

The treatment of chronic osteomyelitis with a biodegradable antibiotic-impregnated implant

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ABSTRACT

The use of local antibiotics from a biodegradable implant for chronic osteomyelitis is an attractive alternative. The implant delivers high tissue levels, obliterates dead space, aids bone repair and does not need to be removed. The purpose of this paper is to review our early clinical experience with custom-made calcium sulfate (OSTEOSET® BVF Kit) antibiotic-impregnated implants.

Key words: Osteomyelitis, Implant, Antibiotic, Calcium Sulfate, Biodegradable

INTRODUCTION

The treatment of chronic osteomyelitis includes debridement of the dead infected tissue, obliteration of dead space, osseous repair, adequate soft tissue coverage, and systemic antibiotics. The delivery of antibiotics to bone varies considerably. Oral antibiotics are unpredictable with relatively low bone levels and are infrequently used. Intravenous antibiotics are used commonly in the treatment of chronic osteomyelitis.

The appropriate drug is selected based on bacterial sensitivity and an adequate serum level is maintained. Six weeks of intravenous antibiotics is necessary for adequate therapy. Even with prolonged intravenous antibiotics, there is a significant relapse rate. To supplement systemic antibiotics, local antibiotic delivery has been tried for many years. Local antibiotic delivery can be achieved by mechanical pumps, nonbiodegradable implants such as methylmethacrylate, or a biodegradable implant.

Local antibiotic delivery has the advantage of high-tissue concentrations with relatively low serum levels. This avoids some of the toxicity associated with systemic antibiotics, especially aminoglycosides. Antibiotic-impregnated implants are particularly attractive because not only do they deliver high tissue levels of antibiotics but they also help obliterate the dead space that occurs after bone debridement.^{1,6,9,18} Antibiotic pumps do not achieve this desirable effect.

The most common form of local antibiotic delivery by an implant is with the use of methylmethacrylate. Various types of methylmethacrylate have been tested by elution studies.^{2,13,14} The shape of the methylmethacrylate implant along with the type of methylmethacrylate has a significant effect on the amount of antibiotic delivery, as well as duration. Tobramycin, gentamicin, and vancomycin are the antibiotics that have been combined with methylmethacrylate. Nelson et al (1992) found the

delivery of both gentamicin and tobramycin at day one ranged from 88 to 807 ig/ml. There was a significant drop-off in the amounts at day two, and a much more gradual decrease out to 30 days. By day 30, between 1 and 28 ig/ml of antibiotic was delivered. The best delivery profile was with Septopal®. Septopal® beads consist of Palacos® cement impregnated with gentamicin.¹⁵ Several authors have shown the local delivery of antibiotics is quite effective in eradicating osteomyelitis. Animal models of osteomyelitis have been used to test the effectiveness of local antibiotic delivery.⁶ The results suggest that the eradication of bacteria can be accomplished more effectively with local antibiotic delivery over systemic therapy. Methylmethacrylate is not an ideal antibiotic implant. It is a dense acrylic, nonbiodegradable, and generally needs to be surgically removed to avoid becoming a future nidus. Finally, methylmethacrylate does not aid in bone repair. As a result, there has been increased interest in the use of a biodegradable antibiotic implant to treat chronic osteomyelitis. One of the most well known materials studied is calcium sulfate.^{3,4,7,8,11} Calcium sulfate is a bioceramic that occurs naturally. Surgical-grade calcium sulfate is a relatively pure alpha hemihydrate crystal, which can be hydrated producing solid implants. Any water-soluble antibiotics can be incorporated into the crystalline structure, thus loading the implant with antibiotics. Aminoglycosides and vancomycin have been used in this manner. Calcium sulfate is well tolerated, nonimmunogenic, and fully biodegradable.

