CHAPTER **23**

THE EXPANDED USE OF ANTIBIOTIC IMPREGNATED POLYMETHYLMETHACRYLATE (PMMA) BEADS

Myron L. Hall, DPM
Donald R. Green, DPM
Daniel Keays, MS, CLS,
Lizanne Keays, MS, CLS

Polymethylmethacrylate (PMMA) is a self-curing polymer created by the combination of a powder, methyl methacrylate/styrene copolymer and a flammable liquid, methyl methacrylate.[1] Barium is added to the compound for radiopacity. Hydroquinone is added to the compound to prevent premature polymerization. When the powder and liquids are mixed and allowed to set for 10 to 15 minutes, it forms an acrylic cement-like structure. Clinical use of PMMA dates back to the 1940s when the substance was used for dentures and ocular lenses.[2] In 1970 Buckholz described the use of antibiotics with bone cement in joint surgery.[1,3] Two years later Klemm developed the use of antibiotics with spherical PMMA beads for treatment of infected osseous defects. Klemm described the advantages of gentamicin-impregnated beads as shorter downtime, reduction of staff workload and secondary infections and improved hospital hygiene.[1] By 1976, commercially prepared Gentamicin beads were available. Asches in 1978, described the use of antibiotic beads in the foot, developing a smaller size bead. In the early 1980s, numerous articles were published to show that Gentamicin PMMA beads were effective. Subsequently, many studies were published analyzing the use of a variety of other antibiotic classes.

Despite the ground swell of publication and study through the late 1980s, the most frequently utilized antibiotic beads continue to be Gentamicin, Tobramycin, and Vancomycin. Commercially prepared PMMA with Gentamicin has been available for some time, and commercially prepared PMMA with Tobramycin was placed on the US market in 2003. With over 50 years of development, the use of PMMA has vastly expanded. PMMA is indicated in the fixation of prostheses in orthopedic and podiatric surgery and the repair of pathologic fractures that cause an excessive loss of bone. With antibiotics, PMMA is commonly used for treatment of contaminated wounds, dirty open fractures, open fractures with poor soft tissue coverage, chronic osteomyelitis and infected prostheses.[5-7]

Figure 1 shows a 47 year-old male in whom Vancomycin impregnated PMMA beads were used to treat a surgical wound infection that developed 3 weeks following open reduction and internal fixation of a tibial fracture. The expansion of indications of antibiotic impregnated PMMA has increased the patient type for which it is applied; resultantly, a wide variety of patients may present with a broader spectrum of infectious organisms. This may warrant an expanded use of different antibiotic groups with PMMA. The purpose of our study was to test a broad spectrum of antibiotics that are used in the hospital setting.

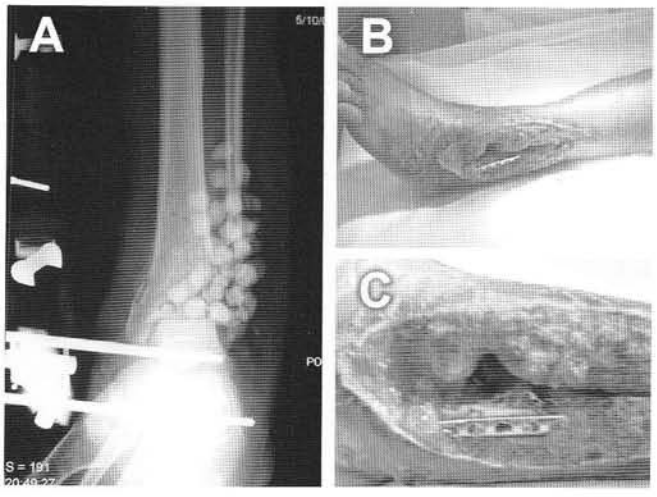

Figure 1. Vancomycin impregnated PMMA beads used to treat a 47-year-old male with a surgical wound infection that developed 3 weeks following open reduction and internal fixation of a tibial fracture.

