texas orthopaedic journal®

ORIGINAL RESEARCH

In Vitro Elution Characteristics of PMMA Cement Intramedullary Spacers Impregnated with Vancomycin and Tobramycin

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ABSTRACT

Introduction: Septic nonunion following intramedullary nail (IMN) stabilization of tibial shaft fractures is typically treated with removal of IMN followed by either intramedullary placement of antibiotic-impregnated polymethylmethacrylate (PMMA) beads with external stabilization or, more recently, with antibiotic-coated PMMA IMNs. Although elution studies have been reported for cement beads, no study, to our knowledge, has assessed the antibiotic elution from PMMA IMNs.
Methods: Two antibiotic-impregnated bone cement groups were prepared. Group 1 (Beads) contained 1.0 g vancomycin and 1.2 g tobramycin mixed in 40 g PMMA and rolled into spheres. Group 2 (Nails) consisted of 2.0 g vancomycin, 2.4 g tobramycin and 80 g PMMA fabricated into an IMN. Ten samples were made for each group. Concentrations of antibiotics eluted from the specimens were then measured and compared.
Results: Group 1 showed high rates of elution early with logarithmic release of vancomycin; however, by the 7th day its concentration dropped below detection (<5 μg/ml). Group 2 showed early elution of vancomycin of less than one third that of Group 1, and by the 3rd day the concentration fell below detection. Although brief, this difference was statistically significant ($P<0.004$). The elution rates of tobramycin showed high rates of release with exponential decay as seen with vancomycin. At each time point, beads showed higher elution rates than nails up to 4 weeks. The mean totals of tobramycin released were 296.0 μg in Group 1 and 81.9 μg in Group 2.
Discussion: Antibiotics elute at a higher rate from PMMA beads than from PMMA IMNs.
Keywords: Septic nonunion; Local antibiotic release; Antibiotic elution kinetics.

INTRODUCTION

Septic nonunion following intramedullary stabilization of tibial shaft fractures is a serious complication. Overall incidence of deep infection increases from about 1% in closed fractures [1] to as high as 9% in open tibial shaft fractures [2]. Removal of the intramedullary nail (IMN) is typical, which poses two problems: loss of stability of the fracture and a non-collapsible cavity hindering local delivery of antibiotics [3].

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External fixation with intramedullary antibiotic impregnated polymethylmethacrylate (PMMA) bone cement beads has been used to address these issues; however, this has several disadvantages, including pin tract infections and decreased patient mobility [4]. Various antibiotic cement-coated IMN techniques have since been described to treat the infection and provide bone stability necessary for fracture healing [5-7]. This technique has shown positive results; however, in a study by Thonse & Conway, 21% of patients required additional procedures after placement of antibiotic IMNs for treatment of infection [8]. As antibiotic PMMA beads and small spacers are historically left in place for 6-8 weeks to treat various orthopedic infections [9,10], it has become the consensus among orthopedists that IMNs also remain 6-8 weeks as is reflected in the literature [5-8]. Although elution kinematics have been described for cement spacer blocks and beads [11-15], no study has evaluated the elution properties of long, cylindrical intramedullary cement spacers. Our hypothesis is that these IMNs will have elution kinematics inferior to PMMA beads; supportive results raise questions about the duration of intramedullary treatment.

MATERIALS & METHODS

Two antibiotic-impregnated bone cement groups were prepared using Surgical Simplex® P radiopaque bone cement (Stryker Howmedica Osteonics; Mahwah, NJ). Group 1 (Beads) contained 1 g powdered vancomycin (Pfizer; New York, NY) and 1.2 g powdered tobramycin (APP Pharmaceuticals; Shaumburg, IL) mixed in 40 g Surgical Simplex P bone cement. The antibiotic and cement powders were mixed well in a plastic container after the addition of 20 ml liquid monomer. Before curing, the cement was hand rolled into small spheres (approximately 7 mm), then placed inside a size 40 French chest tube 34 cm in length. Chest tubes were fenestrated to allow the antibiotic beads to mix with solution, and the ends were sutured with 3.0 Prolene® sutures to prevent bead escape (Figure 1). Group 2 (Nails) consisted of 2 g powdered vancomycin, 2.4 g tobramycin, and 80 g Simplex P bone cement, which was mixed with 40 ml liquid monomer. While the mixture

Figure 1. Group 1 included PMMA antibiotic beads enclosed within a size 40 French chest tube by 3.0 Prolene® suture on each end.

was still in the semiliquid state, it was poured into a 60-ml syringe and then injected into 34 cm of non-fenestrated size 40 French chest tube and allowed to cure. After hardening, the antibiotic cement nails were cut out of the chest tube using a scalpel (Figure 2). A total of 20 samples were made: 10 beads and 10 nails.

The samples were enclosed in water-tight tubes constructed using 1-inch PVC pipes and threaded end caps. The enclosures were tested for potential leaks before the initiation of the elution studies. Group 1 (Beads) and Group 2 (Nails) were placed in individual tubes with 220 ml of normal saline. Ten of the 20 tubes were randomly selected

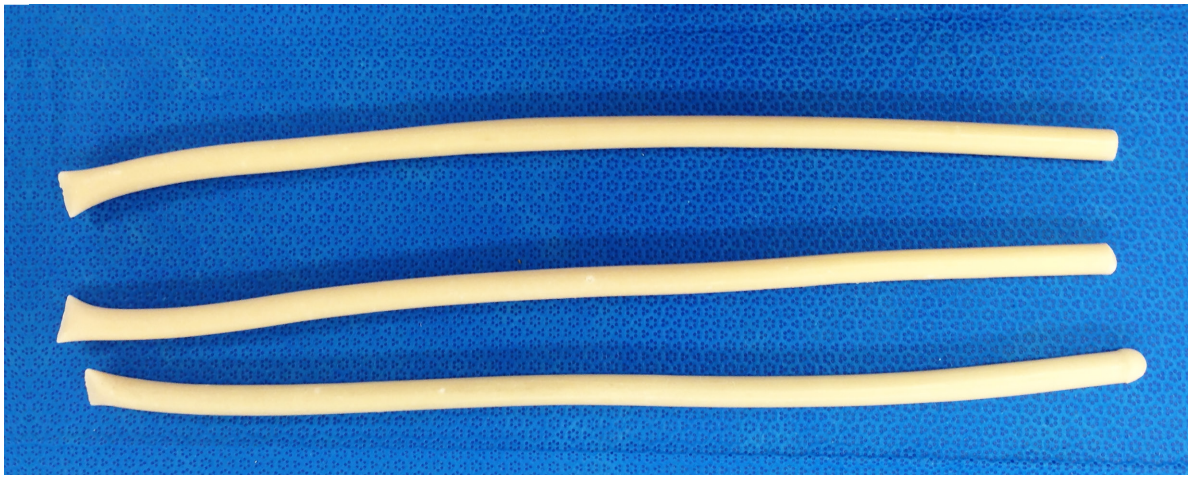

Figure 2. Group 2 included antibiotic nails after PMMA cement hardening and removal from the size 40 French tube.

for study and placed in a Julabo SW22 shaking water bath at 37°C with oscillations at 110/min. One-millimeter samples were taken from the tubes at 24-hour intervals for the first 7 days, the 220 ml saline was refreshed, and the tubes returned to the shaker bath. After the daily sampling for the first 7 days, samples were taken at 7-day intervals for a total of 6 weeks. This process was repeated for the remaining 10 tubes. The 1-ml saline samples were then tested for concentrations of vancomycin and tobramycin at our institution's chemistry lab.

Analysis was by t-tests with the Bonferroni adjustment for multiple comparisons with a $p<0.004$ being significant. Mean concentration at each time point for the 6 weeks and total sum of these values were assessed.

RESULTS

Vancomycin

The elution rates of vancomycin from the Group 1 (Beads) and Group 2 (Nails) are shown in Figure 3. Group 1 (Beads) showed high rates of elution early with logarithmic release of vancomycin; however, by the 7th day of testing the concentration dropped below the detection threshold of 5 µg/ml. The early elution of vancomycin in Group 2 (Nails) was less than one third that of Group 1 (Beads) and by the 3rd day of testing the concentration fell below 5 µg/ml. Despite the brevity of the results, this difference was statistically significant ($p<0.004$).

Tobramycin

The elution rates of tobramycin from Group 1

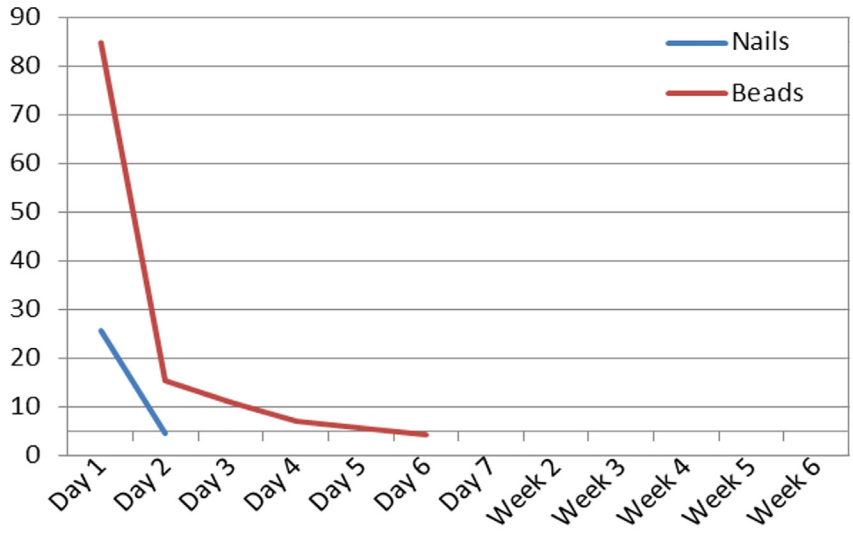

Figure 3. Vancomycin elution kinetics. The antibiotic nails fell below the detection threshold on day 2 while antibiotic beads fell below the detection threshold on day 6.