The rate of resorption is dependent upon the density of the crystal. Implants can resorb either quickly or slowly depending upon how they are produced. Elution testing of 4% by weight loaded calcium sulfate pellets revealed a maximum concentration of 828 ig/ml and undetectable levels by day 15. *In vivo* measurements of antibiotic delivery from calcium sulfate have also been performed. Calcium sulfate pellets impregnated with 2% and 4% by weight of tobramycin were tested in the dog humerus.¹⁷ Systemic levels peaked at one hour (1.8 ig/ml and 3.6 ig/ml for the 2% and 4% concentrations, respectively) and was undetectable by 24 hours.

Tissue levels reached a mean 1,964 ig/ml (2%) and 3,297 ig/ml (4%) at one hour. By day 14, the tissue level was 2 ig/ml (2%) and 4 ig/ml (4%) and was greater than 0.1 ig/ml for up to 28 days. Not only did these calcium sulfate implants fully degrade, they aided in the bone repair. This is an added value when treating osteomyelitis.^{8,10,12,17,19} Sulo (1993) reported on 409 patients from Albania treated with plaster of Paris antibiotic beads impregnated with gentamicin. 95% of these patients were felt to be cured of chronic

osteomyelitis after 37 months mean follow-up. 42% of the patients had complete filling of the osseous defect with this technique. The purpose of this paper is to present our early clinical experience with calcium sulfate as a local antibiotic delivery implant for chronic osteomyelitis. Infection control and bone repair will be reported.

Preparation of the Calcium Sulfate Antibiotic Implants and Surgical Technique

The calcium sulfate used in this study was the OSTEOSET® BVF (Bone Void Filler) Kit (Wright Medical Technology, Arlington, TN). This bone void filler kit consists of surgical-grade calcium sulfate alpha hemihydrate powder and a sodium chloride diluent. Each kit contains 25 gms of calcium sulfate powder and 7.8 cc of diluent. Two forms of the bone void filler kits are available; standard-cure and fast-cure. The fast cure kit contains an accelerant that speeds the hardening process. Vancomycin is an antibiotic that accelerates the hardening process and thus should be used with the standard-cure kit while tobramycin, a retardant, is used with the fast-cure kit. The mixing is done as follows: 1 gm of vancomycin hydrochloride or 1.2 gm of tobramycin sulfate powder is first mixed with the diluent provided in the kit. These doses will yield implants with antibiotic concentrations of 3.64% and 4.25% by weight, respectively. Once the antibiotic powder is fully blended with the diluent, the solution is poured over the powder, allowed to wet the powder for 30 seconds, and then blended with a spatula. The material is evenly blended until a free flowing paste is obtained. The bottom half of a silicone mold, containing thirty cavities, is completely filled with the paste (Fig. 1a–1d). The top half of the mold is applied, and the assembly is maintained, in a compressed manner, until hardening is achieved. It takes approximately 30 minutes for the material to fully harden, and then the mold is broken. The implants are removed by flexing the mold, yielding thirty each 7 mm diameter spheres. Each OSTEOSET® BVF Kit can produce sixty 7 mm spheres.

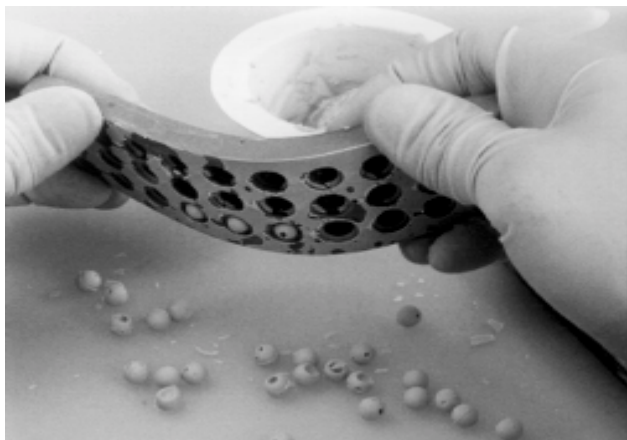
The area of osteomyelitis is approached surgically with a longitudinal incision. Standard surgical approaches are made down to the bone. The area of the osteomyelitis is completely exposed by either removal of a cortical window with an osteotome or saw. An alternative would be to expose the area of osteomyelitis with a high-speed dental bur. The purulent material is then excised with curettes, and then the bone is further debrided with a high-speed dental bur. The burring continues until good bleeding bone is encountered at the margins of the chronic



