Use of Sterile Pre-Fabricated Antibiotic Beads in the Combat Hospital Setting

Lt Col Wade T. Gordon, USAF MC*; OCC Michael G. Petrides, USN*;
Capt Philip A. Gunn, USAF†; Maj Michael Howard, USAF MC‡

ABSTRACT   Time and manpower constraints associated with acute combat casualty care can make antibiotic bead production at the point of care prohibitively difficult, if not impossible. The purpose of this study is to evaluate our technique for the sterile prefabrication of antibiotic-impregnated polymethylmethacrylate (PMMA) beads in the combat hospital environment by assessing their sterility at the time of use. This investigation is a prospective study of a consecutive series of specimens. Imipenem-impregnated antibiotic beads were sterilely prepared, threaded on a suture strand, and packaged. Over a 6-week period, 50 consecutive packages were evaluated for sterility with aerobic and anaerobic culture swabs performed at the time of opening. Culture results, as well as number of shelf days for each specimen, were then reviewed. Of the 50 packages of antibiotic-impregnated PMMA beads, the average number of days on the shelf before use was 9.3 (range: 2–17). None of the packages showed growth of organisms from the cultures, indicating that antibiotic-impregnated PMMA beads can be sterilely produced and maintained in their sterile state for future use in the combat hospital environment. This practice should be considered a safe adjunct in the management of contaminated, open traumatic injuries in this setting.

INTRODUCTION

Combat extremity injuries routinely present with large open wounds, and are often associated with extensive foreign contamination. These wounds also evolve over time and produce a large and progressive zone of injury. As a result, serial debridements are required to obtain a soft tissue envelope amenable to definitive fixation and wound closure. In addition, wound management adjuncts, such as antibiotic beads and negative pressure wound therapy (NPWT), are often used to help decrease the risk of deep wound infection. The primary indications for the use of antibiotic beads in the management of combat extremity injuries are (1) the management of dead space associated with cavitary defects, (2) local antibiotic delivery in the setting of known infection to assist with eradication of infection, and (3) local antibiotic delivery for infection prophylaxis in the setting of at-risk, complex, and contaminated traumatic wounds.

Infection rates in the treatment of combat casualty wounds have been reported between 35 and 89%.[1–3] With such a high risk of infection, a multimodal approach to controlling bacterial contamination is used from the outset of care. Early and frequent surgical debridement with high volume irrigation is often augmented with the use of antibiotic beads with or without NPWT. Antibiotic beads, in particular, have the advantage of delivering a high concentration of antibiotics at the local level while systemic levels remain low.[4] Their use is well documented in the management of combat extremity

injuries,[5–7] and in open fractures, antibiotic beads have been shown to decrease rates of infection when combined with contemporary debridement principles.[8–13]

In a combat setting, surgical resources can become strained. Multiple casualties often present simultaneously, and require fracture stabilization and debridement of wounds. Given the inherently time-consuming process of generating polymethylmethacrylate (PMMA) antibiotic beads, time and manpower limitations often make their use untenable. Gentamicin- and tobramycin-impregnated antibiotic beads are commercially available; however, cost, limited antibiotic choices, and supply issues render them inappropriate for use in the combat hospital environment.[14] Therefore, most patients initially receive systemic antibiotics and surgical debridement with irrigation alone. Use of local antibiotic delivery modalities is usually not initiated until the patient arrives at a higher echelon of care. This delay can be days to weeks later, thereby transitioning therapy from one of contamination eradication to early infection treatment.

One potential solution to this problem is the sterile prefabrication of antibiotic-impregnated PMMA beads during periods of lower tempo clinical operations, which can then be maintained on the shelf until needed. The purpose of our study was to describe an "all-sterile" technique to prefabricate and sterilely package PMMA antibiotic beads, as well as to validate this technique by confirming their sterility at the time of implantation. This is in contrast to previously described methods involving the production, and subsequent gas sterilization, of bead packages.[9–11] Our hypothesis is that these bead strands remain sterile over the relatively short time interval expected before use in the combat hospital setting.

