

Tobramycin-impregnated Calcium Sulfate Prevents Infection in Contaminated Wounds

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Open fractures often are associated with increased rates of infection and nonunion, multiple surgical procedures, and delayed return to preinjury activity. Antimicrobial bone graft substitutes used as an alternative to antibiotic cement beads and/or delayed autologous bone grafting may provide a useful adjunct in patients with open fractures. A stable, unicortical defect was created and contaminated with 30 μ L of 5×10^6 colony-forming units/mL of *Staphylococcus aureus* in the proximal tibial metaphysis of Spanish goats. The negative control group received no treatment, the carrier group received synthetic bone graft alone, the positive control group received tobramycin antibiotic cement, and the treatment group received tobramycin antimicrobial synthetic bone graft (calcium sulfate). After a 3-week evaluation period, intraosseous microbiologic specimens were obtained. The *Staphylococcus aureus* contaminant was recovered in 11 of 12 animals (mean = 6.9×10^7 colony-forming units/g marrow) in the negative control group and in all animals (mean = 2.2×10^8 colony-forming units/g marrow) in the carrier group. Bacteria were not found in the antibiotic-treated groups. The tobramycin-impregnated calcium sulfate was effective in preventing infection in a contaminated defect. It could be beneficial in reducing the number of surgeries and recovery time because it is bioabsorbable and osteoconductive.

An open fracture, frequently the result of high-energy impact, involves a soft tissue injury that allows communication of the fracture site with the environment.^{1,16,18,22} Treating the associated bacterial contaminations, which are associated with increased patient morbidity, present an enormous surgical challenge. Despite thorough treatment, patients with open fractures have high rates of delayed union and nonunion, and complications such as the development of chronic osteomyelitis can threaten the viability of the limb and the life of the patient.^{14,22} In addition, open fractures often involve significant bone loss resulting from the fracture comminution or from the surgeon's efforts to remove grossly contaminated and devitalized tissue.^{13,22} These bone defects typically require bone graft treatment to augment fracture healing. Because of contamination and a high risk of infection, the bone graft cannot be placed immediately in the wound. Local antibiotics, typically reserved for treatment of established infections and infected nonunions, have been used in severely contaminated wounds.^{2,3,5,11,15,20}

The standard for local antibiotic delivery is antibiotic-impregnated cement. Despite clinical studies showing the efficacy of this local antibiotic delivery technique, there are several disadvantages.^{2,3} First, polymethylmethacrylate (PMMA) is not biologic, necessitating a second surgical procedure for removal. Second, because the beads have no osteoinductive or osteoconductive potential, definitive bone grafting and mature fracture healing cannot begin until the beads are removed. This delays the patient's recovery. Third, autologous bone graft harvest may result in morbidity including increased blood loss, prolonged operative time, persistent postoperative pain, and difficulty with ambulation.²³ A safe and effective alternative to autologous bone grafting would alleviate many of these problems.

Using an antiinfective bone graft that promotes healing early during the course of treatment could increase the fracture healing rate, avoid the need for additional surgical procedures, and decrease medical costs. A calcium sulfate

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Each author certifies that his or her institution has approved the animal protocol for this investigation and that all investigations were conducted in conformity with ethical principles of research.

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product impregnated with tobramycin may help because it can be produced in large quantities, is osteoconductive, and contains the broad spectrum antibiotic tobramycin.¹⁵ This product, and other biodegradable antibiotic delivery systems, have been used in Europe for many years with excellent clinical results.^{4,17} However, these biodegradable products have not been approved for clinical use in the United States.^{3,15}

Given the available clinical results, we presumed tobramycin-impregnated calcium sulfate would prevent intramedullary infection in a caprine-contaminated bone defect model, providing additional support under controlled conditions.

MATERIALS AND METHODS

Forty-eight castrated male Spanish goats weighing approximately 39.3 ± 1.6 kg were studied. All animals were housed in runs in a climate-controlled facility and were fed commercial food and water ad libitum. All animals were examined by a veterinarian and quarantined for 10 days before the study to allow for acclimation and to screen for preexisting disease.