(a)



(b)



(c)

Figure 1 (a) The mixed antibiotics are placed into the 30 wells in the silicone mold. (b) The mold is opened after 30 minutes. (c) The antibiotic implants are removed from the mold. (d) 7mm implants are produced.

osteomyelitis. Appropriate cultures need to be taken both prior to the surgical procedure and at the time of the surgical debridement. After complete debridement the cavity is lavaged with a high-pressure pulsatile antibiotic solution. Copious amounts of fluid are used to completely clean the bone. Finally, the antibiotic implants are placed into the debrided cavity. The entire cavity is filled with the 7 mm spherical implants. The implants are not crushed as this will effect the antibiotic delivery profile and resorption rate. The maximum number of implants used is one 7 mm sphere per kilogram of patient body weight. Residual defect is filled with off the shelf nonmedicated OSTEOSET® surgical-grade calcium sulfate pellets to ensure obliteration of the dead space. The antibiotic is selected based on bacterial sensitivity. Methicillin-resistant *S. aureus* is generally treated with vancomycin impregnated implants, while all other bacterial infections are treated with implants impregnated with

tobramycin. The wound is closed in multiple layers trying to obtain muscle coverage over the area of osteomyelitis. Closed suction drainage is used for 48 hours to minimize the hematoma and seroma. Systemic antibiotics are administered in standard fashion. Six weeks of intravenous antibiotics are delivered based on bacterial sensitivity. The limb is appropriately protected, with crutches or a fracture type orthosis, post-operatively for six to twelve weeks until adequate bone repair is evident radiographically.

MATERIALS AND METHODS

Six consecutive patients with chronic osteomyelitis treated with both systemic antibiotics as well as local antibiotics with a calcium sulfate biodegradable implant were reviewed (Fig. 2). All patients had radiological evidence of chronic osteomyelitis with



Figure 2 Demographics of clinical cases. Note S.A. is *Staphylococcus aureus*. The mixed infection was methicillin resistant *S. aureus*, *Klebsiella pneumoniae*, and *E. coli*.

osteolysis, cortical thinning, sequestration, involucrum, and both medullary and soft tissue swelling. All patients had culture-documented chronic osteomyelitis. The clinical records, radiographs, bone repair, sedimentation rate, and functional outcome using the Enneking/ Musculoskeletal Tumor Society System were evaluated.⁵ The defect size was measured post-debridement using 2-plane film radiographs. The osteomyelitic cavity was measured from edge to edge, and maximum dimensions were determined. The defect volume, in cubic centimeters, was calculated using the maximum dimensions on both the anterior-posterior and lateral views (Fig. 3). Pre-operative cultures and bacterial classification were performed on all patients with cultures at the time of presentation

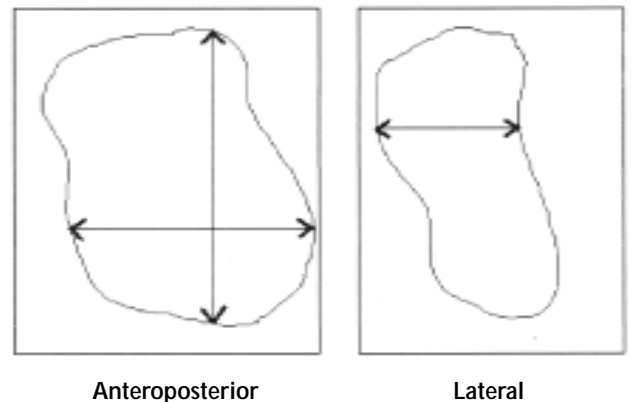


Figure 3 Method to measure defect size. Note, the maximum dimensions are chosen on the anteroposterior and lateral radiographs (arrows). The defect volume, in cubic centimeters, is determined

or surgery. All patients were treated surgically with debridement and placement of antibiotic impregnated calcium sulfate beads based on bacterial sensitivity. When the bacterial culture was not known pre-operatively, the local antibiotic delivered was tobramycin, and the systemic antibiotic delivered was based on final cultures at the time of surgical debridement. Post-operatively the patients were followed with 2-plane film radiographs. At most recent follow-up, the bone defect was again measured and residual cavity measured. Typically the bone is repaired with new bone evidenced by trabeculation at the defect site. Amorphous mineralization was not counted as bone repair. The Enneking Functional Evaluation System is a 30-point system for both upper