MATERIALS AND METHODS

Over a 6-week period between December 2010 and January 2011, 50 sterile packages of PMMA antibiotic beads were

*Walter Reed National Military Medical Center, 8901 Rockville Pike, Bethesda, MD 20889.
†Seymour-Johnson Air Force Base, 505 Cashwell Place, Goldsboro, NC 27534.
‡David Grant Medical Center, 101 Bodin Circle, Travis Air Force Base, CA 94535.

produced and implanted in combat-related open wounds. All wounds were additionally treated with NPWT. Aerobic and anaerobic culture swabs were obtained from each set of beads at the time of opening the sterile package. The beads themselves, as well as their suture string, were cultured. Cultures were then incubated for 3 days and were considered negative if there was no bacterial growth after 72 hours of incubation. Documented outcome measures were the culture results, the number of shelf days before implantation, and number of patients, as well as the type of wounds treated.

Statistical analysis was performed by χ^2 test, using available historical controls for accepted contamination rates for surgical instrument trays.

Bead Preparation Technique

For each strand of beads, one 40-g package of Palacos PMMA cement (Zimmer; Warsaw, Indiana) was mixed with 1 g imipenem antibiotic powder. Imipenem was chosen on the recommendation of the infectious disease specialist at our institution based on the local antibiogram and the preponderance of *Escherichia coli* isolates in our facility as the dominant pathogen encountered. The cement was hand-mixed under sterile conditions in the operating room during periods of low casualty flow. The beads were prepared by individuals who had scrubbed their hands per standard technique, and who were masked, gowned, and gloved as is standard for the performance of sterile procedures. A sterile table was prepared, and the beads were produced using the same technique as is used when made intraoperatively. Approximately 1-cm-diameter beads were produced and strung onto a Number 1 Ethicon Prolene suture (Johnson & Johnson; New Brunswick, New Jersey). Approximately 15 to 20 bead packages were prepared at a time, as determined by the available supply of PMMA cement and antibiotic powder. The operating staff and surgeons involved in bead production were all familiar with producing antibiotic beads. The beads were then sealed into sterilized pouches. Each package was then marked with the date of production and an arbitrary expiration date 30 days after production (Fig. 1).

RESULTS

The beads were implanted in 42 extremities in 23 patients with open wounds, all resultant from blast injuries. Some patients returned to the operating room for debridement and irrigation procedures on multiple occasions when antibiotic beads were implanted. Thirty-one of the wounds were residual limbs of combat-related traumatic amputations. The remainder of the wounds included six open fractures and five open wounds involving volumetric soft tissue loss without fracture.

Cultures were taken at the time of implantation of all bead strands. The average time between preparation and implantation of bead packages was 9.3 days (range: 2–17 days). None of the cultures taken from any of the 50 specimens showed any growth from the aerobic or anaerobic cultures.

Based on the lowest reported value in prior investigations of the rate of contamination of surgical trays, a 4% positive culture rate was used as a historical acceptable value for the purpose of statistical analysis. The zero percent rate of positive cultures from our specimens could represent a random finding. Using the χ^2 test, however, we can be 87% confident that the culture-positive rate in this study is less than or equal to this historical control ($p < 0.15$). This finding is not statistically significant (Fig. 2).