MATERIALS AND METHODS

This study was conducted at Scripps Mercy Hospital Microbiology Laboratory with the assistance of the laboratory staff and Lizanne Keys of the UCSD Microbiology Laboratory.

Bead Preparation

The powder form of Ampicillin, Unasyn, Zosyn, Cefazolin, and Clindamycin was obtained from Scripps Mercy Hospital Pharmacy. The powder form of Levofloxacin was not available; thus, 500mg tablets were obtained and crushed to powder consistency and used in the trial (Figure 2). Two antibiotic beads were created for each antibiotic, one using the Simplex P product and one using the Endurance product. Quantities were adjusted to 1/16 of total package contents. 62.50mg of each antibiotic was added to 2.5g of methyl methacrylate powder. Then 11/4ml of the liquid monomer was added to this powder combination. The components were mixed in accordance with manufacturer instructions under sterile conditions. One oval bead was created for each mixture, resulting in the formation of 12 beads. After mixing and molding for 5 minutes, the beads were allowed to solidify for 10 minutes. The beads were then placed in normal saline at time zero to form eluant for the bioassay.

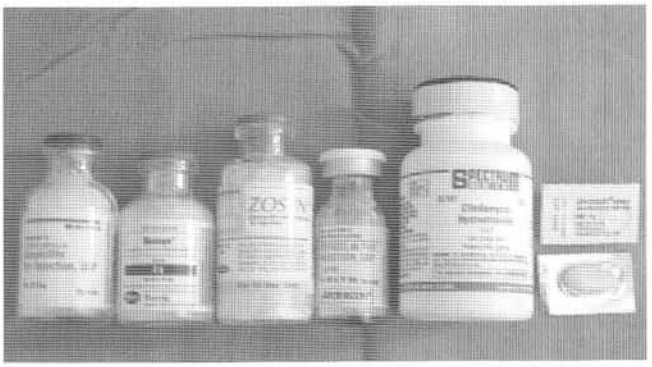

Figure 2. Vials of Ampicillin, Unasyn, Zosyn, Cefazolin, Clindamycin and Levaquin Tablets.

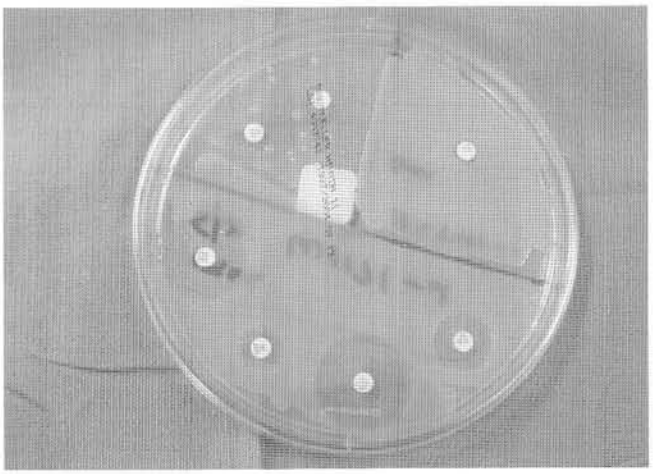

Figure 3 TSA after incubation, showing various zones of inhibition.

Bioassay

Eluant quantification was conducted by standardized bioassay with Staphylococcus aureus ATCC strain25922 for Clindamycin and Escherichia coli ATCC strain 25923 for all other antibiotics. Bacterial suspensions were made in saline to approximated 10,000/ml concentration of organisms. Tripticase agar (TSA) slants were heated to boiling and allowed to cool to 55 C. 50 ul of bacterial suspension was added to each TSA tube. The agar was then poured into 55mm Petri dishes and allowed to solidify. Filter paper disks were applied to each agar plate. Control samples for each antibiotic were obtained from the UCSD Microbiology Laboratory. A total of 25 ul of known quantities of each antibiotic was placed on filter paper disks. Agar plates were incubated at 35 C. Zones of inhibition were measured in mm for standard inhibition control (Table 1). A total of 25ul of eluant was taken from each bead solution at 2 hours, 24 hours, 48 hours, and 72 hours and placed on TSA plates. Zones of inhibition were measured for the test antibiotics at these times and extrapolated to determine elution concentration. (Table 2, Figure 3).