Table 1
Demographics of clinical cases. Note S.A. is *Staphylococcus aureus*. The mixed infection was methicillin resistant. *S. aureus*, *Klebsiella pneumoniae*, and *E. coli*.

Patient	Sex	Age	Site	Organism	Defect Size	Sed Rate	F/U	Sed Rate	Bone Repair	Function	Infection Status
					(cc)	(mm)	(mo.)	(mm)	(%)	(MSTS)	
1.	TW	F/32	Femur	S.A.	84	105	40	12	96	29/30	Quiescent
2.	EK	F/43	Tibia	S.A.	34.5	26	27	3	94	30/30	Quiescent
3.	JH	M/85	Femur	S.A.	60	90	20	10	95	28/30	Quiescent
4.	JB	M/70	Tibia	S.A.	21	30	38	2	96	26/30	Quiescent
5.	JD	M/26	Femur	S.A.	28	50	18	5	97	30/30	Quiescent
6.	PS	F/44	Tibia	Mixed	12	22	28	15	65	22/30	Quiescent

and lower extremity lesions. The functional score was reported as a raw score out of 30 possible points. The patients were evaluated for complications related to the osteomyelitis or the local antibiotic therapy.

RESULTS

There were six patients, three male and three female (Table 1) The mean age was 50 years. The osteomyelitis was located in the tibia and femur each in three patients. Five patients had a *S. aureus* infection, and one patient had a mixed bacterial infection of MRSA, *Klebsiella pneumoniae* and *E. coli*. All patients had a closed infection without active drainage or a sinus. The mean defect size was 40 cc (range 12 to 84). The mean pre-operative sedimentation rate was 54 mm (range 22 to 105). The local antibiotic used was tobramycin (5 patients) and tobramycin plus vancomycin (1 patient). The mean follow-up was 28 months (range 18 to 40). The mean sedimentation rate at most recent follow-up was 8 mm. The defect size at most recent follow-up was 2.5cc, thus making the bone repair 91%. The mean functional score at follow-up was 27.5 out of 30 points. The one patient with a mixed infection ended up with a functional score of 22. This patient scored 3 points for pain, 3 points for function, 3 points for emotional acceptance and 3 points for gait. There were no fractures, infection relapses, or additional surgery to date. In all patients the local antibiotic calcium sulfate implants fully biodegraded. In all patients, the bone showed progressive repair without evidence of either residual or new osteolysis. There were no unusual periosteal changes during the course of therapy such as onion skinning. No patient had significant drainage or adverse reaction to the local antibiotic implants.

Case Example

TW was a 32 year old female who presented with a 3 month history of severe left knee pain. There was no history of trauma and the patient had no significant past medical history. A radiograph was performed and a destructive lesion was found involving the left distal femur (84 cc). It was originally felt to be a malignant neoplastic process. A magnetic resonance image scan revealed a medullary fluid filled cavity with surrounding edema. The initial sedimentation rate was 105 mm (normal less than 20) and white cell count of 9.4. The patient was taken to surgery for a biopsy. The femur was approached through a longitudinal anterolateral incision. The cortex was drilled open and purulent material exuded. Frozen section pathological