DISCUSSION

The use of antibiotic-impregnated PMMA beads in the management of open fractures and in combat extremity injury is well documented.[5–13] They have been shown to effectively decrease the rate of osteomyelitis in open fracture management, and to be an effective adjunct in the treatment of chronic osteomyelitis. They have also been shown to be a cost-effective adjunct in the management of open fractures, with an average cost of $419.[12] Antibiotic beads have also proven to be helpful in the management of extremity blast injuries,[5,6] and have been used both in conjunction with NPWT and in bead pouches. In applying these two techniques, the method by which antibiotic beads are prepared

FIGURE 1. Sterilely prefabricated package of antibiotic-impregnated PMMA beads.
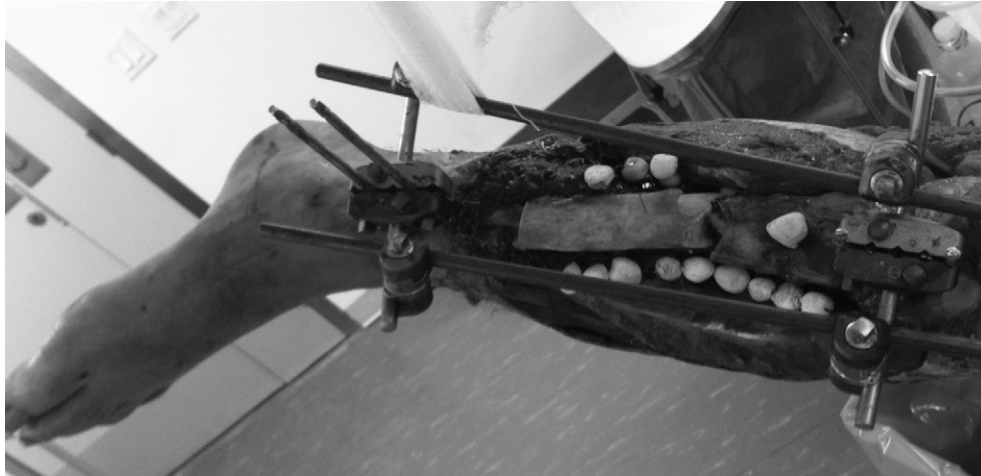
FIGURE 2. Antibiotic beads after implantation in a combat-related open tibia fracture.

and implanted is identical. When creating an antibiotic bead pouch, the wound is then sealed in an impervious dressing, which contains the wound effluent, and the wound remains bathed in a high concentration of antibiotics. When an NPWT is used, this effluent is drawn from the wound, along with much of the eluted antibiotic.

Although there are other compelling reasons for the use of NPWT in open wounds associated with combat-related blast injury, there is evidence that the use of a bead pouch may result in decreased infection rates when compared to the use of NPWT alone.[7] There is also recent evidence that the bead pouch is superior to antibiotic beads used in conjunction with NPWT. In a study at the U.S. Army Institute of Surgical Research, NPWT decreased the effectiveness of antibiotic beads in a goat complex musculoskeletal wound model inoculated with *Staphylococcus aureus*. However, in that investigation, antibiotic beads used in conjunction with NPWT was more effective in decreasing bacterial burden than NPWT alone.[8]

Prefabrication of antibiotic PMMA beads is not a new technique. The production of tobramycin-impregnated beads, and their "off-the shelf" use, has been previously described by Cunningham et al,[9] and others.[15–17] Their technique used gas sterilization of nonsterilely prepared bead strands to avoid heat denaturation of the antibiotic during sterilization. Although effective, this method of ensuring sterility of the prefabricated beads is not possible in the combat hospital environment. It is for this reason that we decided to attempt an "all-sterile" prefabrication method, and decided to validate the sterility of this technique by culturing the beads at the time of implantation. Acceptable antibiotic release from prefabricated beads has also been previously shown. The antibiotic elution profile of tobramycin-impregnated beads undergoing gas sterilization remained unchanged at 1 year after production compared to the time of production.[15] This shelf life interval is substantially longer than we would expect in the combat hospital environment.

To date, all investigations involving prefabricated beads have used tobramycin, whereas imipenem was used in this study. Imipenem is a heat-stable carbapenem antibiotic, which has a proven record of incorporation into PMMA beads.[16] In our combat hospital, antibiotic-impregnated PMMA beads are used nearly exclusively in the management of blast injuries, as an adjunct in the prevention of infection. Multiple drug-resistant *E. coli* is the predominant pathogen infecting the wounds of blast-injured patients in our combat hospital. In accordance with local clinical practice guidelines, we chose to use imipenem-impregnated PMMA in this study in response to the local institutional antibiogram.

