

Scientific Publication Summary Form

Title of article: A Prospective, Randomised Clinical Trial Comparing an Antibiotic-Impregnated Bioabsorbable Bone Substitute with Standard Antibiotic-Impregnated Cement Beads in the Treatment of Chronic Osteomyelitis and Infected Nonunion

Author(s): Michael D. Mc.Kee, MD, FRCSC, Esther A. Li-Bland, MD, Lisa M. Wild, BSc(N), and Emil H. Schemitsch, MD, FRCS(C)

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Publication Summary

Abstract

Objectives: We sought to compare the effectiveness of an antibiotic-impregnated bioabsorbable bone substitute (BBS, tobramycin-impregnated medical-grade calcium sulfate) with antibiotic-impregnated polymethylmethacrylate (PMMA) cement beads after surgical débridement in patients with chronic nonhematogenous osteomyelitis and/or infected nonunion.

Design: A prospective, randomized clinical trial.

Setting: A university-affiliated teaching hospital.

Patients/Participants: Thirty patients requiring surgical treatment for chronic long bone infection or infected nonunion were included: BBS (15 patients, mean age 44.1 years) PMMA (15 patients, mean age 45.6 years).

Intervention: Patients were randomized to receive either BBS or PMMA to the bone void created by surgical débridement.

Main Outcome Measurements: Eradication of infection, new bone growth, rate of union, repeat operative procedures complications.

Results: Patients were followed for a mean 38 months (range, 24-60 months). One patient was lost to follow-up in each group. In the BBS group, infection was eradicated in 86% (12 of 14) of patients. Seven of eight patients achieved union of their nonunion, and five patients underwent seven further surgical procedures. In the PMMA group, infection was eradicated in 86% (12 of 14) of patients. Six of eight patients achieved union of their nonunion, and nine patients required 15 further surgical procedures. There were more reoperations in the PMMA group (15 versus seven, $P = 0.04$), and these procedures tended to be of greater magnitude.

Conclusions: The results of this preliminary study suggest that, in the treatment of chronic osteomyelitis and infected nonunion, the use of an antibiotic-impregnated BBS is equivalent to standard surgical therapy in eradicating infection and that it may reduce the number of subsequent surgical procedures. A larger, definitive study on this topic is required.

Publication Highlights

Multiple prior studies have demonstrated that Osteoset T has high clinical effectiveness in infection removal and plays a role in new bone formation. However, none of these studies had a comparable control group of the standard therapy with PMMA beads, followed by iliac crest bone graft insertion, to help bone void or nonunion healing. This the FIRST STUDY (Prospective randomized) to compare standard PMMA beads with Osteoset T in the treatment of bone infection.

Chronic osteomyelitis is in most cases caused by bacteria growing in biofilm communities, which cause the infecting organism to be resistant to systemic antibiotic levels up to 1000 times higher than normal therapeutic levels. This explains the persistent, recurrent nature of osteomyelitis and the difficulty in removing established infection in bone. That is why high local antibiotic levels after surgical débridement are a crucial component in the long-term resolution of chronic osteomyelitis or infected nonunion.

Current standard protocol for the treatment of chronic nonhematogenous osteomyelitis is normally a two-staged procedure and includes surgical débridement, obliteration of dead space with local antibiotic delivery through implantation of antibiotic-impregnated synthetic material, and subsequent antibiotic therapy. PMMA (Polymethylmethacrylate) cement beads are considered the golden standard with autogenous iliac crest bone grafting as the second stage.

Disadvantages: PMMA is not biodegradable and can even serve as a site for recurrent infection when left in the bone void past effective antibiotic elution. The antibiotics embedded within the PMMA beads may not elute completely, which leads to release of sub-therapeutic levels of antibiotics over a sustained period. This increases the risk of developing antibiotic-resistant organisms. PMMA does not allow nor assist in bone regrowth, in most cases an additional surgical procedure is required for removal of the PMMA beads and subsequent bone grafting, delaying the healing process. Donor site morbidity, additional pain, anesthesia time, blood loss, instability, infection and fatigue fractures at the donor site are associated problems with bone grafting.

These disadvantages lead to an interest in a bioresorbable bone substitute, which can be impregnated with antibiotic, are osteoconductive, and do not require a two-staged procedure for removal.

Osteoset T (medical grade alpha-hemihydrate calcium sulfate) has been well characterized clinically as such a bone void filler.

