistical analysis was performed using SPSS15.0 statistical software. The *t*-test was used to measure the data, and the χ^2 test was used to count the data. A $P < 0.05$ was considered significantly different.

Results

Efficacy results

In the study group, none of the patients had systemic adverse reactions postoperatively, and their liver and kidney function indices and bacterial cultures were normal. Inflammatory indicators did not reach the normal level in 2 patients in the study group. At the end of the 1-year follow-up period, in the study group, there were 0 recurrences and 30 patients were healed, 16 were improved, and 3 had non-healing incisions. Conversely, in the control group, 3 patients developed a fever postoperatively with body temperatures exceeding 38.5 °C. Local secretion bacterial cultures were positive in 6 cases in the study group. Patients' liver and kidney function indices were all normal in the control group. Inflammatory indicators did not reach the normal level in 9 patients in the control group. At the end of the 1-year follow-up period, in the control group, 11 patients had recurrences, 16 were healed, 20 were improved, and 13 were unhealed and needed to undergo re-operation. The results of the χ^2 test showed that the differences in the healed, improved, ineffective, total effective, and recurrence rates were significant between the two groups ($P < 0.05$); however, the differences in relation to the safety results between the two groups were not significant ($P > 0.05$; see *Table 2*).

Imaging results

At 1 week post-surgery, the medullary cavity of the lesion was filled with CPC synthetic bone particles, and the transmission gap between the particles was obvious. At 6 months (on average) post-surgery, the synthetic bone particles were not displaced, and the shadow of the synthetic bone particles had become blurred, indicating that the synthetic bone particles were gradually being absorbed by the body. At 1-year post-surgery, the shadow of the synthetic bone particles had generally disappeared without sequestrum and cavity formation, and the bone defect areas were healed.

Typical case

A middle-aged man suffered a postoperative infection of the left tibia and fibula fracture with sinus formation for 2 years. After multiple operations at other hospitals, the sinus remained unhealed, and osteomyelitis recurred. Preoperatively, chronic osteomyelitis complicated by sinus formation was found in the tibia. X-rays suggested infection in the lower part of the tibia, with bone destruction, sclerosis and hyperplasia, and sequestrum formation (see *Figure 1*). The man received a 1-stage treatment of vancomycin-loaded CPC after debridement (see *Figure 2*). Two months postoperatively, X-rays showed that the site was well filled with CPC (see *Figure 3*). that the CPC particles were absorbed, the bone defect area was healed, after 1-year postoperatively (see *Figure 4*).

The Consolidated Standards of Reporting Trials (CONSORT) diagram is shown in *Figure 5*.

