Management of a Diabetic Patient Presenting with Forefoot Osteomyelitis: The use of Cerament™ | Bone Void Filler Impregnated with Vancomycin – An Off Label Use

Authors: Jeffrey C. Karr, DPM, ACCPPS, CWS, FAPWCA, FCCWS1

Abstract:

Several non-biodegradable and biodegradable antibiotic cement delivery systems are available for the delivery of antibiotics for adjunctive therapy in the management of osteomyelitis. A major representative of the non-biodegradable delivery system includes the polymethylmethacrylate (PMMA) beads. Antibiotics that can be incorporated into this delivery system are limited to the heat stable antibiotics such as vancomycin and the aminoglycosides; tobramycin being the more popular. Cerament™ | Bone Void Filler (calcium sulfate and Hydroxyapatite (HA)) is both a biocompatible and biodegradable ceramic bone void filler that can successfully deliver heat stable and heat unstable antibiotics in musculoskeletal infections. Subsequent surgery for a bone infection and staged removal off the antibiotic beads are not necessary. A case of osteomyelitis in the diabetic foot is presented that was successfully managed with surgical bone resection and the off-label use of vancomycin impregnated Cerament™ antibiotic beads.

Key words: Diabetes mellitus, Vancomycin, osteomyelitis, diabetic foot ulcer, bone void filler.

Introduction

Bone infection (osteomyelitis) can perhaps be one of the most daunting challenges to a surgeon. Treatment is tailored to the patient but generally involves prolonged antibiotics, surgical debridement when indicated, and management of the patient’s co-morbidities.1,2 Antibiotic impregnated beads as an adjunctive treatment of surgical debridement offers advantages in the treatment of osteomyelitis.3-8 The concept of applying PMMA beads as a means of local antibacterial therapy was first introduced in the literature in 1970 by Buchholz, et al.9

Antibiotic beads allow high local antibiotic concentration while the systemic antibiotic levels are low with no systemic toxicity.10-12

Antibiotic beads are relatively easy to insert, generally well tolerated by the patient, and also offer the benefit of managing dead space created by bone debridement. Antibiotic beads can be classified as biodegradable or nonbiodegradable. A disadvantage of nonbiodegradable PMMA bead implantation is their required removal, thus requiring additional surgery.

The PMMA antibiotic bead delivery system has been generally limited to the incorporation of only the heat stable antibiotics vancomycin and aminoglycosides: the more commonly used aminoglycoside is tobramycin.
The selection of these types of antibiotics for PMMA beads is based on the antibiotic’s stability at high temperatures (up to 100 degrees C) at which polymerization occurs.

Cerament™ Bone Void Filler (BSAB, Lund, Sweden) is biocompatible ceramic bone void filler consisting of Calcium sulfate and hydroxyapatite (HA) that acts as an osteoconductive scaffold and does not need to be removed after bead implantation due to its biodegradability. The calcium sulfate is reabsorbed over an eight to twelve week period by a process of dissolution.13 HA and the calcium sulfate are highly biocompatible and biodegradable materials.14-23 Hydroxyapatite is a calcium phosphate mineral and is the primary constituent of human bones and teeth. Cerament™ Bone Void Filler has excellent injectability and moldability, high penetrability and is non-exothermic, radiopaque, fully biocompatible, non-toxic, and available sterile. Rauschmann, et al., showed the calcium sulfate and HA composite material demonstrated no cytotoxicity towards fibroblasts and minimal cytotoxicity towards human osteoblasts in an in vitro study.24 Furthermore, when the Cerament™ Bone Void Filler is added to Iohexol solution 180 mg I/ml (Omnipaque 180 mg I/ml), heat stable and unstable antibiotics may be successfully used.