Advantages: Osteoset has a steady and gradual resorption, it is osteoconductive, lacks systemic side effects and has consistent clinical results. The incorporation of tobramycin into the calcium sulfate hemihydrate crystal structure produces an extremely high local concentration of antibiotics as the pellets are reabsorbed. Blaha et al. demonstrated that osteoset supports infiltration of new blood vessels and osteogenic cells (osteoblasts attach to the surface of the pellets) and prevents ingrowth of soft tissue.

Why Tobramycin?: Tobramycin is chosen because it is generally effective against Staphylococcus (65%-85% cause of osteomyelitis), Pseudomonas and Escherichia species. Even though systemic Tobramycin levels may not always be effective against all bacteria, the extremely high local concentrations released by Osteoset T may nevertheless result in removal of the infection.

A Prospective, Randomized Clinical Trial Comparing an Antibiotic-Impregnated Bioabsorbable Bone Substitute With Standard Antibiotic-Impregnated Cement Beads in the Treatment of Chronic Osteomyelitis and Infected Nonunion

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group, infection was eradicated in 86% (12 of 14) of patients. Six of eight patients achieved union of their nonunion, and nine patients required 15 further surgical procedures. There were more reoperations in the PMMA group (15 versus seven, $P = 0.04$), and these procedures tended to be of greater magnitude.

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Key Words: bone infection, antibiotic-impregnated bone substitutes, randomized clinical trial

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INTRODUCTION

The current standard protocol for the treatment of chronic nonhematogenous osteomyelitis includes surgical débridement, obliteration of dead space with local antibiotic delivery through implantation of antibiotic-impregnated synthetic material, and subsequent systemic antibiotic therapy. Polymethylmethacrylate (PMMA) cement beads are considered the standard vehicle for local antibiotic delivery.^{1–6} However, there are disadvantages: PMMA is not biodegradable, the material does not allow bone regrowth, and in most cases, an additional surgical procedure is required for removal of the beads and subsequent bone grafting.^{1,6,7} As a result of these disadvantages, there has been interest in bioabsorbable bone substitutes (BBS), which can be impregnated with antibiotics, are osteoconductive, and do not require a “two-stage” procedure for removal. One such material is medical-grade alpha-hemihydrate calcium sulfate, which has been well characterized clinically as a bone void filler.^{8–20} Advantages include its steady and gradual resorption, its osteoconductive nature, the lack of systemic side effects, and its consistent clinical results.^{8–10,14,17–20}

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From the Division of Orthopaedics, St Michael's Hospital and the University of Toronto, Toronto, Ontario, Canada.

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This study was presented in part at the Annual Meeting of the Orthopaedic Trauma Association, Boston, MA, 2007.

Reprints: Michael D. McKee, MD, FRCSC, 800-55 Queen Street East, Toronto, Ontario, Canada (e-mail: McKeeM@smh.toronto.on.ca).

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The incorporation of tobramycin into the calcium sulfate hemihydrate crystal structure produces an extremely high local concentration of antibiotics as the pellets are resorbed.^{8,15–17,19} Numerous animal and human studies support the efficacy of antibiotic-impregnated calcium sulfate. Sulo et al used gentamycin-impregnated calcium sulfate beads as a bone void filler in 409 patients with chronic osteomyelitis and reported approximately 95% of the patients had no recurrence of infection at a mean of 37 months post-operatively,²¹ and Gitelis and Brebach treated six osteomyelitic patients successfully with a similar compound.¹¹ A prospective, single-arm study reported eradication of infection in 23 of 25 patients (92%) treated with tobramycin-impregnated calcium sulfate pellets for infected bony defects.¹³ However, to our knowledge, there has been no direct comparative study between the standard of care for infected bony defects (PMMA) and the newer antibiotic-impregnated BBS. We hypothesized that a BBS compound would result in a lower repeat operative rate while maintaining a high level of infection eradication when compared with standard PMMA use in infected bony defects and nonunions.

The objective of this randomized, prospective study was to compare the effectiveness and safety of an antibiotic-impregnated BBS (alpha hemihydrate calcium sulfate) with standard antibiotic-impregnated PMMA cement beads when used to fill voids created by surgical débridement in patients with chronic osteomyelitis and/or infected nonunion.