All of the tested antibiotic beads eluted bactericidal concentrations of antibiotics at the 2 hour point; however, Ampicillin, Unasyn and Cefazolin did not elute significant amounts of antibiotic after the first 2 hours. Conversely, Zosyn, Levofloxacin and Clindamycin continued to elute 48-72 hours. Beads made with Clindamycin and Levofloxacin provided effective levels of antibiotic through 72 hours. Howmedica Simplex P and DePuy Endurance appeared to provide similar elution quantities in all antibiotics except in Cefazolin. With the Depuy Endurance product Cefazolin continued to elute between 24-48 hours. In the Simplex P product Cefazolin provided zero bacterial inhibition at the 24 hour point. Zosyn

Table 1

CONTROL BIOASSAY

mcg/ml	100	50	25	12	6		20	10	5	2.5	1.2	0.6
Zones of Inhibition (mm)												
Ampicillin	18	15	12	8	0							
Unasyn	17	14	12	8	0							
Zosyn	30	24	19	13	9							
Cefazolin	18	14	12	9	0							
Clindamycin							30	22	19	16	10	0
Levaquin								24	20	15	11	0

Table 2

ANTIBIOTIC ELUTION

Antibiotic								
	2hr	mcg/ml	24hr		48hr		72hr	
Ampicillin								
Simplex P	26	>100	0	<6	0	<6	0	<6
DePuy	25	>100	0	<6	0	<6	0	<6
Unasyn								
Simplex P	24	>100	0	<6	0	<6	0	<6
DePuy	24	>100	0	<6	0	<6	0	<6
Zosyn								
Simplex P	30	>100	23	100	11	12	0	<6
DePuy	31	>100	28	>100	14	12	0	<6
Cefazolin								
Simplex P	21	>100	0	<6	0	<6	0	<6
DePuy	25	>100	13	12	0	<6	0	<6
Clindamycin								
Simplex P	38	>20	30	20	19	5	13	2
DePuy	37	>20	28	18	13	2	12	2
levaquin								
Simplex P	42	>10	32	>10	23	10	16	2.5
DePuy	37	>10	35	>10	25	10	21	5

maintained elution for 48 hours, while Unasyn did not elute any appreciable levels after the 2 hour point. While both are Beta-lactamase inhibitors, the difference in structures appears to render Unasyn more effective in use with PMMA.

DISCUSSION

Authors have discussed the effectiveness of utilizing various antibiotics PMMA bone cement. The majority of the literature in this area involves studies Gentamicin. After becoming commercially available in 1976 Gentamicin was the antibiotic of choice because of its good water solubility and its ability to withstand the heat generated in the formation of the PMMA beads. The temperature of the chemical reaction required in the production of the beads is 130 to 150 degrees C. More recently, Tobromycin and Vancomycin have been proposed for the use in antibiotic impregnated-PMMA bead therapy in the management of open fractures.[8] The benefits of use of aminoglycosides are that they are broad spectrum and gentamicin and tobramycin is bactericidal.[2] The successful use of antibiotic impregnated beads is well documented in the literature.

Marcinko reported a review of 1,054 cases in 890 patients in which Gentamicin impregnated PMMA beads were utilized to treat osteomyelitis. In this study the theraputic success rate was recorded as 97%.[1] In 1976, Marks et al tested the in vitro activity of Oxacillin, Cefazolin, and Gentamicin impregnated acrylic cement against Staphylococcus aureus, Escherichia coli and Pseudomonas. His study showed plain Simplex and Palacos had no antibacterial properties. His study also showed that all three antibiotics diffused from the bone cement in active amounts for 12, 19 and 13 days respectively.