The sample size in our study was limited by the available resources of our combat hospital, both with respect to the supply of culture swabs themselves and to the laboratory resources available for incubation of culture specimens. Although no specimens in this investigation were culture positive at the time of implantation, the statistical significance of this finding depends on how this compares to historical controls.

Historical controls for an acceptable percentage of contaminated surgical instruments and implants are difficult to assess. In one study, the percentage of culture-positive surgical instrument trays was 4% at 30 minutes and 14% at 1 hour after opening.[17] Another study showed positive cultures in 10% of wooden surfaces, and 33% of metal surfaces were culture positive at 90 minutes.[18] The specimens in these studies were collected using appropriate sterile technique, and the same process of specimen collection was used in this investigation. These rates of culture positivity can be considered to be additive between the true rate of contamination and any false positives resultant from contamination of the cultures themselves. This rate of positive cultures taken from instruments is accepted in clinical practice. It remains despite modern infection control procedures, modern sterilization techniques, and with much more sophisticated air purification processes than exist in a combat surgical setting. Despite this,

there were no positive cultures in this investigation, whereas there is a not insignificant rate of culture positivity historically shown from open instrument trays after just 1 hour of surgery. This is likely to be at least partially because of the inherently antibacterial nature of the beads when compared to surgical instruments. Secondary to the high rate of bead use at our combat hospital, the number of shelf days of the sterile bead packages was reasonably low.

The average number of bead packages used in each surgical case was greater than two. This shows the potential benefit of this technique, as it is applied to multiply injured patients in the combat hospital environment. In that clinical setting, multiple surgeons may be working on multiple limbs simultaneously, which places significant time pressure on the surgical technician assisting with the case. This is not only compounded by the potential need to fabricate antibiotic cement beads at the point of care, but further multiplied by the need shown in this study for multiple strands of antibiotic cement beads.

The sample size in this investigation is relatively small, and the average shelf life of our bead packages was short. It is possible that with either a larger number of specimens or a longer period of shelf time, that the rate of culture positivity could be significantly higher. Repeating this investigation with a longer period of shelf storage and increasing sample size could account for these limitations in potential future investigations. In addition, in the future, the use of calcium sulfate prefabricated antibiotic beads could be considered, as they have been shown to have superior antibiotic elution profiles over the short duration typically used in the management of combat extremity injuries.[19–21] Production of antibiotic-impregnated PMMA beads at the point of care in the operating room is a time-intensive process. In the combat environment, casualty flow is seldom constant, with frequent periods of low clinical load, punctuated by intervals where a large number of severely injured patients present within a narrow window of time. In these instances, time and manpower resources can be significantly strained, making the time required to produce antibiotic beads prohibitive. We believe that antibiotic beads represent an important adjunct to surgical debridement and wound irrigation in the management of combat extremity blast injuries. In addition, the sterile prefabrication of antibiotic-impregnated PMMA beads during ebbs in casualty flow is a safe and effective way to expand the capability to use this adjunct even in cases of high casualty flow. We recommend that this technique of prefabrication of antibiotic beads be considered for use in blast-injured patients in the combat hospital setting.