PATIENTS AND METHODS

Inclusion/Exclusion Criteria

Between 2000 and 2003, 30 patients requiring surgical treatment for chronic osteomyelitis or infected nonunion were enrolled in a prospective, randomized trial at a tertiary care university-affiliated hospital. The study was reviewed and approved by the Research Ethics Board at St. Michael's Hospital. Adult patients (older than 16 years of age) who gave consent were entered into the study if they were diagnosed with osteomyelitis or infected nonunion characterized by clinical symptoms present for greater than 90 days, the presence of necrotic bone, and bacteria cultured from prior procedures, surgical biopsy, or draining sinuses. Standard diagnostic imaging modalities,²² including radiography, computed tomography, and bone/gallium scintigraphy, were used to establish the diagnosis. Definitive wound closure at the conclusion of the procedure was a prerequisite for inclusion in the study. Immunocompromised, mentally incompetent, or pregnant individuals were excluded as were children (younger than 16 years of age) and patients with uncontrolled diabetes; hypersensitivity to aminoglycosides; severe vascular, neurologic, or degenerative bone disease; hypercalcemia; myasthenia gravis; and those receiving neurotoxic and/or nephrotoxic drugs.

The antibiotic-impregnated BBS (Osteoset T; Wright Medical, Arlington, TN) is made from medical-grade calcium sulfate and is provided in 5-, 10-, and 20-cm³ vials. The pellets are biodegradable and radio-opaque. Each pellet weighs 0.1 g ± 0.02 g and is approximately 4.8 mm in diameter and 3.3 mm in height. Each BBS pellet contains 4% tobramycin sulfate,

which corresponds to 4.0 mg tobramycin sulfate (equivalent to 2.6 mg tobramycin per pellet). Approximately 10 pellets are required to fill each cubic centimeter of bone void. The pellets, in this prepared form, are currently not Food and Drug Administration-approved.

The patients receiving PMMA received implantation of tobramycin-impregnated PMMA cement beads. One package (40 g) of Simplex P cement (Stryker, Hamilton, Canada) was mixed with 2.4 g tobramycin and the mixture shaped into beads by hand. The beads were strung onto a surgical wire and once hardened applied to the defect.

Randomization

Patients were assigned to either the control or study group based on blocked randomization with respect to time; among every sequential set of eight patients meeting all inclusion and exclusion criteria, four were assigned to the study group and four were assigned to the control group. Random orders were generated from a computerized random number generator. Immediately before surgery, the investigator opened a sequentially numbered envelope in a series of numbered and sealed randomization envelopes and enrolled the patient into the study arm indicated on the slip of paper.

Patient Demographics

The PMMA group included 15 patients (11 male, four female) with a mean age of 45.6 years (range, 24–70 years). Three of the patients had a history of diabetes, seven were active smokers, one had osteoporosis, three had a history of substance abuse, and one was obese. The BBS group comprised of 15 patients (10 male, five female) whose mean age was 44.1 years (range, 16–86 years). Two of the patients had a history of diabetes, five were active smokers, three had a history of substance abuse, and four were obese (Table 1).

Classification

The PMMA group included 14 infections that were posttraumatic in origin, and patients had undergone a mean of 3.7 previous surgeries on the involved site (range, 1–8). In the BBS group, 14 of the 15 infections were posttraumatic in origin, and each patient had undergone previous surgery at the infection site (mean, 3.5 procedures; range, 1–15).

Patients' infections were classified according to the Cierny-Mader classification system.²³ The PMMA group included one patient with Stage I medullary osteomyelitis, four patients with Stage III localized osteomyelitis, and 10 patients with Stage IV diffuse osteomyelitis. There were eight systemically compromised (B) hosts and seven locally compromised (B) hosts. In the BBS group, five patients had Stage I medullary osteomyelitis, four had Stage III localized osteomyelitis, and six had Stage IV diffuse osteomyelitis. In terms of host physiological status, three were normal (A) hosts, seven were systemically compromised (B) hosts, and five were locally compromised (B) hosts.

Structural Defects

Involved bones in the PMMA group included the tibia (10 cases), femur (three cases), and humerus (two cases). There were eight cases of infected nonunion and seven cases of chronic osteomyelitis. Bone defect/void size ranged from 4.4 to 126 cm³

with a mean of 27.5 cm³ (measured and calculated immediately after débridement). In the BBS group, infected bones included the tibia (eight cases), femur (four cases), humerus (two cases), and ulna (one case). Eight patients were diagnosed with infected nonunion, and seven were diagnosed with chronic osteomyelitis. Mean bone defect/void size was 37.5 cm³ with a range of 3.1 to 120 cm³ (measured and calculated immediately after débridement). With the number of patients available, we were unable to detect a statistical difference in the bony defects between the two groups ($P = 0.77$).

Surgical Treatment

All procedures were performed by the lead author (MDM). The treatment of infection followed a standard surgical protocol with multiple sequential operative steps: removal of implanted hardware, débridement of granulation, scar and necrotic bone tissue (with tissue sent for definitive culture), copious irrigation, obliteration of dead space using either PMMA beads or BBS pellets, refixation or splinting, soft tissue closure or coverage, and postoperative systemic antibiotic therapy.¹³ The principles and sequence of surgical treatment for the PMMA and BBS groups were identical except for the material added to fill the bone defect or void (Figs. 1 and 2).