Preoperatively, the animals had no food for 48 hours and water was withheld for 12 hours. The animals were sedated with ketamine hydrochloride (2.2–7.0 mg/kg IM) and midazolam (0.125–0.250 mg/kg IM), an endotracheal tube was inserted, and general anesthesia was induced with a mixture of isoflurane and oxygen. Oxygen saturation, heart rate, ventilation rate, end tidal CO₂, and agent concentration were monitored. All animals received epidural analgesia using morphine sulfate preoperatively for pain control.

After adequate regional and general anesthesia, the operative lower extremity (as determined by randomization to the right or left side) was prepared with Hibiclens® (Zeneca Pharmaceuticals, Wilmington, DE) and draped in a sterile fashion. First, a 2.5-cm longitudinal incision was made over the proximal medial metaphyseal region of the tibia centered approximately 2 cm medial and 2 cm distal to the tibial tubercle. After elevating the periosteum with a periosteal elevator, a unicortical, 12-mm circular defect was produced with a coring reamer. Thrombin-soaked gel foam (Gentrac, Inc., Middleton, IN) assisted in medullary hemostasis. Next, a sterile pipette containing an aliquot of bacteria [30 µL of 5×10^6 colony-forming units (CFU)/mL *Staphylococcus aureus* (*S. aureus*)] was used to inoculate the bony defect. The bacterial strain used, American Type Culture Collection (ATCC) 29213, is a strain of a fixed and known virulence. We modified it to be resistant to streptomycin (*S. aureus*-R). Briefly, aliquots of *S. aureus* were plated on streptomycin plates. The isolates with the highest concentration were recovered and grown overnight in brain-heart infusion broth. This process was repeated two more times. After the third pass, the mutant was streaked on plates containing various concentrations of streptomycin (50–1000 µL/mL) to ensure resistance.

After inoculation, the defects were treated with one of four designated treatments. The inoculation and treatment were done in the same setting. Intravenous antibiotics were not adminis-

tered to the goats, and the wounds were not debrided or irrigated. The treatment groups were randomized and assignments to left and right legs were balanced, resulting in four groups of 12 animals each. The first group (negative control group) received no treatment. The second group (positive control group) was treated with PMMA and tobramycin beads. These beads were made in standard clinical fashion by combining one packet (40 g) Palacos® (Smith & Nephew Richards Orthopaedics, Memphis, TN) and 20 mL monomer cement with 2.4 g Nebcin® tobramycin sulfate powder (Eli Lilly & Co., Indianapolis, IN). Fifteen beads (4% tobramycin sulfate by weight) were placed into the bone defect in each goat, totaling 79.3 ± 4 mg tobramycin sulfate per goat. In the third group (carrier group), 15 pellets of the calcium sulfate product OSTEOSET® (Wright Medical Co., Arlington, TN) were used. The last group (treatment group) received 15 pellets of the tobramycin-impregnated OSTEOSET T® (Wright Medical Co.). These pellets were 10% tobramycin by weight. The mean tobramycin sulfate dose was 160 mg per goat. After receiving the designated treatment, the skin was reapproximated with surgical staples, and a dry, sterile dressing was applied. Neither intravenous nor intramuscular antibiotics were given to the goats before or during the study.

Immediate postoperative radiographs of the extremities were obtained to check for possible intraoperative fracture and to document baseline characteristics of the bone graft or antibiotic beads in the bony defect. Radiographs also were taken at the completion of the study and examined for signs of infection such as new periosteal bone growth that produces involucrum.

The animals were followed up for 21 days for clinical signs of wound contamination. The operatively placed sterile dressing remained intact until postoperative Day 4 when the dressing and surgical staples were removed. Wound cultures were taken using a sterile swab placed into the bony defect for standard qualitative microbiologic analysis. All *S. aureus* isolates were tested for streptomycin resistance to determine if the cultured strain was identical to the original inoculated bacteria. At postoperative Day 21, all animals were sedated with xylazine hydrochloride (10 mg/kg IM), euthanized with pentobarbital (90 mg/kg IV), and necropsies were done.