In review of the literature, there are consistent, reproducible in vitro, in vivo, and human reports of successful utilization of calcium sulfate, HA, and Iohexol with antibiotics as antibiotic beads against bacteria.18,20,22,25,27-37 Klessig, et al., demonstrated in vitro that the minimum inhibitory concentrations (MIC) of gentamycin, cefazolin, and clindamycin remained efficacious in combination with Iohexol against Escheria coli, Staphylococcus aureus, and Staphylococcus epidermidis.37 Another study revealed that when calcium sulfate, HA, and a binder sodium silicate were combined with vancomycin the zones of inhibition seen demonstrated an inhibitory effect against methicillin resistant Staphylococcus aureus (MRSA).18 When the authors compared their study to other studies using PMMA cement antibiotic beads, they stated a four times higher antibiotic concentration release of the antibiotic from the calcium sulfate and HA. Bowyer also noted at least a four-fold greater antibiotic release from calcium sulfate pellets than from corresponding PMMA pellets.26 The authors concluded that hydroxyapitite had higher efficiency to be an antibiotic carrier than that of the PMMA antibiotic beads.18,25 In vivo studies by Nikulin and Ljubovic27 in rabbit femurs and later confirmed by Peltier38 in dogs indicated that calcium sulfate can be used safely and conveniently in a wide variety of bone defects. In vivo studies in a rat model with calcium sulfate and HA gentamycin blocks demonstrated antibiotic concentration five times the MIC needed for Staphylococci susceptibility.20 An in vivo study of inoculated Staphylococcus osteomyelitis in a rabbit population treated with gentamycin loaded calcium sulfate resulted in a cure in some, but not all of the rabbits and confirmed that a relatively large dose of gentamycin can be delivered locally with relatively safe serum gentamycin levels.29 Turner, et al., in a canine in vivo study concluded that calcium sulfate is an effective osteoconductive medicated bone-graft substitute achieving a predictable local response, a long term release of the antibiotic achieved without adverse systemic effects and that the calcium sulfate antibiotic beads were a safe and effective method for local antibiotic treatment and dead space management.30 A HA gentamycin-impregnated cement study in an in vivo rat osteomyelitis model concluded this was an effective adjunctive modality when compared to debridement alone, debridement with intraperitoneal gentamycin, and debridement with gentamycin-PMMA cement.33 Gitelis presented six patients with osteomyelitis of the tibia or fibula managed with surgical debridement and placement of vancomycin calcium sulfate (Osteoset) beads. The author presented complete quiescence of the osteomyelitis in all six cases.31
In a study of twenty-five patients with post-traumatic long bone osteomyelitis, twenty-three patients (92% success rate) had eradication of their bone infections with surgical debridement, hardware removal, and tobramycin-impregnated calcium sulfate and alpha-hemihydrate pellets.\(^\text{32}\)

In an eighteen patient chronic osteomyelitis study managed with debridement with placement of calcium sulfate and hydroxyapatite antibiotic blocks the authors stated all infected sites healed within three months with no recurrence of infection in a follow-up of 24 to 75 months.\(^\text{34}\)

**Case Presentation**

A 42-year-old, non-smoking diabetic male presented with chronic foot ulcers and underlying 4\(^{th}\) metatarsal osteomyelitis and 4\(^{th}\)/5\(^{th}\) toe gangrene. (Fig.1) The MRSA osteomyelitis involved the fourth metatarsal and forth toe proximal phalanx. (Fig. 2)
The patient’s past medical history was significant for poorly controlled type 2 diabetes, hypertension, coronary artery disease with history of myocardial infarction and chronic renal insufficiency. The patient had a previous partial fifth metatarsal resection one year ago for osteomyelitis with no fourth toe, fifth toe, or fourth metatarsal involvement at that time. Lower extremity arterial non-invasive vascular studies demonstrated no significant stenotic disease. Surgical intervention was planned.

In the operating room a 10 ml Cerament™|Bone Void Filler kit was mixed with 2 grams of vancomycin utilizing the following 1-2-3-4 technique. First, the Omnipayque was mixed with the Cerament™|Bone Void Filler with rotation of the wrist for two minutes. (Fig. 3A) At two minutes the Cerament™|Bone Void Filler was placed in a sterile bowl. (Fig. 3B) At three minutes, two grams of Vancomycin was added and mixed with a wide spatula in a rolling fashion. (Fig. 3C) By four minutes the placement of the mixture in the bead mold was completed. (Fig. 3D) At 15-20 minutes the antibiotic beads were removed from the mold and were ready for implantation. (Fig. 3E). This is an off-label use of the Cerament.

Surgical management included ulcer debridement, amputation of the 4/5th toes, and partial resection of the fourth metatarsal. (Fig. 4) The Cerament™|Bone Void Filler beads were place in apposition to the remaining fourth metatarsal. (Figs. 5, 6) Typical closure followed. The patient progressed very well. Bone cultures demonstrated MRSA. No systemic antibiotics were given after bone resection, Bactrim DS was given orally for two weeks after the partial bone resection. The Cerament™|Bone Void Filler-vancomycin impregnated beads started to show signs of reabsorbing at fourteen days after surgery and were completely resorbed at four weeks. The diabetic ulcers were healed at eleven weeks after surgery and there were no formed beads remaining. There was HA remaining that elicited no foreign body or immune host response.

The osteomyelitis was unresponsive to both to oral and intravenous antibiotics. The gangrene had started the day before surgery.
Conclusion

Cerament™ Bone Void Filler calcium sulfate and hydroxyapatite antibiotic beads can be an effective, safe, and easy therapy in conjunction with surgical debridement for the management of osteomyelitis. A diabetic foot with MRSA osteomyelitis with successful management with surgical debridement and vancomycin Cerament antibiotic beads is presented.
There was no local adverse reaction to the antibiotic beads and there was no osteomyelitis reoccurrence. An advantage of the Cerament™ Bone Void Filler calcium sulfate and hydroxyapatite antibiotic beads is that because they are biodegradable, a subsequent second surgery to remove the beads is not necessary. This is an off-label use of the Cerament™.

References