Both groups had skeletal stabilization performed as appropriate: six patients received internal fixation (five compression plates and one Kirschner wire fixation) and nine received external fixation (seven Ilizarov frames and two AO large external fixators). One patient was treated with a cast. Soft tissue coverage was achieved in all patients (including the use of three free flaps and one skin flap) and closure of the operative sites were accomplished using standard closure techniques. Drains were not used in any case.

Microbiology

In the PMMA group, eight of 15 patients had active draining sinuses. A single infecting organism was found in 10 cases: *Staphylococcus aureus* (three); *Staphylococcus epidermidis* (two); and one each of *Corynebacterium amycolstum*, *Streptococcus milleri*, anaerobic Gram-positive cocci, *Neisseria weaveri*, and *Streptococcus pyogenes*. The infections were polymicrobial in five cases and included *S. epidermidis* and diphtheroid bacilli (two) and one each of *Pseudomonas aeruginosa* and *Peptostreptococcus magnus*; *S. aureus*; and *S. epidermidis*; and *S. epidermidis* and *Enterococcus faecium*. Ten of 15 patients in the BBS group had active draining sinuses before surgery. Single infecting organisms were found in nine cases, including *S. epidermidis* (three); *S. aureus* (three); and one each of *Serratia marcescens*, *Staphylococcus lugdunensis*, and *Enterococcus casseliflavus*. Six patients had polymicrobial infections, including one each of *S. epidermidis* and diphtheroid bacilli; *S. aureus* and *Pseudomonas aeruginosa*; *Serratia marcescens*, and coliform bacilli; *Enterococcus faecalis* and *Citrobacter*; *S. aureus*, *S. epidermidis*, and *Enterococcus faecalis*; and *S. aureus*, *S. epidermidis*, and *Peptostreptococcus anaerobius*.

Antibiotic Therapy

Patients receiving antibiotic therapy before surgery had their antibiotics stopped 14 days preoperatively so as to allow definitive cultures to be obtained from bone and soft tissue taken at the time of surgical reconstruction. As opposed to the traditional six week course of intravenous antibiotics, our postoperative protocol called for a short course of intravenous antibiotics followed by appropriate oral therapy, consistent with more recent treatment regimens.^{13,24} In the PMMA group, intravenous antibiotics were administered for a mean of 11.9 days followed by oral antibiotics for a mean of 19.2 days. In the BBS group, intravenous antibiotics were administered for a mean of 11.6 days followed by oral antibiotics for a mean of 20.4 days. Postoperative antibiotic coverage was based on bacterial sensitivities from deep tissue cultures obtained at the time of surgery and included cefazolin (14 cases), clindamycin (14), cephalexin (13 cases), ciprofloxacin (12 cases), vancomycin (six cases), cloxacillin (five cases), sulfamethoxazole (two cases), linezolid (one case), amoxicillin (one case), and gatifloxacin (one case) (some patients received combinations of medications). After the initial antibiotic course, further antibiotic treatment was initiated on an individualized basis in the event of complication, reinfection, or additional surgical procedures.

Outcome Measures

The safety and effectiveness of BBS compared with PMMA was assessed using one primary and three secondary end points. Absence of active infection (primary end point), new bone growth into the void, healing of nonunion, and complications/repeat operations (secondary end points) were the defined outcome parameters.^{13,24} The rate of complications and adverse events in the BBS group, as compared with the PMMA group, was used to assess safety. Absence of active infection was defined as a clean, dry wound with no drainage or local erythema/swelling/pain, no systemic signs/symptoms of infection (fever, malaise), and no evidence of infection on blood tests (elevated erythrocyte sedimentation rate) or radiographs (evidence of progressive bone destruction) at 24 months postoperatively. Assessment of new bone growth into the void was based on the percentage of bone regrowth (measured on a categorical scale from 0% to 100% with 20% increments) as determined by the reading of radiographic films by an independent reviewer. Healing of nonunion was defined as bridging of three of four cortices on two orthogonal radiographs. Complications were recorded. Repeat operative interventions were performed at the discretion of the operating surgeon.

Follow-Up

Patients were followed for a minimum of 24 months postoperatively (range, 24–60 months; mean, 38 months). Clinical, radiologic, and serologic assessment was performed immediately postoperatively and at 2 weeks, 1 month, 2 months, 3 months, 6 months, 1 year, and 2 years. In the PMMA group, one patient was lost to follow-up at 2 weeks postoperatively, leaving 14 patients with complete follow-up. Within the BBS group, one patient died of causes unrelated to

the study at 6 months. This left 14 patients with complete follow-up in the study group.