Clinical signs of wound infection included erythema, inflammation, warmth, and purulent drainage. After the dressing was removed on postoperative Day 4, each wound was scored daily by three independent examiners who were blinded from the treatment type. A clinical grading system, which was established in a previous study done in our laboratory, was used.⁸ The condition of the wound was graded by the following criteria: 0 = showing no signs of infection; 1 = showing inflammation, swelling, or serous drainage without frank purulence; and 2 = showing frank purulence at the wound site. A score for each wound was calculated by adding the score from each of the three observers each day for 21 days. A clinical determination of infection was defined by a score of 5 on two consecutive days for a given wound. By this definition, an infected wound had two consecutive days of purulent drainage as identified by two of the three examiners.

After animals were euthanized, the hindlimb was disarticulated at the stifle (knee). After taking a radiograph of the treated

hindlimb, a final culture of the superficial wound was done using a sterile swabbing technique. Next, using a sterile technique, the soft tissue was removed from the tibia, and the bony defect was transected at its midportion with a Gigli saw. Ex vivo, the bone was protected from contamination by cleaning the surface of the outer cortex with alcohol-soaked gauze before cutting it with a sterile saw. After obtaining another culture swab from the proximal and distal intramedullary canals, a Number 5 surgical curette (approximately 0.5 g tissue) was used to harvest marrow and trabecular tissue from the canal for standard quantitative and qualitative microbiologic analysis.

The primary outcome measure for deep wound infection was the recovery of the streptomycin resistant *S. aureus* isolate from deep tissue cultures at postoperative Day 21. The threshold for infection was set at 10^4 CFU/g marrow of *S. aureus*-R.⁸ Wounds with *S. aureus*-R strain ATCC #29213 but with less than 10^4 CFU/g marrow were considered contaminated or colonized.

Clinical assessment of the presence of infection and bacterial presence from superficial swabs were analyzed using Fisher's exact test. Nonparametric median tests were used to test the final culture results because of lack of variance in the groups. When global differences were detected, a step-down Bonferroni adjustment was used for error correction to determine the significance of subsequent comparisons. A *p* value less than 0.05 was considered significant. Data are expressed as mean \pm standard error.

RESULTS

There were no signs of systemic infections in any of the goats. One goat in the positive control group fractured its tibia through the bone defect on postoperative Day 4 and was euthanized.

The tobramycin-impregnated calcium sulfate pellets prevented intramedullary infection in the contaminated bone defect. No *S. aureus*-R was recovered in any of the bony defects of the goats in the positive control group and treatment group (Table 1). *Staphylococcus aureus*-R was found in the deep wounds in 11 of the 12 goats in the negative control group ($6.9 \times 10^7 \pm 4 \times 10^7$ CFU/g) and in all 12 wounds in the carrier group ($2.2 \times 10^8 \pm 1.1 \times 10^7$ CFU/g). There was less ($p < 0.002$) bacteria recovered from the intramedullary cavity in the tobramycin-treated compared with the untreated groups. However, there was no difference in bacterial presence from superficial swabs (taken on postoperative Days 4, 7, 14, and on the first day of purulent drainage) between groups.

Clinical observation indicated that the carrier group had a greater ($p < 0.02$) infection rate (11 of 12) than the positive control (three of 11) and treatment (two of 12) groups. Six of the 12 wounds from the negative control group were determined to be clinically infected.

Qualitative analysis of the gross pathologic specimens and radiographs of the wounds confirmed a difference in the presence of infection between the tobramycin-treated and untreated groups. There was purulent replacement of marrow and trabecular bone in the negative control (11 of

12) and carrier groups (12 of 12) in all animals that had bacteria present in the intramedullary canal, whereas the positive control and treatment groups had normal marrow and trabecular bone. The radiographic evaluation of the negative control and carrier groups (Fig 1A) suggested infection with the evidence of periosteal new bone formation that produced involucra in all of the infected bony defects. The bony defects in the positive control and treatment groups (Fig 1B) appeared normal.

