Treatment of chronic long-bone infections by dissolvable antibiotic beads (pure synthetic calcium sulfate impregnated with vancomycin and gentamicin)

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Background
This study reviews the clinical results using synthetic calcium sulfate impregnated with vancomycin and gentamicin dissolvable beads in 70 patients who suffered from chronic long-bone infection that was not responding to several trials of treatment.
Patients and methods
All patients prepared for surgical debridement and calcium sulfate impregnated with vancomycin and gentamicin beads were inserted into the wound.
Results
The main follow-up was 12 months; the mean age of the patients was 37.94. *Staphylococcus aureus* was the organism that had been reported in 45.71% of all swabs. In the final results 61 (87.14%) patients were completely healed while only nine (12.86%) patients still had infection.
Complication
Blood loss occurred in 15 (21.42%) patients and five (7.15%) patients developed deep venous thrombosis (DVT).
Conclusion
Dissolvable beads of calcium sulfate impregnated with vancomycin and gentamicin are an effective and safe tool for the treatment of chronic long-bone infections.

Keywords:
antibiotic beads, biodegradable material, calcium sulfate, chronic osteomyelitis, vancomycin

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Introduction

Osteomyelitis was described many years ago, but is still incompletely understood as there is still no consensus on either the definition of osteomyelitis or the criteria for its diagnosis. The clinical picture of chronic osteomyelitis has changed markedly in the past 70 years [1,2].

Most of the published studies cannot be compared with one another, and there is a lack of scientific evidence to guide treatment. The reason for this is the most important characteristic of the disease: the extreme variety of symptoms that can be manifested in chronic osteomyelitis [3,4].

The standard treatment of osteomyelitis often includes the use of intravenous antibiotics. The effectiveness of an antimicrobial agent is dependent on its concentration in the affected tissue. Concentration is dependent on a number of factors, primarily vascular supply. The infusion of intravenous agents can lead to adverse effects, such as complications at the infusion site and systemic drug toxicity [5,6].

Treatment-refractory acute infectious complications were the most frequent cause of chronic osteomyelitis in developed countries [7]. In elective trauma surgery, these occurred at a rate of 1–5% after closed fractures and depending on the severity in 3–50% after first to third-degree open fractures [8,9]. Overall, infectious complications occur in 5% of traumatic/orthopedic implants during the lifetime of the implant [10,11].

In around 75% of cases of chronic osteomyelitis, the causative pathogens are *Staphylococcus aureus* and coagulase-negative staphylococci, streptococci, Gram-negative pathogens (enterobacteria, pseudomonads), and anaerobic bacteria [4,12,13].

The local use of antibiotics to prevent skeletal infections was incorporated into the general practice with the development of joint arthroplasty in Europe in the 1970s. Buchholz and Engelbrecht reported in a sentinel paper that penicillin, erythromycin, and gentamicin mixed into the cement used to affix prostheses to the bone was found to provide high concentrations of antibiotics for extended periods of time, facilitating the use of antibiotics in infection prophylaxis for joint arthroplasty [14,15].

Calcium sulfate has been used as a bone graft substitute since the late 1800s. In 1977, a medical-grade calcium sulfate impregnated with tobramycin was introduced commercially overseas [16,17].

The advantages of calcium sulfate include its biodegradability, its predicable elution characteristics, its osteoconductivity, and its ability to fill dead space [16,18].

The safety of this type of treatment has been reviewed in the joint arthroplasty literature; local antibiotic treatment is also substantially less expensive than systemic therapy [19].

Patients and methods

In the period between June 2013 and June 2018, this study was carried out as a single-surgeon, single centered (Orthopaedic Surgery Department, Suez Canal University, Ismailia, Egypt) prospective, cohort study. It was carried out on 70 patients presented to the Orthopedics and Trauma Department of Suez Canal University Hospitals by osteomyelitis of more than 6 months duration was diagnosed by plain film, MRI, computed tomography, and/or direct bone biopsy. All patients have written consents. Following Departmental Research Committee approval and Research Ethics Committee approval.