examination revealed chronic osteomyelitis with both acute and chronic inflammatory cells, fibrosis and necrotic bone. The anterior cortex of the femur was removed with a burr and the cavity completely debrided. All soft tissue from the cavity was debrided and the surrounding bone burred until bleeding bone was encountered. Appropriate cultures were taken and the cavity was lavaged with high pressure pulsatile antibiotic solution. The cavity was next packed with sixty 7 mm tobramycin impregnated implants (patient weight 60 kgm). The wound was closed over a suction drain. The final cultures grew *S. aureus* sensitive to tobramycin and ciprofloxacin. The patient received six weeks of intravenous ciprofloxacin. The limb was protected with a knee-ankle-foot fracture orthosis for three months. The follow-up was 40 months. At most recent follow-up of 40 months the sedimentation rate was 12 mm. The functional score was 29/30 points. The bone repair was 96%(Fig. 4a & 4b). There has been no relapse of osteomyelitis and there have been no complications.

DISCUSSION

The local delivery of antibiotics for chronic osteomyelitis is potentially an advantage over standard intravenous therapy. Not only does this biodegradable antibiotic implant obliterate the dead space, it delivers high doses of tissue antibiotics and aids in bone repair. Furthermore, this implant does not need to be removed like methylmethacrylate. In the present study the patients showed evidence of excellent osseous repair, and none have required follow-up surgery such as autogenous iliac bone grafting despite the size of the defect and their location in weight-bearing bones (Fig. 5a-5d). To date there have been no relapses of infection. Most of the infections were due to *S. aureus*, and all but one of these were sensitive to tobramycin. The one mixed infection (*E. coli*, *Klebsiella pneumoniae* and methicillin resistant *S. aureus*) was treated with a combination of tobramycin and vancomycin implants. These implants were selected based on the mixed flora and the fact that the staphylococcus present in this patient was methicillin resistant. It's interesting that this patient had the lowest bone repair score and the lowest functional outcome. Mixed bacterial bone infections are the most difficult to treat. This study is relatively small, although promising. Only six patients were reviewed, but the performance of the local antibiotic implants was quite consistent. Full degradation occurred, and bone repair occurred in an orderly manner. Two important questions remain unanswered. Can this technique be used without

systemic antibiotics? If further studies prove successful without systemic antibiotics, there could potentially be significant cost savings. Turner et al. (1998) showed in an animal model that calcium sulfate delivers adequate killing levels in tissue for up to six weeks with safe serum levels. If the same holds true in humans, then perhaps systemic antibiotics can be avoided. The cost savings would not only be in intravenous antibiotics but also in the venous catheter needed to deliver systemic drugs. Hospitalizations would be shortened and overall care easier. The second important question is late relapse. Chronic osteomyelitis is notorious for late relapse, even with

aggressive systemic therapy and surgical treatment. At least in this small series with relatively short-term follow-up, the control of the infection was excellent. Since the bone repair was substantial, follow-up surgery with autogenous iliac bone grafting and all its inherent problems hopefully will be avoided. This is one added advantage with the use of this biodegradable and osteoconductive implant. In conclusion, local antibiotic delivery with calcium sulfate proved to be effective for infection control and bone repair. This implant does not need to be removed and may be an adjunct to systemic antibiotics for chronic osteomyelitis.



(a)



(b)

Figure 4 (a) One year post-operative radiograph. Note the calcium sulfate (OSTEOSET®) implants have fully degraded. The dimensions of the cavity (previously 84 cubic centimeters) have diminished significantly. The bone repair is 96%. The radiolucency on the anteroposterior radiograph is the cortical defect created to debride the osteomyelitis. (b) One year lateral radiograph. The medullary defect has been replaced with bone. Only a cortical defect remains which has remodeled. The medullary defect is filled with bone.



(a)



(b)



(c)



(d)

Figure 5 (a) Post-operative anteroposterior radiograph of the proximal tibia after debridement of chronic osteomyelitis (Fig. 1, patient 2). The defect (34.4 cc) is filled with calcium sulfate antibiotic impregnated implants. (b) Lateral radiograph of the same patient. Note the cortical window created to debride the infection. (c) Anteroposterior radiograph at 27 months showing degradation of the implants and bone repair (94%). (d) Lateral radiograph showing the bone repair. Note the bone formation in the medullary space with remodeling of the cortical window.

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