Hessert and Ruchdeschel, in a German-published report, showed the effective elution of Ampicillin.[9] Bowyer et al demonstrated elution over 72 hours from benylpenicillin, Flucloxacillin, Amoxycillin, Augmentin, Ciprofloxacillin, Imipenem and Gentimicin. They showed a significant decrease in antibiotic elution after the initial 24 hours in all of the antibiotics. Gentimicin, Flucloxacillin, amoxycillin maintained appreciable elution through 72 hours; however, the study indicated that the clavulonic acid component of the augmentin was rendered ineffective after being mixed with PMMA.[10] Temperature of the reaction caused by mixing the PMMA has been shown to reach 72 to 85 degrees

Table 3

COST ANALYSIS

Product	Form	Amount	Price
Stryker Simplex P		40g	$ 80.52
DePuy Endurance		40g	$ 86.52
Simplex P w/ Tobramycin		40g	$ 268.00
DePuy w/ Gentamicin		80mg	$ 475.00
Clindamycin	U.S.P Bulk Powder	5 gm	$ 9.60
Unasyn	Inj. Powder Vial	3 gm	$ 12.07
Zosyn	Inj. Powder Vial	3.375gm	$ 13.40
Ampicillin	Inj powder vial	1 gm	$ 6.63
Eloquent	Tablet	500 mg	$ 7.63
Cefazolin	Inj. Powder vial	1 gm	$ 1.00
Tobramycin	U.S.P. Bulk Powder	1.2 gm	$ 126.49
Vancomycin	U.S.P. Bulk Powder	1 gm	$ 4.70
Gentamicin	U.S.P. Bulk Powder	5 gm	$ 18.89

centigrade, and this is thought to make some antibiotics unstable.[11] There is varying opinion on if this applies to cephalosporins. However, Levin showed effective elution of a first generation cephalosporin up to 20 days.[12]

An in vitro done with K-9 showed that PMMA blocks containing Cefazolin eluted antibiotic above the mean inhibitory concentration an average of 9 days.[13] The results of this study show no appreciable elution of Cefazolin, Ampicillin and Unasyn at 24 hours. However, the study did show active elution of these antibiotics at 2 hours. This indicates that some amount of these antibiotics, while small, remained stable and active through the reaction to form the PMMA. Perhaps beads prepared with larger amounts of these antibiotics will continue to provide eluant for longer period. Significantly longer time periods may not be necessary. Current orthopedic practice in the treatment of open fractures and infected wounds is to leave the wounds open with planned delayed primary closure in 3 to 7 days or to repeat debridements at 24-48 hours. This permits the use of antibiotic bead pouches and decreases the risks of clostridial myonecrosis.[7] While the results of the study are promising for Zosyn, a trial with a resistant strain of Staphylococcus aureus should be conducted to form more concrete conclusions.

Cost savings is another consideration. While Gentimicin, Tobramycin and Vancomycin beads are most frequently used, it may be more cost effective to use other antibiotics when possible (Table 3). The commercially prepared Simplex with Tobramycin costs $268. The manual preparation of the same amount would cost $207.01. Manual preparations of Clindamycin, Unasyn, Zosyn, Ampicillin, Levaquin, Cefazolin or Vancomycin would be nearly $200 less expensive. One may argue that Vancomycin is inexpensive at $4.70 per 1g and that has stood test of numerous clinical trials. However, when using Vancomycin one must consider the increased risks of developing VRE infections.

CONCLUSION

The results of our in vitro study indicate that Clindamycin and Levoquin impregnated PMMA beads elute appreciable concentrations of active antibiotic up to at least 72 hours. Although less effective, Zosyn impregnated PMMA beads continued to elute antibacterial concentrations of antibiotic for at least 48 hours. Conversely, the results for Ampicillin, Unasyn and Cefazolin were not as encouraging. Additionally, the study demonstrated no apparent difference in antibiotic elution from the Simplex P and the Endurence PMMA products. These results, while based on a limited trial, show that a broader spectrum of antibiotics may expand the use antibiotic-impregnated PMMA beads. Moreover, our cost analysis shows that the use of manually prepared antibiotic-impregnated beads would save money.

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