This study aimed at evaluating the results of using synthetic pure calcium sulfate impregnated with vancomycin and gentamicin of antibiotic-loaded dissolvable beads in the treatment of chronic long-bone infection (chronic osteomyelitis).

Patients who met inclusion to this study had (a) intact vascular status. This was determined by either palpable pulses with evidence of intact local perfusion, (b) confirmation of osteomyelitis, (c) bone infection of more than 6 months duration, and (d) patients with chronic long-bone infections that were not responding to several trials of treatment. These treatments included oral and/or intravenous antibiotics, local wound care, offloading where indicated, appropriate dressings, negative-pressure wound therapy, and/or management of comorbidities. Patients who were excluded from the study were those who had active peripheral vascular disease.

All patients were examined at presentation; swabs are obtained in each different setting, full history was taken, laboratory examinations were preoperative, 3 days postoperative, and every month for 6 months postoperative on the basis of erythrocyte sedimentation rate, C-reactive protein (CRP), and total leukocyte count, and radiological examination (infection and union signs) by means of plain radiograph and computed tomographic scan if needed; all these data will be provided in a sheet (Table 1).

All patients prepared for surgical debridement following induction of general or spinal anesthesia. The use of a tourniquet is the choice of the surgeon. Devitalized or infected bone was debrided to the level of healthy cancellous and cortical bone. Compromised soft tissue was resected. Wide resection of the bone with an extra 2–3-mm resection to expose the healthy bone was performed. External fixator was ready to be used when the affected bone became weak and increase the risk of its integrity.

During this time, we prepared dissolvable antibiotic beads. The antibiotic combination used in this series consisted of 2 g of vancomycin powder and 240 mg of liquid gentamycin mixed with 10 ml of Stimulan powder; antibiotic beads were inserted at the end stage of debridement [20].

After pouring vancomycin into a sterile cup, liquid gentamicin was added and thoroughly mixed until all of the vancomycin dissolved. Next, 10 ml of synthetic calcium sulfate powder was added and mixed to a uniform paste consistency acceptable for spreading onto the beads.

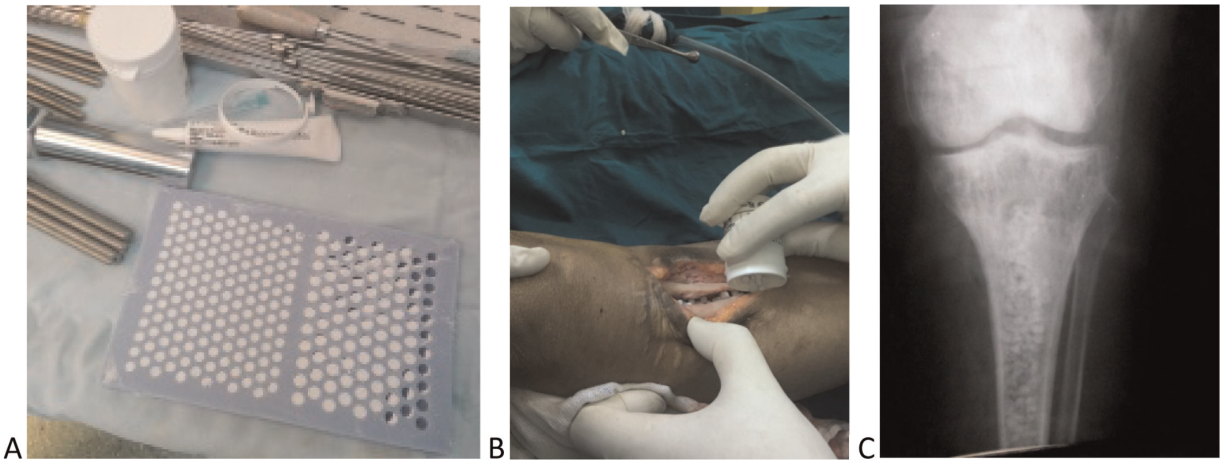
Then the wound was flushed with sterile saline (with or without antimicrobial agent added) and suctioned. The beads were released from the mold into a sterile basin and inserted, usually one at a time, into the wound. Starting at the deepest aspect of the wound, the beads were gently packed (Fig. 1a–c).