Statistical Analysis

Statistical analysis was performed using the SPSS (Version 13) software package (SPSS Inc, Chicago, IL). Student *t* test was used for continuous variables such as age, sedimentation rate, percent bone regrowth, and so on. A chi square test was used for categorical variables between the two groups such as sex, absence or presence of infection, reoperations, and so on. A traditional Pearson chi square was used when statistical conditions were met. Fisher exact test was used in cases in which one or more of the expected variables was less than five. A value of $P < 0.05$ was considered to be statistically significant.

RESULTS

Polymethylmethacrylate Group

Infection

For those treated with standard antibiotic-impregnated PMMA cement beads, eradication of infection was achieved in 12 of 14 (86%) patients at 24 months postoperatively, according to the definition of the study. In this group, the mean erythrocyte sedimentation rate dropped from 38.9 mm/hr preoperatively to 19 mm/hr at 6 months postoperatively. Two patients had recurrence of their infection: one underwent amputation (*P. aeruginosa*) and the other was treated medically with chronic suppressive antibiotic therapy (*S. epidermidis*).

Union/Bone Formation

Bony union was eventually achieved in seven of eight cases, although refracture occurred in one case that healed with splinting. For the eight infected nonunion cases, radiographic union was achieved at 4 months (one case), 6 months (one case), 9 months (one case), 8 months (one case), 12 months (one case), 18 months (one case), and 24 months (two cases) to give a mean union time of 14 months. Void consolidation for the remaining six patients occurred at 3.5 months (one case), 6 months (one case), 8.5 months (one case), and 12 months (three cases) for a mean void consolidation time of 9 months. Overall, mean time to bony healing for both void and nonunion cases was 10.8 months.

Additional Surgical Procedures

Eight patients returned to the operating room for additional surgery for a total of 15 additional surgical procedures. Six patients underwent an operation to remove the implanted PMMA cement beads, and autogenous iliac crest grafting (one case with concomitant fixation) was performed on the same occasion (mean, 18 weeks postimplantation; range, 8–28 weeks). Cement beads were left in the operative site for the remaining eight patients, who experienced bone healing around the beads. Three surgeries were for revision of fixation, two for removal of hardware, and two for open reduction and internal fixation after refracture. There were two patients in

this group who required amputation as a result of recurrent infection (one) or refracture (open, one).

Bioabsorbable Bone Substitute Group

Infection

For those treated with BBS, eradication of infection was achieved in 86% of patients (12 of 14 participants with complete follow-up) as defined by the definition of this study at 24 months. The mean erythrocyte sedimentation rate dropped from 32.2 mm/hr preoperatively to 16 mm/hr at 6 months postoperatively. There were two persistent infections (one *S. epidermidis*, one *Serratia marcescens*).

Union/Bone Formation

All patients achieved bony union, although there was one case of refracture, which later healed. For the infected nonunion cases, radiographic union occurred at 2 months (one case), 3 months (one case), 6 months (three cases), 12 months (two cases), and 24 months (one case) to give a mean union time of 9 months. For patients with a bony defect, consolidation occurred at 3 months (two cases), 4 months (one case), 6 months (two cases), and 9 months (two cases) for a mean void consolidation time of 6 months.

Pellet Resorption

The BBS pellets were no longer radiographically visible after 4 weeks (one case), 6 weeks (four cases), 8 weeks (four cases), 10 weeks (two cases), and 12 weeks (three cases) to give a mean 100% pellet resorption time of 8 weeks.

Additional Surgical Procedures

Five patients experienced complications during the course of the study requiring seven additional operative procedures. One patient experienced a broken plate and refracture at 1 year postoperatively, which required repeat operative intervention twice. One patient experienced reinfection and refracture requiring repeat irrigation and débridement followed by revision of fixation. One patient had a wound infection that resolved after irrigation, débridement, and antibiotic treatment. One patient had a stiff knee (less than 90° of flexion), which required surgical release. Another patient had a tibial nerve neuropraxia which resolved after Ilizarov wire removal in the clinic. This patient developed nonunion and required repeat fixation. Three patients in the BBS group (all tibiae) developed sterile draining sinuses that resolved spontaneously without treatment, a phenomenon that has been previously described.^{9,12,13} One patient in whom infection recurred was treated with antibiotic suppression (*S. epidermidis*).