DISCUSSION

Despite continuing innovation in orthopaedic implants and antibiotic therapy, infection remains the most serious potential complication in the treatment of open fractures. Although antibiotic therapy, external fixation, and early flap coverage of soft tissue defects have helped to reduce the rate of infection, wound irrigation and débridement are the most important aspects of open fracture care.^{13,16,18,22} Achieving a clean wound is imperative, and removal of all gross debris, devitalized tissue, and bone often requires repeat débridements over several days or weeks. By the time the fracture bed is clean and ready for definitive treatment, there are often segments of bone loss, which makes complete fracture fragment apposition difficult. Disruption of the extramedullary blood supply from extensive periosteal stripping can contribute to a delay in fracture healing.^{1,6,18,21,22} Although many surgeons choose to use bone grafts at fracture sites to alleviate these problems and augment healing, this cannot be done until several weeks to months after the injury because of inherent wound contamination. We focused on reducing the delay in definitive open fracture management.

Autologous bone grafts at open fracture sites have been shown to increase the quality and rate of fracture union.^{20,22} Some surgeons have suggested the use of allograft bone because of the morbidity associated with harvesting autologous bone. In studies using allograft bone fracture, authors have reported union rates approaching those associated with autograft bone.^{6,7,9} Allografts, demineralized bone matrix, and synthetic bone graft products are osteoconductive and often contain a mineral component such as hydroxyapatite or calcium sulfate that provides a scaffold for adhesion of newly healing bone. In addition, some of these compounds contain osteoinductive proteins that have been shown to enhance fracture healing.^{7,9,10} A major advantage of these synthetic bone graft products is their availability.

Despite the potential benefits of using allograft bone, the risk of bacterial contamination in an open fracture bed is still a concern. Autologous bone grafting too early during open fracture treatment can result in infection and excessive graft resorption. Allograft bone likely would have similar risks for the development of chronic osteo-

TABLE 1. Wound Evaluation

Animal Number	Animal Group	Wound Infection	Surface Swab Organism	Bone Organism (week 3)	CFU/g Tissue (week 3)
1	Negative Control	Negative	<i>S. viridans</i>	<i>S. aureus</i> -R	4.1×10^8
2	Negative Control	Positive	<i>S. aureus</i> -R	<i>S. aureus</i> -R	7.5×10^6
3	Negative Control	Positive	<i>S. aureus</i> -R	<i>S. aureus</i> -R	2.4×10^7
4	Negative Control	Positive	No growth	<i>S. aureus</i> -R	1.2×10^5