Discussion

CPC is an alternative material for synthetic bones made

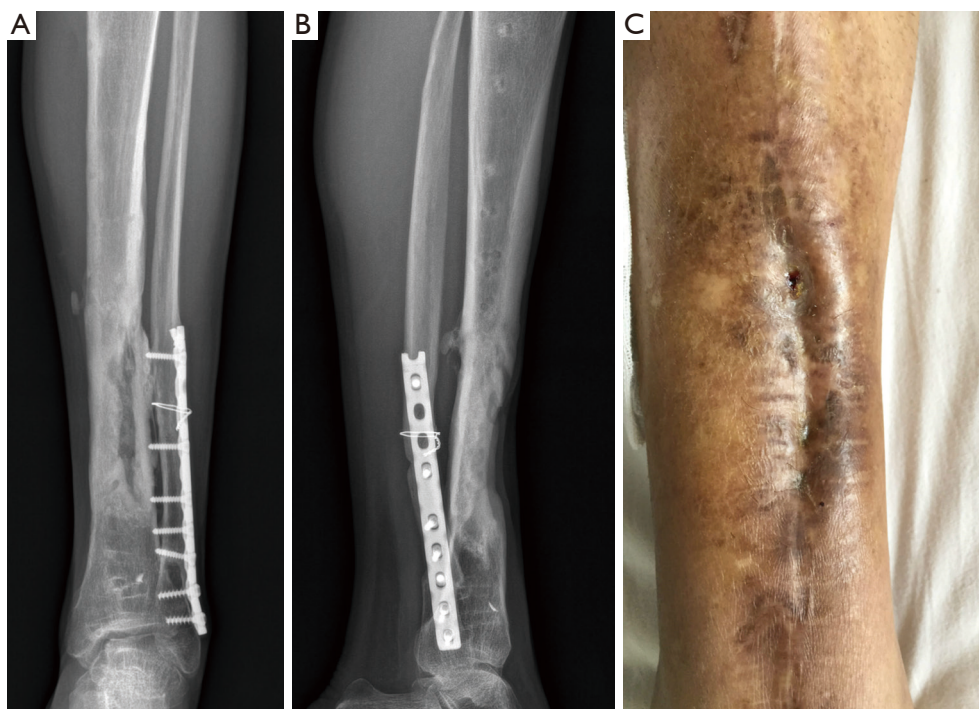


Figure 1 A male patient, aged 55 years who had suffered from a postoperative infection of the left tibia and fibula fracture with sinus formation for 2 years. (A,B) X-rays suggested infection in the lower part of the tibia, bone destruction, sclerosis and hyperplasia, and sequestrum formation; (C) chronic osteomyelitis complicated by sinus formation was found in the tibia.

of self-setting non-ceramic hydroxyapatite (HAP). It is composed of calcium carbonate powder and curing liquid (re-distilled water). After reconciling the two phases, they self-solidify and transform into HAP crystals with a large number of microporous structures at room temperature or in an *in vivo* environment for 5–20 min (9). CPC can be flexibly shaped. CPC particles prepared intraoperatively contain micropores that gradually release the drug, and the small particle shape can increase the contact area, leading to better antibacterial effects. CPC is nontoxic and hardly exothermic during curing. Additionally, it cannot cause damage to surrounding tissues, and does not affect the drug activity. After curing, it has high compressive strength, is highly capable of inducing bone formation, and can induce bone growth and simultaneous degradation. Thus, it is an ideal drug carrier (10).

Osteomyelitis is a largely drug-resistant bacterial infection that produces polysaccharide protein complexes and forms a biofilm to protect bacteria inside the film (11). To kill the bacteria lurking inside the biofilm, a high local concentration of sensitive antibiotics must be maintained. After the 1-stage implantation of vancomycin-loaded

CPC synthetic bone into the osteomyelitis lesion, a local high concentration of vancomycin is sufficient to inhibit bacterial growth. In the present study, the patients had a bacterial infection in the sinus preoperatively, and bacterial cultures of drainage fluids from the lesion were negative 3 consecutive times postoperatively. This strongly suggested that the high concentration of vancomycin released by vancomycin-loaded CPC not only inhibits the growth of bacteria but also kills them (12). From a systemic point of view preoperatively, the patients erythrocyte sedimentation rate increased, the high-sensitivity CRP decreased significantly, the patient's whole body had no fever, and the wound did not show redness, swelling, heat, or pain. This further confirmed that vancomycin-loaded CPC synthetic bone could release an effective concentration of bactericidal drug locally to effectively control the local inflammation of the osteomyelitis lesion. Once the local inflammation was cured, systemic inflammation was also controlled. Thus, inflammatory indicators, such as blood routine results, dropped to normal level postoperatively.

Chen *et al.* (13) treated 26 patients with chronic osteomyelitis with lesion removal and CPC implantation,

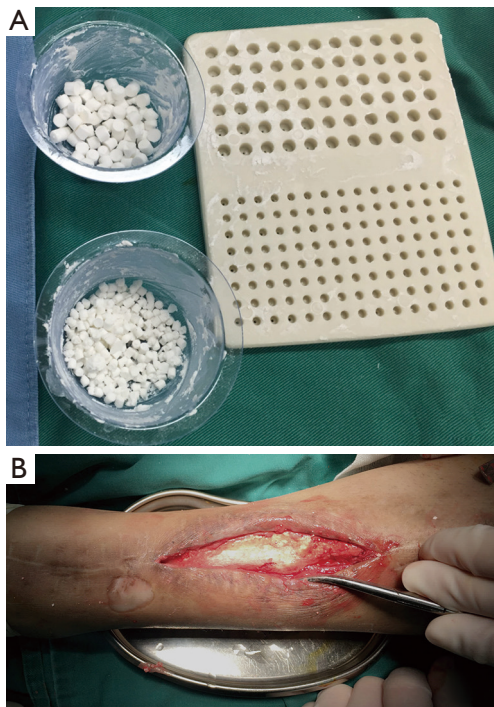


Figure 2 CPC was configured intraoperatively. (A) The vancomycin-loaded CPC was prepared as required and solidified into particles to fill the lesion; (B) the bone window was completely closed with the CPC. CPC, calcium phosphate cement.

and observed wound healing by following up with X-ray examinations postoperatively. The incisions of 21 patients healed by first intention, and the incisions of 5 patients had a small amount of extrudates, which completely healed after dressing change and rinsing. All 26 patients achieved satisfactory results. The lesion removal plus implantation of vancomycin CPC beads was considered an effective treatment for chronic osteomyelitis. Bi (14) randomly assigned 75 patients with chronic osteomyelitis to either vancomycin-loaded CPC or polymethylmethacrylate (PMMA) bead chains treatment groups. A comparative analysis of the treatment effects showed that CPC had significant advantages over PMMA in terms of treatment cycles and effects. In this study, patients were followed up for 1 year, and no recurrence was observed, which also

confirms the advantages of CPC.