Although there was no difference in the number of patients requiring repeat operative intervention (PMMA, eight versus BBS, five; $P > 0.05$), the total number of repeat surgical procedures required in the PMMA group was more than the BBS group (PMMA, 15 versus BBS, seven; $P = 0.04$) (Fig. 3).

DISCUSSION

Successful surgical eradication of osteomyelitis requires radical débridement of affected tissues and is aided by the administration of local antibiotics in addition to systemic

therapy.^{2,4,8-12,14-21} Prior research shows that chronic osteomyelitis in most cases is caused by bacteria growing in biofilm communities,²⁵⁻²⁷ which cause the infecting organism to be resistant to systemic antibiotic levels up to 1000 times higher than normal therapeutic levels.²⁸ This helps to explain the persistent, recurrent nature of osteomyelitis and the difficulty in eradicating established infection in bone. Inducing high local antibiotic levels after thorough surgical débridement is thus a crucial component in the long-term resolution of chronic osteomyelitis or infected nonunion.^{13,26,28}

Although there is consensus regarding the surgical treatment of osteomyelitis (radical débridement of infected/necrotic tissue combined with local antibiotic delivery), the question of how to obliterate the dead space left by surgical débridement while concurrently inducing high local antibiotic levels is currently a topic of scrutiny. Although the use of antibiotic-impregnated PMMA cement beads followed by autogenous bone graft is still considered the gold standard, its disadvantages are well recognized.¹⁻⁸ Because PMMA is not biodegradable and represents a foreign body, the beads have the potential to serve as sites for recurrent infection if left in the void past the period of effective antibiotic elution.^{4,5} PMMA does not assist in bone regrowth, and in most cases, significant new bone growth cannot take place until the beads are removed and a bone graft inserted, delaying the healing process. Additionally, the antibiotics embedded within the cement beads may not be completely eluted, which leads to release of subtherapeutic levels of antibiotics over a sustained period of time.^{4,29} This may increase the risk of developing antibiotic-resistant organisms. PMMA itself has also been associated with decreased immune function,

impairing the body's ability to eradicate any remaining infection.³⁰ In addition to the problems associated with the cement beads themselves, there is the morbidity associated with autogenous iliac crest bone grafting, which is most commonly performed as the second stage of the standard treatment. This procedure results in additional pain, anesthesia time, and blood loss and is associated with risks, including instability, infection, and fatigue fractures of the donor site. It is clear that an osteoconductive, resorbable bone substitute that is as effective as PMMA in eradication of infection has many potential clinical advantages.¹³

Multiple prior studies have demonstrated that tobramycin-impregnated calcium sulfate hemihydrate has high clinical efficacy in infection eradication and plays a permissive role in the formation of new bone. However, none of these studies had a comparable control group of the standard therapy of antibiotic-impregnated PMMA beads followed by iliac crest bone graft insertion to promote bone void or nonunion healing. To the best of our knowledge, our study is the first prospective, randomized clinical trial to compare standard PMMA therapy with a BBS (tobramycin-impregnated calcium sulfate hemihydrate) in the treatment of bone infection. The results of our study support previous findings regarding the effectiveness and safety of antibiotic-impregnated calcium sulfate in the treatment of osteomyelitis. PMMA and BBS groups experienced comparable healing rates, and new bone growth corresponded with pellet resorption rates, indicating that the BBS plays an osteoconductive role in new bone growth. Blaha et al demonstrated that calcium sulfate hemihydrate is osteoconductive, supports infiltration of new blood vessels and osteogenic cells (osteoblasts were shown to attach to the