5	Negative Control	Positive	<i>S. aureus</i> -R	<i>S. aureus</i> -R	3.2×10^8
6	Negative Control	Negative	No growth	<i>S. aureus</i> -R	1.6×10^7
7	Negative Control	Positive	<i>S. aureus</i> -R	<i>S. aureus</i> -R	1.1×10^7
8	Negative Control	Negative	<i>S. aureus</i> -R	<i>S. aureus</i> -R	1.9×10^7
9	Negative Control	Negative	<i>P. aeruginosa</i>	<i>S. aureus</i> -R	3.4×10^6
10	Negative Control	Negative	<i>S. aureus</i> -S and <i>P. aeruginosa</i>	No growth	0
11	Negative Control	Positive	No growth	<i>S. aureus</i> -R	1.2×10^7
12	Negative Control	Negative	<i>S. aureus</i> -R	<i>S. aureus</i> -R	7.2×10^6
13	Carrier	Positive	<i>S. aureus</i> -S	<i>S. aureus</i> -R	2.2×10^7
14	Carrier	Positive	<i>S. viridans</i>	<i>S. aureus</i> -R	3.2×10^7
15	Carrier	Negative	<i>S. aureus</i> -R	<i>S. aureus</i> -R	1.4×10^9
16	Carrier	Positive	<i>S. aureus</i> -R	<i>S. aureus</i> -R	3.6×10^8
17	Carrier	Positive	<i>S. aureus</i> -R	<i>S. aureus</i> -R	1.6×10^8
18	Carrier	Positive	<i>S. aureus</i> -R	<i>S. aureus</i> -R	1.6×10^8
19	Carrier	Positive	<i>S. aureus</i> -R	<i>S. aureus</i> -R	2.5×10^8
20	Carrier	Positive	<i>S. aureus</i> -R	<i>S. aureus</i> -R	6.4×10^7
21	Carrier	Positive	<i>S. aureus</i> -R	<i>S. aureus</i> -R	5.9×10^7
22	Carrier	Positive	<i>S. aureus</i> -R	<i>S. aureus</i> -R	4.0×10^6
23	Carrier	Positive	<i>S. aureus</i> -R	<i>S. aureus</i> -R	1.4×10^8
24	Carrier	Positive	<i>S. aureus</i> -R	<i>S. aureus</i> -R	1.6×10^7
25	Positive Control	Positive	β Strep not Group A	No growth	0
26	Positive Control	Positive	β Strep Group A	No growth	0
27	Positive Control	Negative	<i>S. aureus</i> -S	No growth	0
28	Positive Control	Negative	CNS	No growth	0
29	Positive Control	Negative	<i>S. viridans</i>	No growth	0
30	Positive Control	Euthanized	Euthanized postoperative Day 4	Fractured tibia	Euthanized postoperative Day 4
31	Positive Control	Negative	<i>S. aureus</i> -R	No growth	0
32	Positive Control	Negative	<i>S. viridans</i>	No growth	0
33	Positive Control	Negative	No growth	No growth	0
34	Positive Control	Negative	No growth	No growth	0
35	Positive Control	Positive	<i>S. viridans</i>	No growth	0
36	Positive Control	Negative	No growth	No growth	0
37	Treatment	Negative	<i>S. aureus</i> -S	No growth	0
38	Treatment	Positive	<i>S. viridans</i>	No growth	0
39	Treatment	Positive	<i>S. viridans</i>	No growth	0
40	Treatment	Negative	<i>S. aureus</i> -S	No growth	0
41	Treatment	Negative	<i>S. aureus</i> -S	No growth	0
42	Treatment	Negative	CNS	No growth	0
43	Treatment	Negative	CNS	No growth	0
44	Treatment	Negative	<i>S. aureus</i> -R	No growth	0
45	Treatment	Negative	<i>S. aureus</i> -S	No growth	0
46	Treatment	Negative	No growth	No growth	0
47	Treatment	Negative	CNS	No growth	0
48	Treatment	Negative	No growth	No growth	0

