Effect of Varying Antibiotic Ratios on Elution from Bone Cement and the Resulting Mechanical Properties
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Introduction
Antibiotic-loaded polymethyl-methacrylate (PMMA) bone cement spacers are currently used to treat patients with an infected total joint arthroplasty. Mixing antibiotics into PMMA spacers offers distinct advantages over oral and/or intravenous administration, including localized delivery of a higher concentration of antibiotics with reduced toxicity. Combining two, or more types of antibiotics within PMMA gives surgeons the ability to treat multiple infectious organisms, such as Staphylococcus aureus, Staphylococcus epidermidis and Pseudomonas. Recent research has shown that the release of antibiotics from PMMA is dependent on a number of factors, including types of antibiotics incorporated within the cement. Penner, et al found that combining vancomycin and tobramycin in PMMA lead to a net increase in the rate of release of both antibiotics[1]. To the contrary, Klekamp et al found that if vancomycin and tobramycin were combined in the PMMA under vacuum mixing conditions, leads to a decrease in the release of tobramycin [2]. Klekamp cited differences in antibiotic molecular weight as a potential cause for elution properties. Understanding the relationship between antibiotic molecular weight, concentration ratio and elution rates in PMMA bone cements and the resulting mechanical strengths must be thoroughly characterized to allow surgeons to effectively treat infected total joint arthroplasties.

Methods
Varying antibiotic ratios of daptomycin and tobramycin were mixed with 40g packets of Simplex P SpeedSet (Stryker Orthopaedics, Mahwah, NJ) in a commercially available vacuum mixing system. Antibiotics were combined in a binary fashion to examine several combinations of each antibiotic formulation (3.6g tobramycin, 2.4g tobramycin, 2g daptomycin, 1g daptomycin, 1g daptomycin and 3.6g tobramycin, 1g daptomycin and 2.4g tobramycin, 1g daptomycin and 1.2g tobramycin, 2g daptomycin and 3.6g tobramycin, 2g daptomycin and 2.4g tobramycin, and 2g daptomycin and 1.2g tobramycin). Antibiotic-loaded PMMA was then dispensed into molds and allowed to cure, which resulted in the formation of a minimum of 6 cylindrical samples with a diameter of 1.5cm and a length of 5cm. The samples were immersed in a saline buffer solution at 37degC and mechanically rocked. Three millimeter fluid samples were drawn at 1, 6, 12, 24, 48, 72 and 96 hours. The fluid samples were then subjected to UV-VIS spectroscopy to determine the amount of each antibiotic eluted from the PMMA as a function of time.

At the completion of the elution phase both eluted and non-eluted PMMA samples were radiographed to observe porosity. Following physical examination the samples were mounted in an MTS Bionix servohydraulic 15Kn load frame for compression testing. Compression testing was conducted to determine the differences in ultimate strength and yield strength.

Results
Antibiotic concentration variation resulted in different elution rates, ultimate strengths and yield strengths. Antibiotic elution rates varied based on the amount of daptomycin present in the formulations. Averaged over 96 hours, PMMA cement concentrations that contained any amount of tobramycin and 2g of daptomycin had a total antibiotic elution rate of 8.7 µg/ml-hr which was 35% higher than PMMA cement samples containing tobramycin and only 1g daptomycin, 92% higher than formulations containing only tobramycin and 41% higher than formulations containing only daptomycin.

However, PMMA cement samples that had higher concentrations of daptomycin resulted in decreased ultimate compression and yield strengths (figure 1). On average, samples containing 2g daptomycin resulted in ultimate compressive strengths of 66 MPa for non-eluted and 69MPa for eluted samples. Compressive yield strengths for PMMA samples containing 2g daptomycin corresponded to values of 49MPa and 51 MPa for non-eluted and eluted, respectively. PMMA sample formulations with 1g of daptomycin had an ultimate compressive strength of 71MPa for non-eluted samples and 75MPa for eluted cement samples (figure 2). Correspondingly, the compressive yield strength for PMMA non-eluted and eluted cement samples with 1g daptomycin were 53MPa and 57MPa, respectively.

Discussion
The inclusion of antibiotics into PMMA bone cement has been shown to effectively treat infection. The type and concentration of antibiotics has been shown to vary the elution rate and potentially vary the efficacy of the antibiotic cement spacer. Combinations of antibiotics containing a minimum of 2g daptomycin resulted in the highest elution rates. Similar to Klekamp, differences in antibiotic molecular weight may explain the observed differences in elution rates (daptomycin mw = 1,620 amu, tobramycin mw = 485 amu). However, the addition of antibiotics into the chemical composition of PMMA has been shown in this study to reduce the mechanical properties of the bone cement. PMMA samples that contained the highest concentration of daptomycin exhibited a reduction in ultimate compressive strength of 21% and reduction in yield strength of 33% after an elution period of 96 hours when compared to PMMA bone cement without antibiotics. Ultimately, patient selection is required in determining the optimum course of treatment for infection in total joint arthroplasty. Patients that require cement spacers with higher yield strengths may require the surgeon to alter the antibiotic composition in the spacer to provide optimum treatment and stability.

Figure 1. Stress – Strain graph demonstrating the different mechanical properties (ultimate and yield strengths) of Eluted and Non-Eluted 2g daptomycin, 3.6g tobramycin PMMA sample.

Figure 2. Percent difference of varied antibiotic formulations for eluted and non-eluted ultimate compression strengths to pure PMMA cement sample.

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References: