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Coated nails: is their use supported by the literature?

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Abstract

Antibiotic-coated intramedullary nails have been popularized in recent decades for treating long-bone infections. They are especially useful in treating diaphyseal infections requiring stability, such as those involving fractures and nonunions. The nails are made by injecting antibiotic-impregnated polymethylmethacrylate or "cement" around a metal core using a silicone tube as a mold. There are a variety of techniques that can be used to customize the nail to the affected site. Antibiotic cement has long been demonstrated as an effective local antibiotic delivery system. It is able to elute high concentrations of antibiotics while having little systemic toxicity. Several case series have reported good outcomes using this technique, defined by bone union and infection control. Further research is needed to determine the amount of weight that can safely be transferred through the nail and to optimize antibiotic elution.

Keywords: antibiotic cement-coated nails, antibiotic-impregnated polymethylmethacrylate, diaphyseal infections, intramedullary nails, long-bone infection

1. Introduction

The treatment of long bone osteomyelitis or fracture-related infections requires a multifocal approach.[1] Patient optimization including the management of comorbidities, addressing metabolic abnormalities, and modifiable risk factors like nicotine use, and optimization of nutrition are required to provide the best chance for clearing the infection. A thorough surgical debridement and administration of culture-specific antibiotics are standard. Antibiotic-impregnated absorbable or nonabsorbable cement beads have been used successfully to locally deliver a high concentration of antibiotics to the affected area. However, in the setting of an infected fracture or nonunion, beads do not provide the fracture stability needed and are difficult to remove after the ingrowth of granulation tissue. The standard intramedullary nails required to provide osseous stability unfortunately can also serve as a continued source of contamination. In these situations, antibiotic-coated nails utilizing antibiotic-impregnated polymethylmethacrylate (PMMA) or "cement" can provide both a source of local antibiotic delivery and fracture stability. They can also be used for infection prophylaxis in the setting of open fractures. In this paper, we discuss the use and efficacy of antibiotic-coated intramedullary nails. Of note, all uses are currently off-label and not approved by the Food and Drug Administration in the United States of America.

2. What is an antibiotic-coated nail?

Antibiotic-coated nails were first described in 2002 as a treatment for medullary infections in the setting of nonunions.[2] Different types of nails have been described and include those utilizing a thin wire such as a ball-tipped guidewire, Kirschner (K) wire, or threaded Ilizarov rod.[3] A cylindrical mold is required for containment of the cement and shaping of the nail and may include use of thoracostomy (chest), endotracheal, or dilation and curettage tubing. The tubing must be heat-resistant due to the exothermic reaction of the PMMA that is commonly used. The authors prefer the use of dilation and curettage tubing for this reason (Fig. 1 and Supplemental Digital Content, Video 1, http://links.lww.com/OTAI/A12). The amount of antibiotics mixed with the PMMA varies, but is typically 2 to 4 g of a heat stable antibiotic per batch. The authors typically use 2 batches of commercially available tobramycin or gentamicin-impregnated low-viscosity PMMA with 2 g of Vancomycin per batch. If the PMMA is white, the authors add methylene blue to ensure easy identification of loose cement at the time of nail extraction. The antibiotic-impregnated PMMA is typically loaded into a cement gun and injected into the plastic tube into the opposite end from where the threaded rod is inserted. Prior to cement injection, coating the inside of the tubing with mineral oil can facilitate nail removal after the cement has cured and has not been found to affect antibiotic elution properties.[4] The nail and tubing are then placed in a room temperature saline bath to minimize the nail melting to the tubing [5] (see Supplemental Digital Content, Video 1, http://links.lww.com/OTAI/A12).

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Figure 1. Dilation and curettage (D&C) tubing, cement mixer, 6 mm Ilizarov rod used to make the antibiotic nail.

After the cement cures, the plastic is cut away and the nail is implanted (see Supplemental Digital Content, Video 1, http://links.lww.com/OTAI/A12). If the situation dictates, like spanning a knee joint or a cephalomedullary nail is required, a dual-hinged rod using threaded Ilizarov rods can be utilized by attaching a single post to each end of the threaded rod and connecting the two using a bolt and nut.[6] Alternative methods of fabrication have been reported and include manual rolling of the cement[4] and use of a reusable metal mold with prolonged fabrication time of 1 hour.[7]

Alternatively, antibiotic nails can be fabricated using a traditional interlocking nail with a thin coating of antibiotic cement on the outside. This technique provides increased size options with increased stability including interlocking bolts. Barger et al[8] report that a cement mantle of 1.5 to 2.5 mm is necessary to prevent shearing of the cement coating upon insertion.

In addition to infected fractures, antibiotic nails may be used to treat intramedullary infections associated with prosthetic joint infections. The role of antibiotic cement spacers in the treatment of total hip and knee infections is well documented.[9] The addition of an intramedullary portion to traditional knee spacers can be used to manage extension of infection into the medullary canals or add stability to nonarticulating antibiotic spacers.[10] Tibial nails or threaded Steinman pins are inserted into the femoral and tibial medullary canals, and a static block of cement can create a nonarticulating spacer. For hip prosthetic joint infections, Kamath et al[11] describe an articulating antibiotic nail made from a commercially available cephalomedullary nail after resection of a total hip arthroplasty. The proximal aspect of the nail was shaped into a ball to provide a spacer that simulates the shape of a femoral head. Another way to address an infected total hip arthroplasty with intramedullary extension is to join a standard femoral nail to a commonly used antibiotic cement-coated femoral component (Prostalac, Johnson & Johnson, New Brunswick, NJ).[12]

3. Are any prefabricated antibiotic nails available commercially?

Prefabricated antibiotic-coated interlocking nails provide the advantage of decreased operating room time for fabrication of the nail and have reported to provide good outcomes.[13] However, they are associated with a substantial increase in cost, even when a standard intramedullary nail is used as the metallic core and with operating time taken into account.

The only commercially available nail is the ETN Protect (De Puy Synthes, Raynham, MA) and is not available in the United States (US). A titanium alloy medullary tibial nail is coated in poly-lactide containing gentamicin. Several case series, outside the US, have documented effectiveness using the PROtect nail for acute fractures and nonunions[14,15] compared with standard medullary nails, antibiotic beads, or fabricated antibiotic nails.

4. Is antibiotic cement effective at eluting antibiotics?

The exact rate of antibiotic elution from a fabricated nail is difficult to predict given the variability in dosage of antibiotic added, the mixing technique, and the difficulty in replicating the infectious environment in an in vitro model.[16] Most studies report a high rate of antibiotic release in the first 24 hours after implantation followed by an exponential decrease.[17] A second spike in elution occurs 5 to 10 days after initial implantation.[18] However, the levels found weeks after implantation are still above the threshold necessary for bacterial inhibition.[19] Palacos (Zimmer, Warsaw, IN) has been demonstrated to be superior to other cements in eluting antibiotics.[20,21] This may be due to its higher porosity. The elution properties of nails, beads, and spacers change depending on differences in their surface area.

Several antibiotics have been studied as additives to PMMA. Tobramycin and vancomycin have been used together given their synergistic effect on antibiotic release from PMMA.[22] It has been recommended to include at least 3.6 g tobramycin and 1 g of vancomycin per 40 g batch of cement.[23] Karek et al[24] studied the elution properties of antibiotic nails formed around a standard interlocking nail versus a 3.5 mm guidewire. They found that both constructs released antibiotics for 6 weeks at a level that inhibit *Staphylococcus aureus*. Masri et al[25] demonstrated elution of antibiotics from a prefabricated PMMA spacer up to 16 weeks after implantation. Other antibiotics that have been demonstrated to have elution properties from PMMA include linezolid, teicoplanin, amikacin, and daptomycin.[26–29] Furthermore, adverse systemic toxicity due to high local elution of antibiotics is exceedingly rare.[30]

The elution properties of commercially available antibiotic nails have also been published. For the PROtect nail, 40% of the gentamicin elutes within 1 hour of insertion, 70% by 24 hours, and 80% by 48 hours.[14] The coating is made of poly-lactide and resorbs at approximately 6 months after implantation.[31]

5. Do antibiotic-coated nails provide adequate stability for infected nonunions and osteotomies?

The amount of load that can be safely transferred through an antibiotic nail has not been formally investigated. Wasko and

Borens[32] allowed patients to weight bear up to 10 to 15 kg through the nail in infected nonunions without mechanical complications. However, Shyam et al[33] found that patients with bone defects greater than 4 cm required significantly more time to heal than those with defects less than 4 cm. Bone defects greater than 6 cm did not heal. In these situations, additional stability to the bone may be necessary. Weight bearing can be tailored to the amount of osseous stability present based on the patient's preoperative weight-bearing status and imaging. Coating a standard interlocking nail creates a biomechanically stronger construct than using an Ilizarov rod or ball-tipped guidewire.

6. Are antibiotic nails effective at treating infected fractures and nonunions?

Several case series have described successful treatment of infected fractures and nonunions using antibiotic-coated nails. Reilly et al[34] reported on 41 patients with infected tibia fractures that achieved 76% success rate of clearing the infection. They fabricated nails using threaded Ilizarov rods or ball-tipped guidewires. The patients averaged 2 debridement and antibiotic nail surgeries, followed by definitive implant placement at 6 weeks. Thonse and Convey[7] achieved 85% rate of infection clearance in 52 patients using antibiotic-coated standard interlocking nails.