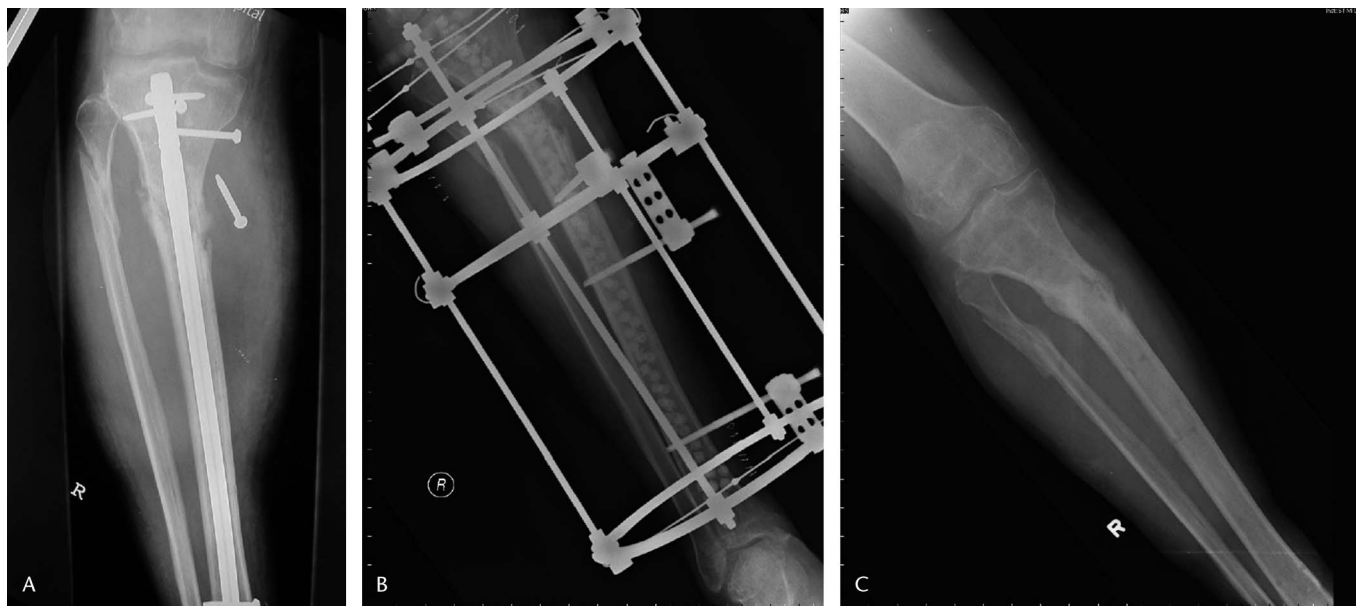


FIGURE 1. (A) Anteroposterior radiograph of infected an proximal tibial nonunion in a 47-year-old male physician with intramedullary sepsis, active drainage, loss of fixation, and significant varus deformity. (B) Anteroposterior radiograph after hardware removal, radical débridement, irrigation, insertion of antibiotic-impregnated calcium sulfate pellets, and the application of a ring external fixator. (C) Anteroposterior radiograph 1 year postoperatively after fixator removal demonstrating solid bony union and anatomic alignment. Clinically and radiographically, the patient was infection-free.



FIGURE 2. A–B, Anteroposterior and lateral radiographs of 54-year-old man with posttraumatic chronic osteomyelitis of the proximal tibia after hardware removal, radical débridement, irrigation, and insertion of tobramycin-impregnated polymethylmethacrylate beads. The nonunion was relatively stable clinically and no additional fixation was used. (C–D) Anteroposterior and lateral radiographs after bead removal, iliac crest bone grafting, and revision internal fixation. At 3 years postoperatively, solid bony union was evident and there was no evidence of recurrence of infection.

surface of the pellets), and prevents ingrowth of soft tissue.³¹ Others have shown that calcium sulfate is osteoconductive and acts as a scaffold for bone repair.^{14,18–20} In our study, the BBS group demonstrated similar eradication of infection to the PMMA group indicating comparable microbiocidal abilities with the clinical benefit of requiring fewer subsequent procedures.

Although any water-soluble antibiotic can be incorporated into the calcium sulfate hemihydrate crystal or PMMA, the ideal choice of antibiotic(s) remains controversial. Although current microbiologic resistance profiles may make combination therapy more attractive, we felt that it was necessary to choose a single consistent antibiotic to minimize variables and have as scientifically valid a study as possible. When beginning this study in 1999, we chose tobramycin as the antibiotic for a number of reasons. The common bacteria responsible for osteomyelitis are *Staphylococcus*, *Pseudomonas*, and *Escherichia* species with the *Staphylococcus* species

being the causative bacteria for 65% to 85% of osteomyelitic cases^{7,13,24,26,27,29}; tobramycin is generally effective against most of these species. Additionally, although certain organisms are not sensitive to tobramycin at levels obtainable with systemic therapy, the extremely high local concentrations released by the implant may nevertheless result in eradication of infection.^{7,32} However, we believe it is probable that tobramycin alone was not the optimal choice of antibiotic for some patients in our study, especially when one considers the treatment failures (two *S. epidermidis*, one *Serratia*, one *Pseudomonas*). There is abundant information on the elution characteristics of tobramycin from both PMMA and calcium sulfate. Turner et al conducted studies on the elution characteristics of tobramycin from calcium sulfate pellets.^{18,19} After implanting calcium sulfate pellets containing 10% tobramycin within medullary defects of canine humeri, they found that serum levels rose to 30.3 µg/mL within the first hour (but did not exceed toxic levels) and were undetectable