(Beads) and Group 2 (Nails) are shown in Table 1. High rates of antibiotic release occurred early with exponential decay as with vancomycin (Figure 4). At each time point, beads showed higher elution rates than nails with statistical significance shown through week 5 of testing. The mean total of tobramycin released was 296 µg in Group 1 (Beads), and 81.9 µg in Group 2 (Nails.)

DISCUSSION

Elution characteristics of PMMA bone cement blocks and beads impregnated with

Table 1. Tobramycin elution kinetics from PMMA Group 1 (Beads) vs. Group2 (Nails).

Time	Group 1	Group 2	P value
Day 1	48.549	207.94	<0.0001
Day 2	8.488	25.243	<0.0001
Day 3	5.298	15.655	<0.0001
Day 4	3.292	10.279	<0.0001
Day 5	3.247	9.079	<0.0001
Day 6	3.049	7.823	<0.0001
Day 7	2.722	6.659	<0.0001
Week 2	1.522286	4.111714	<0.0001
Week 3	1.447531	2.612184	<0.0001
Week 4	1.257496	1.882545	0.0005
Week 5	1.066072	1.258208	0.1488
Week 6	0.797704	1.103113	0.0239

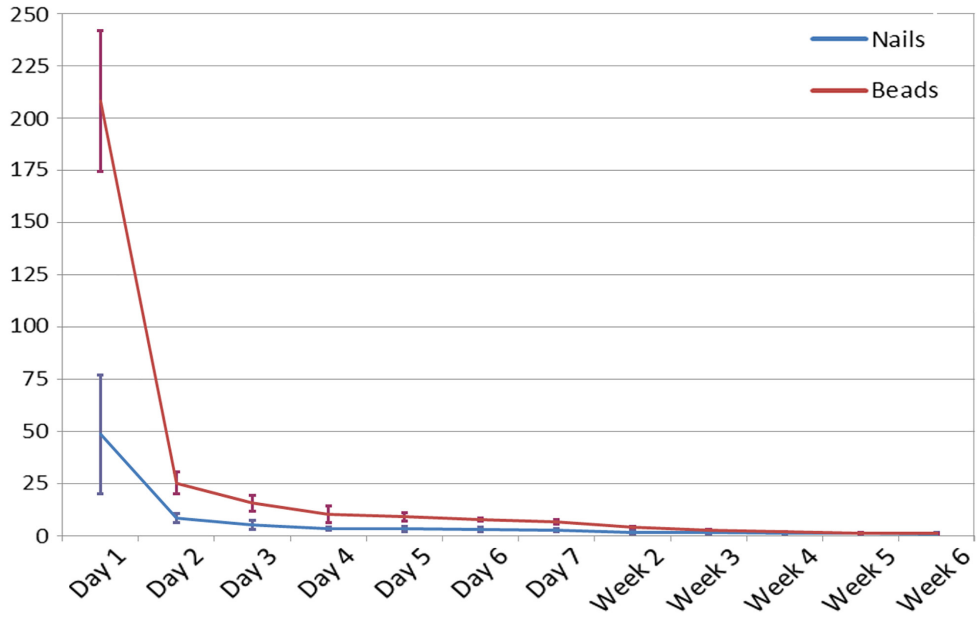

Figure 4. Tobramycin elution kinetics. Beads showed statistically significant higher elution through week 4 of testing.

antibiotics have been studied extensively [11-14]. Surface to volume ratio [15], type of bone cement [16,17], specific antibiotic [14], and number of different antibiotics used [13] all affect elution properties in vitro. Despite the extensive literature, no prior study compared elution characteristics of PMMA beads versus long, cylindrical IMNs.

In this evaluation of elution rates of PMMA antibiotic-impregnated beads and long, cylindrical IMNs, the antibiotic beads proved significantly superior to IMNs. Elution of tobramycin remained higher for beads than for nails at all testing intervals. Although data for vancomycin concentration were incomplete because of our chemistry laboratory capabilities, the PMMA beads showed much higher early elution and remained above the lowest concentration threshold for twice as long. Tobramycin concentrations demonstrated higher elution rates, which is not surprising given that its molecular weight is one third that of vancomycin [14]. Although we attempted to simulate physiological conditions, this study has several limitations. As noted, the capabilities of our chemistry lab prevented analysis of mid to late vancomycin concentrations. As our study was in vitro, antibiotic concentration levels will differ from those in vivo and can only compare concentrations between beads and nails.

With the drawbacks of external fixation [4], more surgeons are looking for treatment options to avoid its application. Different implants have been used for stability of PMMA IMNs, including Ender nails [18], tibial nails [8] and K-wires [19]. While all these metallic implants will provide stability for the fracture, it will be at the expense of antibiotic-impregnated bone cement's further decreasing its volume and elution rate. In the study by Thonse & Conway, IMNs remained indefinitely unless infection or nonunion persisted at 6-8 weeks [8]. The reduced antibiotic-impregnated cement volume from the use of an IMN with a large diameter may contribute to the high rate of persistent infection/nonunion.

Further, our results question whether antibiotic concentrations are sufficient to combat infection throughout the 6-week treatment period when antibiotic cement-coated nails are used. Additional research might change the time frame of re-operation in a persistent infection/nonunion.

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