Many case reports and series also describe the success of using antibiotic-coated nails in the treatment of infected diabetic intramedullary infections.[3,35] Tomczak et al[36] described an 87% limb salvage rate in 8 patients with infected and ulcerated ankles treated with both an antibiotic nail and external fixator. Pawar et al[37] described a series of 5 neuropathic patients with infected ankles who all cleared their infection using an antibiotic-coated standard retrograde ankle arthrodesis nail. Average time of healing the tibiotalocalcaneal fusion was 4.1 months.

7. Are antibiotic nails effective at infection prophylaxis for high-risk patients?

Due to the high rate of infections seen with open tibia fractures, prophylactic use of antibiotic intramedullary nails has been proposed. Animal studies have found effective prophylaxis in rat tibiae contaminated with *Staphylococcus aureus*.[38] Gentamicin-loaded poly-lactide cement was found to prevent 80% to 90% of infections without systemic antibiotics. Pinto et al[39] found a higher rate of healing at 6 months and lower erythrocyte sedimentation rate and C-reactive protein values in the patients treated with commercially available gentamicin-loaded polylactic acid coated nails compared with standard nails in an observational study of 28 patients. However, this group excluded Gustilo and Anderson Type III open fractures. In Schmidmaier et al's cohort of 68 (half open and half closed) fractures, 5.8% of patients subsequently developed surgical site infection.[31]

8. Are there new innovations in the development of antibiotic nails?

Several recent studies have reported on new variations of the antibiotic nail. A group from the United Kingdom has reported on a case using a hindfoot fusion nail coated with a bioabsorbable calcium sulphate hydroxyapatite product (Cerament-V, Bone-support, Boston, MA).[40] This product comes in both gentamycin and vancomycin formulations. The nail was coated freehand using a syringe. This led to the advantage of leaving the interlocking holes free and not requiring tubing for a mold. Utilizing tubing, Mauffrey et al[41] described coating a carbon fiber interlocking nail to create an MR-compatible nail. Lastly, the idea has been proposed for a patient-specific nanoparticle-coated nail with a bioabsorbable coating with targeted antibiotics to provide a more predictable and patient-specific product.[42]

9. How are antibiotic nails fabricated and used at our institution? (Video 1)

Antibiotic-coated nails are indicated for use at our institution for long-bone fractures and nonunions complicated by infection. Patients undergo routine lab testing including erythrocyte sedimentation rate, C-reactive protein, complete blood count, and metabolic evaluation. Preoperative radiographs include orthogonal radiographs of the involved bone, extremity alignment series (if the lower extremity is involved), and a computed tomography scan of bilateral involved extremities to determine the presence of deformity that may need to be corrected at the time of the definitive procedure. We follow the guidelines set by Cierny and Mader[43] and begin the treatment with complete debridement of necrotic and infected tissue. The medullary canal is reamed, often using the Reamer Irrigator Aspirator to assist in the removal of necrotic and infected tissue (Depuy Synthes, West Chester, PA). If Reamer Irrigator Aspirator is not available, we will vent the long bone prior to reaming to minimize the intramedullary pressure, and avoid the spread of septic emboli.

Our institution currently fabricates nails using 2 batches of tobramycin-impregnated commercially available low-viscosity PMMA cement plus 2 g of vancomycin powder per batch injected around a single Ilizarov 6 mm threaded rod of the appropriate length. The PMMA cement is mixed with methylene blue dye to aid with visualization upon removal. Two nuts are threaded onto the distal aspect of the nail, and a single low-profile female hinge is threaded onto the proximal end to aid in eventual nail removal with a bone hook. A dilation and curettage tube is used as the mold and mineral oil is spread along the interior of the tube to minimize risk of melting the tubing to the nail. This makes between an 11- and 12-mm nail. After mixing the PMMA, and once it is in the dough stage, the threaded Ilizarov rod is placed retrograde in the tube, and the cement gun is used to inject the antibiotic cement into the tube from the opposite end. Once the cement is injected and the tube filled, the cement gun is removed, and low-profile female hinge is applied. The nail is cured in a room temperature saline bath. A 22-blade knife is used to cut the tubing upon hardening. Prior to placing the nail, the medullary canal is over-reamed by 1.5 mm.

The management of the patient is then individualized. Typically, in the setting of infection, the patient's intraoperative cultures will be followed and targeted antibiotics will be prescribed. Inflammatory markers will be followed in coordination with the infectious disease team. Clearance of the infection is demonstrated by improved pain, healed soft tissue envelope, normalization of inflammatory labs, and completion of the antibiotic course. This typically occurs by 8 weeks after the placement of the antibiotic nail and the patient is then scheduled for definitive surgery.

10. Conclusion

Antibiotic-coated nails offer an adjunct to the treatment of infected long bone fractures and nonunions. They are straightforward and relatively inexpensive to fabricate in the operating room depending upon which type of metal component is used. Based on the available literature, we believe that antibiotic-coated nails are an effective method for the local delivery of antibiotics and mechanical support. Further research regarding the optimal construct to provide biomechanical stability and ways to increase antibiotic elution will continue to optimize the treatment of long bone infections.

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