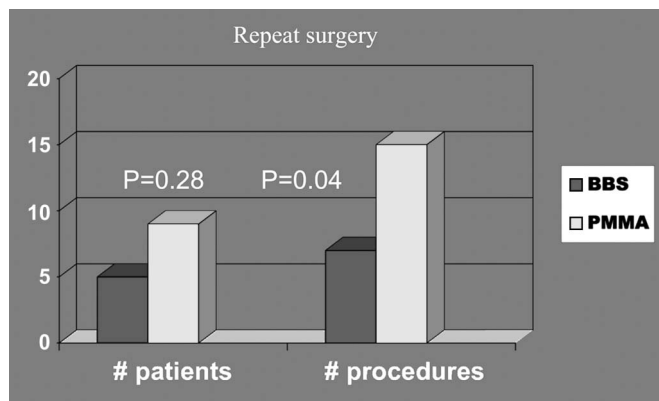


FIGURE 3. Repeat surgical procedures after the initial operative procedure. Although there was no difference in the number of patients who required reoperation, there were significantly more subsequent procedures required in the polymethylmethacrylate (PMMA) group. BBS, bioabsorbable bone substitute.

after 24 hours regardless of the number of pellets implanted. Therapeutic local concentrations of tobramycin were maintained for 14 days after an initial burst to a maximum of 1099 µg/mL (thousands of times greater than the minimal inhibitory concentration for most staphylococcal species) at 1 hour after which a steady decline occurred. Elution was 3.1 µg/mL at 7 days and 2.6 µg/mL at 14 days; these levels are still well above the minimal inhibitory concentration for *S. aureus*, the leading infecting organism in osteomyelitis. Previous studies reported similar findings and showed that therapeutic local levels of tobramycin were maintained for 22 to 28 days.^{15,16}

TABLE 1. Patient Demographics and Classification

Demographics	BBS Group (n = 15)	PMMA Group (n = 15)
Male	10	11
Female	5	4
Mean age (years)	44.1 (range, 16–86)	45.6 (range, 24–70)
Infection posttraumatic in origin	14	14
Mean number of previous surgeries to operative site	3.5 (range, 1–15)	3.7 (range, 1–8)
Location of void/defect		
Femur	4	3
Humerus	2	2
Tibia	8	10
Ulna	1	0
Cierny-Mader classification		
Stage 1—medullary osteomyelitis	5	1
Stage 2—superficial osteomyelitis	0	0
Stage 3—localized osteomyelitis	4	4
Stage 4—diffuse osteomyelitis	6	10
Diagnosis		
Infected nonunion	8	8
Chronic osteomyelitis	7	7

BBS, bioabsorbable bone substitute; PMMA, polymethylmethacrylate.

Our study is subject to significant limitations, especially the small sample size (30 patients). First, this small sample size resulted in a lack of statistical significance in the differences observed between the study and control groups for most outcomes. This could result in a potential beta error: an inability to statistically show a true difference as a result of a small sample size. Similarly, although not statistically different, there were more patients with systemic conditions (smoking, diabetes) in the PMMA group than the BBS group (10 of 15 versus seven of 15), which could influence results. Also, it is difficult to base clinical recommendations on so few patients, and our study should be considered a preliminary one that suggests that antibiotic-impregnated bone substitutes seem safe and relatively effective clinically. We are not implying that our results represent a definitive clinical reference or induce a change in practice, but rather that it is a pilot study on which a larger, comprehensive trial can be based.

Another limitation is the length of the follow-up period; osteomyelitis is notorious for its recurrent nature and infections are known to resurface many years after a perceived cure.^{1,2,7,13,30} Our minimum follow-up of 2 years (mean follow-up, 34 months) may therefore be an insufficient period of time to conclude that absolute eradication of infection has occurred. Also, although we used objective criteria for our primary end point (eradication of infection), one of our secondary end points (repeat surgical intervention) was based on surgeon decision-making and thus subject to potential bias.

Our preliminary work adds to the building evidence that antibiotic-impregnated calcium sulfate pellets are an effective and safe alternative to standard antibiotic-impregnated PMMA beads in the treatment of chronic osteomyelitis and infected nonunion. In addition to demonstrating an equivalent rate of infection eradication, they decrease the rate of secondary surgical procedures and may help to eliminate the morbidity associated with the additional surgery required for cement bead removal and bone grafting in the standard two-stage procedure. The treatment of this condition remains a clinical challenge; further work is required to confirm our findings and elucidate the ideal antibiotic or antibiotic combination in the face of changing microbiologic sensitivity profiles.

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