S. viridans = *Streptococcus viridans*; *S. aureus*-R = *Staphylococcus aureus*-streptomycin resistant; *S. aureus*-S = *Staphylococcus aureus*-streptomycin sensitive; *P. aeruginosa* = *Pseudomonas aeruginosa*; β Strep not Group A = Beta-hemolytic *Streptococcus*, not Group A; β Strep Group A = Beta-hemolytic *Streptococcus*, Group A; CNS = Coagulase negative *Staphylococcus*; CFU = Colony-forming unit

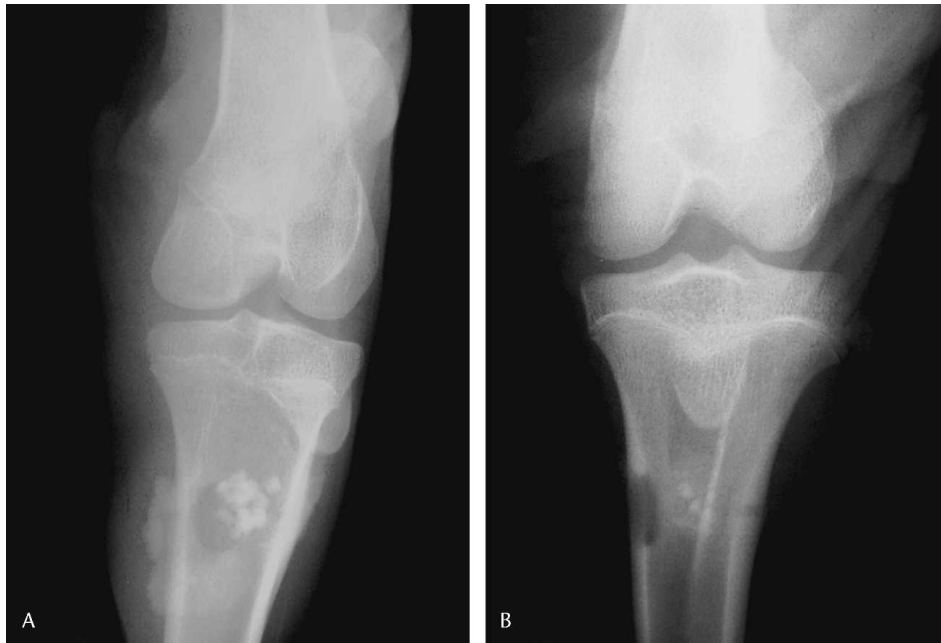


Fig 1A–B. (A) The radiographic evaluation of the carrier group bone defect site on postoperative Day 21 is shown. The new periosteal bone formation (involucrum) adjacent to inoculated bony defect suggests early osteomyelitis in the carrier group. (B) Radiographic evaluation of the treatment group shows a bone defect with a normal appearance, suggesting no infection, on postoperative Day 21.

myelitis with foreign body sequestra. To reduce these potential complications, an ideal allograft for open fractures would include an antimicrobial agent. This would allow the allograft bone to prevent or treat deep wound infection while facilitating the fracture healing response. In addition, this compound could be used soon after the fracture wound is debrided, potentially obviating the need for delayed autologous bone grafting.

When analyzing the results from the control group, the modified organism was found to reproducibly cause deep wound infection. The majority of the animals' wounds (11 of 12 wounds) had clinical and microbiologic evidence of infection by the end of the 3-week evaluation. Without any antiinfective material present, the untreated organism was allowed to proliferate and replace the marrow with bacteria and acute inflammatory cells.

The positive control group was included in this study because it represents the current clinical standard of care for local antibiotic delivery. Most often used for chronic fracture nonunions, authors from several trauma centers have reported antibiotic cement application in the early treatment of grossly contaminated wounds.^{2,3,20} The antimicrobial beads were able to completely eradicate the contaminant organisms in all 11 animals (100%). Although three animals had early clinical evidence of superficial infection, *S. aureus* strain ATCC #29213 was not found in any of the final deep tissue cultures.

The carrier group was included to evaluate the treatment's ability to reduce open wound contamination in a more controlled environment. This calcium sulfate product is not known to have any inherent antimicrobial properties, and it was expected that the results of this group would be similar to those of the untreated control. All of the goats had clinical and microbiologic evidence of wound contamination. Just as in the control group, radiographs showed evidence of early osteomyelitis with involucrum formation.

As with the other tobramycin-treated group, infections in all 12 wounds were effectively prevented in the treatment group. Final pathologic analysis showed normal trabecular architecture in the area of inoculation without marrow replacement by acute inflammatory cells. The radiographs support these results with no early evidence of osteomyelitis in any of the 12 animals.

There are a few limitations in this study. This caprine model was not designed to exactly mimic an open fracture. Animal care and housing issues limit the use of hardware to achieve rigid fixation, and the creation of similar extensive soft tissue injuries seen in some open fractures create confounding variables. Our daily open wound care differed from that considered common clinical practice. However, the conditions are controlled without confounding variables, and we think the model is appropriate for testing the effectiveness of antimicrobial bone graft sub-

stitutes in preventing infection in a contaminated bone defect. This study used a strain of *S. aureus* that was not methicillin resistant. It is thought that methicillin-resistant *S. aureus* is more resistant to tobramycin than *S. aureus* is susceptible to methicillin.¹⁹ Therefore, there is a distinct probability that any treatment that uses tobramycin will be effective against *S. aureus*. However, the use of PMMA cement with aminoglycosides continues to be used effectively in preventing infection in open fractures.

We were able to show the efficacy of a calcium sulfate bone graft substitute combined with tobramycin to prevent intramedullary infection in wounds that clearly were contaminated. This was confirmed by four independent measurements. As more bone graft products with osteoinductive and antimicrobial properties become available, additional research will be needed for clinical application. Other future work will include use of different or multiple bacterial strains and delayed treatment. Local administration of aminoglycoside antibiotics has been used in orthopaedics to treat and prevent infections. Most often used in combination with cement, the detrimental side effects with systemic aminoglycoside use do not seem to apply when administered locally.^{2,5,11,12} If bone graft products enhance fracture healing and reduce infection and the number of procedures required, they may soon replace antimicrobial cement in various orthopaedic procedures.

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