The wounds were primarily closed and allowed for minor drainage expected with synthetic calcium sulfate

Table 1 General information

Serial number	Patient name (optional)	
Age	Sex	Chronic illness
Date and time of trauma	Mode of trauma	Gustilo classification
Complications	Date and time of management	Swab result

Figure 1



Preparation and insertion of calcium sulphate beads. (A) Preparation of beads. (B) Insertion of beads inside the bone. (C) Post operative c ray.

beads. Retention sutures (2-0 or 0 nylon) were used when possible to approximate the wound edges; skin or myocutaneous flaps may be needed in some patients facing problems in closing the skin; daily dressings were done.

All patients received 2 weeks intravemously and oral antibiotics and another 2 weeks-only oral antibiotics based on the culture and sensitivity; in case of no growth the patient received ceftriaxone 1 g per day and clindamycin 300 mg twice per day and then amoxicillin and clavulanic acid for another 2 weeks [21].

Successful treatment was considered achieved for osteomyelitis when the wound/ulceration had completely resurfaced; no clinical signs of infection were noted; and radiographic and/or monitored laboratory values (sedimentation rate, CRP, white blood count) returned to normal.

Results

This study included 70 patients who had been suffering from chronic long-bone infection (chronic osteomyelitis of more than 6 months duration), The mean age of the patients in this study was 37.9428, ranging between 16 and 55 years, while the female to male ratio was 0.371 (Table 2); the average follow up was of 12 months (range. 6–18 months).

The initial mode of trauma: road traffic accidents accounted for 42 patients, 60% (highest) of whom had done open reduction and internal fixation and then developed infection, while the hematogenous ones demonstrated the remaining injury cause with 28 (40%) patients.

Table 2 Distribution of the patients according to their demographic data

	n (%)
Age	
10–30	30 (42.85)
31–40	24 (34.28)
41–50	16 (22.85)
Gender	
Male	44 (62.85)
Female	26 (37.15)
Gustilo and Anderson	
II	12 (17.14)
III	58 (82.86)

Classification of injury, based on the Gustilo and Anderson classification, 17.14% were G II and 82.86% were G III (C1–3).

Bones included: leg bones (tibia and fibula) were the most affected bones in this study (54.28%); femoral bone represented 14.28%; both bone forearm (radius and ulna) affected was 10%; however, the humerus was the least affected bone at 7.14%.

Immediate swab results: *S. aureus* was the organism that had been reported in 45.71% of all swabs. Coagulase-negative staphylococci came second with 15.71%, no growth accounted in 11.42%. Operative swabs results: 18.57% of this study showed no growth in the swabs taken compared with 11.42% of immediate swabs (Table 3).

Laboratory investigation results: laboratory investigations were done preoperatively, after 3 days of the intervention, and every month for consecutive 6 months; postintervention showed 100% of samples taken preoperatively and 3 days after the surgery

Table 3 Swab results

Swab results	Immediate swabs [*n* (%)]	Operative swabs [*n* (%)]
Staphylococcus aureus	32 (45.71)	28 (40)
Coagulase-negative staphylococci	11 (15.71)	13 (18.57)
Pseudomonas spp.	6 (8.57)	6 (8.57)
Escherichia coli	5 (7.14)	5 (7.14)
Klebsiella spp.	3 (4.28)	1 (1.43)
Streptococcus pyogenes	2 (2.86)	1 (1.43)
Serratia spp.	1 (1.43)	1 (1.43)
Acinetobacter spp.	1 (1.43)	1 (1.43)
Proteus spp.	1 (1.43)	1 (1.43)
No growth	8 (11.42)	13 (18.57)
Total	70	70

showed raised inflammatory markers (erythrocyte sedimentation rate, CRP, and total leukocyte count). Laboratory investigations done after 1 month showed a marked decline in the levels of inflammatory markers but not reach the normal in 45 (64.28%) patients but still at the same level or rising in 25 (35.72%) patients.