Some precautions need to be raised in relation to the proposed method. First, complete lesion removal is the basic principle for the treatment of chronic osteomyelitis and is also key to a successful operation. Lesion removal of osteomyelitis should include extensive excision of the sclerotic bone, necrotic bone, and fibrotic ischemic tissue until the bone surface and soft tissue ooze blood normally. Second, when blending the CPC powder, not too many curing agents and antibiotics should be dropped, otherwise, the CPC powder will not be cured normally and could even cause difficulties in surgery. Third, there should be no active bleeding at the CPC filling site, as bleeding will affect the strength of the curing. If this occurs, a balloon tourniquet should be used intraoperatively. Fourth, the debrided lesion cavity should be filled with as many drug-loaded CPC particles as possible without leaving any space. Fifth, for large bone defects, if the amount of CPC used is large or the lesion area is bleeding or oozing excess fluids, a negative pressure drainage device should be installed to drain the effusion. Finally, CPC cannot replace the firm internal and external fixation of fractures, and loads should be progressively added postoperatively as guided by a doctor.

Due to the poor effects and significant side effects related to the systemic administration of antibiotics in the treatment for chronic osteomyelitis, the local medication of osteomyelitis has recently become a trending topic (15). The invention of antibiotic-loaded CPC synthetic bone achieves the dual therapeutic purposes of drug-loaded therapy and bone tissue reconstruction (16). The 1-stage implantation into the osteomyelitis lesion not only treats chronic osteomyelitis effectively but also repairs bone defects, shortens the treatment cycle, and reduces the patient's pain. Compared to local antibiotic irrigation and drainage, CPC could simultaneously complete the local antibiotic treatment of chronic osteomyelitis and the induction of bone regeneration and reconstruction, to avoid the second operation. But CPC treatment is more expensive. Thus, it is an ideal and effective method for the treatment of chronic osteomyelitis.

In the treatment process of chronic osteomyelitis, about



Figure 3 Two-month postoperatively. (A,B) X-rays showed that the site was well filled with CPC; (C) the sinus was healed. CPC, calcium phosphate cement.



Figure 4 One-year postoperatively. (A,B) X-rays showed that the CPC particles were absorbed. The bone defect area was healed. CPC, calcium phosphate cement.

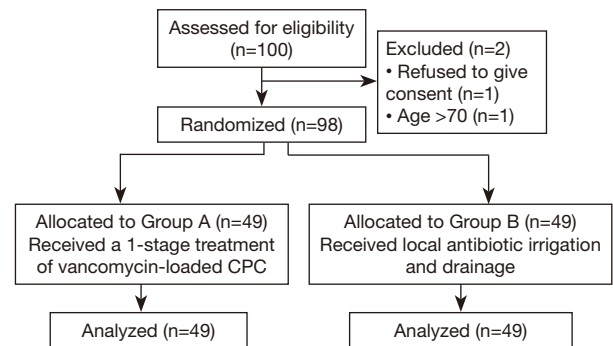


Figure 5 The Consolidated Standards of Reporting Trials (CONSORT) diagram.

50–60% of patients could not find the pathogenic bacteria with the existing bacterial culture technology. At present, the metagenomic next-generation sequencing might be a new technology to change this situation. High-accuracy identification of pathogenic bacteria, found sensitive antibiotics and take advantage of the drug-carrying capacity of CPC might be a new technique for the treatment of chronic osteomyelitis in the future.

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Footnote

Reporting Checklist: The authors have completed the CONSORT reporting checklist. Available at <https://dx.doi.org/10.21037/apm-21-1290>

Trial Protocol: Available at <https://dx.doi.org/10.21037/apm-21-1290>

Data Sharing Statement: Available at <https://dx.doi.org/10.21037/apm-21-1290>

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <https://dx.doi.org/10.21037/apm-21-1290>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by Ethics Committee of Sichuan Orthopaedic Hospital and informed consent was taken from all the patients.

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