ACKNOWLEDGMENTS

REFERENCES

1. Murray CK, Wilkins K, Molter NC, et al: Infections in combat casualties during Operations Iraqi and Enduring Freedom. J Trauma 2009; 66(4 Suppl): S138–44.
2. Johnson EN, Burns TC, Hayda RA, Hospenthal DR, Murray CK: Infectious complications of open type III tibial fractures among combat casualties. Clin Infect Dis 2007; 45(4): 409–15.
3. Gordon WT, O'Brien FP, Strauss JE, Andersen RC, Potter BK: Outcomes associated with the internal fixation of long-bone fractures proximal to traumatic amputations. J Bone Joint Surg Am 2010; 92(13): 2312–8.
4. Wahlig H, Dingeldein E, Bergmann R, Reuss K: The release of gentamicin from polymethylmethacrylate beads. An experimental and pharmacokinetic study. J Bone Joint Surg Br 1978; 60-B(2): 270–5.
5. Geiger S, McCormick F, Chou R, Wandel AG: War wounds: lessons learned from Operation Iraqi Freedom. Plast Reconstr Surg 2008; 122(1): 146–53.
6. Crane DP, Gromov K, Li D, et al: Efficacy of colistin-impregnated beads to prevent multidrug-resistant A. baumanii implant-associated osteomyelitis. J Orthop Res 2009; 27(8): 1008–15.
7. Warner M, Henderson C, Kadrmas W, Mitchell DT: Comparison of vacuum-assisted closure to the antibiotic bead pouch for the treatment of blast injury of the extremity. Orthopedics 2010; 33(2): 77–82.
8. Zalavras CG, Patzakis MJ, Holtom P: Local antibiotic therapy in the treatment of open fractures and osteomyelitis. Clin Orthop Relat Res 2004; 427: 86–93.
9. Cunningham A, Demarest G, Rosen P, DeCoster TA: Antibiotic bead production. Iowa Orthop J 2000; 20: 31–5.
10. Baez LA, Langston C, Givaruangsawat S, McLaughlin R: Evaluation of in vitro serial antibiotic elution from meropenem-impregnated polymethylmethacrylate beads after ethylene oxide gas and autoclave sterilization. Vet Comp Orthop Traumatol 2011; 24(1): 39–44.
11. DeCoster TA, Bozorgnia S: Antibiotic beads. J Am Acad Orthop Surg 2008; 16(11): 674–8.
12. Wright BA, Roberts CS, Seligson D, Malkani AL, McCabe SJ: Cost of antibiotic beads is justified: a study of open fracture wounds and chronic osteomyelitis. J Long Term Eff Med Implants 2007; 17(3): 181–5.
13. Stinner DJ, Hsu JR, Wenke JC: Negative pressure wound therapy reduces the effectiveness of traditional local antibiotic depot in a large complex musculosketeal wound animal model. J Orthop Trauma 2012; 26(9): 512–8.
14. Nelson CL: The current status of material used for depot delivery of drugs. Clin Orthop Relat Res 2004;(427): 72–8.
15. Balsamo LH, Whiddon DR, Simpson RB: Does antibiotic elution from PMMA beads deteriorate after 1-year shelf storage? Clin Orthop Relat Res 2007; 462: 195–9.
16. Mader JT, Shirtliff ME, Bergquist SC, Calhoun J: Antimicrobial treatment of chronic osteomyelitis. Clin Orthop Relat Res 1999; 360: 47–65.
17. Dalstrom DJ, Venkatarayappa I, Manternach AL, Palcic MS, Heyse BA, Prayson MJ: Time-dependent contamination of opened sterile operating-room trays. J Bone Joint Surg Am 2008; 90(5): 1022–5.
18. Da Costa AR, Kothari A, Bannister GC, Blom AW: Investigating bacterial growth in surgical theatres: establishing the effect of laminar airflow on bacterial growth on plastic, metal and wood surfaces. Ann R Coll Surg Engl 2008; 90(5): 417–9.
19. Bowyer GW, Cumberland N: Antibiotic release from impregnated pellets and beads. J Trauma 1994; 36(3): 331–5.
20. Sanicola SM, Albert SF: The in vitro elution characteristics of vancomycin and tobramycin from calcium sulfate beads. J Foot Ankle Surg 2005; 44(2): 121–4.
21. Wichelhaus TA, Dingeldein E, Rauschmann M, et al: Elution characteristics of vancomycin, teicoplanin, gentamicin, and clindamycin from calcium sulfate beads. J Antimicrob Chemother 2001; 48(1): 117–9.