Raised inflammatory markers (ESR, CRP& TLC), Lab. Investigations done after one month showed marked decline in the levels of inflammatory markers but not reach the normal in 45 patients (64.28%) but still at the same level or raising in 25 patients(35.72%) while Investigations done 6 months post operative the inflammatory markers results showed 78.57 % of samples with normal inflammatory markers levels and 21.43 % of samples showed elevated levels.

Radiographs done at 3 months' follow-up visits showed that 75.71% of the patients had callus and new bone formation at the operative site and completely absorbed calcium sulphate beads with no evidence of presence of osteomyelitis.

Radiographs done at 6 months' follow-up visits showed that 78.57% of the patients had proper callus and good bone healing with no evidence of osteomyelitis, and only 15 (21.43%) patients still showed poor healing with osteomyelitis.

Wound healing and hospital stay: 40 (57.14%) patients healed in more than 14 days, 10 (14.28%) patients healed in 15–21 days, five (7.14%) patients needed skin graft as there was difficulty in primary closure and only 10 (14.28%) patients showed unhealed wounds.

Application and removal of external fixator were needed in 48 patients; 68.57% of patients needed external fixator during debridement due to larger defects or those in a compromised host require more aggressive surgical management application of ilizarov while small osseous defects were structurally stable with no need to apply external fixator in 22 (31.43%) patients.

Second trial of debridement was done for the 15 (21.42%) patients and calcium sulfate with vancomycin and gentamycin beads and improvement occurred in six patients only while the remaining nine patients still have signs of chronic infections and raised inflammatory marker after 1 year from initial debridement.

Complication blood loss of more than 1500 ml blood occurred in 15 (21.42%) patients and required blood transfusion of 2–3 U of blood; five (7.14%) patients developed deep venous thrombosis (DVT) and received proper treatment, six patients developed urinary retentions, and three patients developed decubitus ulcer.

Final results: 61 (87.14%) patients showed completely healed wound and complete recovery with no signs of osteomyelitis with normal inflammatory markers while only nine (12.86%) patients showed unhealed wound and presence of chronic infections even after the second operation planned for them.

Discussion

The treatment of chronic osteomyelitis has become a difficult problem in orthopedics as it is difficult to eradicate and remains a challenge in the clinic because it is difficult for the antibiotics to penetrate into local sites due to malformations that are secondary to chronic infection [22]. Due to the availability of new materials and methods, many new concepts and technologies have been developed for the treatment of chronic osteomyelitis on the basis of regular treatment. The uses of nonabsorbable antibiotic-impregnated bone cement and absorbable biological bone cement to treat the infection have been reported recently subsequent to routine antibiotic chains being used [23].

Studies have focused on the effect of administering vancomycin systemically or using a local drug carrier method [24]. Moreover, studies show that methicillin-resistant staphylococcus aureus (MRSA) is sensitive to high local concentrations of vancomycin, and the high success rate that was achieved is encouraging for the clinical use of vancomycin for MRSA-induced bone infections [22,24,25].

Local delivery systems have been explored to minimize systemic toxicity and eliminate concerns about antibiotic penetration, while also achieving high local doses of antibiotics [26]. Jackson *et al.* [27]. reported that initial attempts at local implantation were not successful because of uncontrolled and rapid release of the antimicrobial agent at the target site.

Gentamicin-loaded polymethylmethacrylate tablets have been widely accepted as a local delivery system of antibiotics into the infected tissue; however, Neut *et al.* [28] retrieved implanted polymethylmethacrylate beads (with gentamicin), and the cultures of the beads themselves revealed bacterial growth on 18 of 20 of them. Of the 28 strains cultured, 19 were gentamicin-resistant organisms. This finding suggests that the resistance may occur because the beads act as a biomaterial surface to which bacteria preferentially adhere [28,29].

Despite the fact that Polymethyl Methacrylate (PMMA) has become the gold standard of antibiotic delivery in orthopedic infection treatment and prophylaxis, the need for a second surgical procedure for bead removal and does not participate in the bone-healing process.

As a result of these short comings of PMMA, several alternatives to bone cement have been proposed and investigated as vehicles for antibiotic delivery. The primary area of investigation has focused on biodegradable materials. The degree of biodegradability can vary from weeks to months, allowing variable types of infections to be treated [22,30].

Biodegradable implants also ensure that the entire desired amount of antibiotic is delivered over the course of treatment, in contrast with treatment with acrylic cements. Calcium sulfate has been used as a bone graft substitute since the late 1800s. In 1977, a medical-grade calcium sulfate impregnated with tobramycin was introduced for its low immunoreactivity, ability to be absorbed, and its structural properties [26–28].

One controlled study using an experimental animal model of osteomyelitis induced with *S. aureus* and treated with calcium sulfate beads with tobramycin demonstrated no elevation of serum calcium levels, high tobramycin seroma levels, and no elevation of serum tobramycin levels [31].

Many antibiotics have been shown to maintain efficacy when mixed with calcium sulfate, the requirements of such antibiotics are that they be heat stable and hydrophilic. The most commonly used antibiotics include gentamicin, tobramycin, and vancomycin. Gentamicin sulfate is an excellent additive to calcium sulphate due to its broad spectrum of action, its bactericidal properties, low rate of primarily resistant pathogens, and good thermostability [32]. Vancomycin is water soluble and available in powder form. Mixing of more than one antibiotic into calcium sulfate has been shown to have a synergistic effect [33]. Vancomycin and gentamicin were chosen because they cover a broad spectrum of both Gram-positive and Gram-negative bacteria.

Recent research has focused on the toxicity of high concentrations of antibiotic on tissue and bone healing with vancomycin found to be less toxic than cefazolin. Further in-vitro studies with ciprofloxacin, vancomycin, and tobramycin demonstrated changes in cellular morphology with exposure to antibiotics. Levels of vancomycin and tobramycin at 2000 μg/ml severely decreased cellular proliferation, and ciprofloxacin had similar effects at 100 μg/ml [34,35].

It has been reported that elution levels of antibiotic from calcium sulfate have surpassed 200 times the minimal inhibitory concentration for specific organisms over a minimum of 14 days. Even when large doses of calcium sulfate have been implanted (50 ml calcium sulfate, 5 g vancomycin, and 2.4 g tobramycin), serum levels of calcium sulfate and antibiotics were not detected throughout the treatment process [36,37].

As regards the complication which occurred in this study it was blood loss of more than 1500 ml that occurred in 15 patients which is due to marked fibrosis and adhesion as a result from chronic infection changes and aggressive debridement and required blood transfusion; this must be considered to prepare at least 2 U of blood ready for transfusion, five (7.15%) patients developed DVT and received proper treatment as the patients with chronic osteomyelitis may have increased the risk to develop DVT.

This is attributed to the high concentration of local antibiotic delivery (not possible by systemic means of delivery) and possibly the local effects of the synthetic calcium sulfate itself and the results of this study demonstrate the efficacy of the calcium sulfate beads in the treatment of 61 (87.14%) patients with complete recovery and normal inflammatory markers.

As concern when treating osteomyelitis is whether the infection has been completely eliminated or it has just been placed in remission or slowed to the point where clinical symptoms are not experienced. Although in 15 (21.43%) patients of the cases reported, a second debridement and calcium sulfate beads implantation was performed and this leads to increase the cure rate to 87.14% at final assessment and no any recurrence of osteomyelitis to any specific anatomical location of up to 18 months follow-up in the cured patients.

Finally, these results indicate the efficacy of using calcium sulfate impregnated with vancomycin and gentamycin in the treatment of chronic osteomyelitis of the long bone.

Conclusion

The use of locally implanted antibiotic-impregnated, synthetic calcium sulfate beads is a viable option in the surgical debridement site for chronic long-bone infection (chronic osteomyelitis).

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Conflicts of interest

There are no conflicts of interest

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