Elution Performance of Surgeon-Mixed and Commercially Pre-Mixed Low Dose Antibiotic Loaded Bone Cement

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Introduction:
In 2003 the FDA approved low dose antibiotic loaded bone cement (AL-PMMA). There are now 6 commercially pre-mixed preparations available in the United States to be used for fixation in second stage reimplantations for infected arthroplasties. It has been claimed that the commercial mixing saves operative time and is more homogeneous leading to better drug delivery. Published data on surgeon directed mixing compared to pre-mixed preparations report that commercially pre-mixed preparations release more antibiotic on average in two studies and less in one. None of these studies evaluated how evenly the antibiotic was dispersed in the cement. These inconsistent data lead to our experimental question “Does surgeon-mixed antibiotic loaded bone cement have inferior elution compared to commercially pre-mixed preparations?”

We hypothesized that elution of antibiotic from surgeon-mixed antibiotic loaded bone cement is not inferior to commercially pre-mixed preparations for either total release or homogeneity of distribution.

To test these hypotheses, elution of antibiotic from five premixed antibiotic loaded cements was compared with antibiotic release from five equivalent surgeon-mixed preparations. Four surgeon mixing methods were used.

Materials and Methods
Five AL-PMMA preparations:

1) Simplex® P 1 gram tobramycin (Stryker)
2) Palacos® R+G 500 mg gentamicin (Biomet)
3) Smart Set® GHV 1 gram gentamicin (Depuy)
4) Cobalt™ G-HV 500 mg gentamicin (Biomet)
5) Cemex® G 1 gram gentamicin (Teeres)

Four surgeon-mixing methodologies:

1) suspension of antibiotic powder in the liquid monomer
2) no mixing of antibiotic powder added to polymer powder
3) hand stirred antibiotic powder into polymer powder; one circle per second, five right alternating with five left for 30 seconds
4) commercial mixing bowl antibiotic powder mixed into polymer powder, one handle turn per second, five right alternating with five left for 30 seconds

Test specimens were cylinders of dimensions 6mm diameter x 12mm length (ASTM F 451-99) were made using a Teflon mold from each of the five cements using each of the four mixing methods and the equivalent premixed-preparations. The AL-PMMA was polymerized combining the polymer with the monomer by hand stirring in a bowl without vacuum. The AL-PMMA was introduced into a Teflon mold using a spatula with the PMMA in the dough phase.

Ten randomly selected cylinders were eluted individually in 5 ml of de-ionized water. Total exchange of the eluate was performed on days 1, 3, 7, 15, and 30. The antibiotic concentration in the eluate was measured using the Kirby-Bauer bioassay. The eluate from each test cylinder is a discrete sample from a random location in the cement batch which represents the homogeneity of the antibiotic distribution throughout the batch of AL-PMMA. The quantitative representation of homogeneity is the Coefficient of Variance of the performance of the specimens in each mix.

The data was subjected to statistical analysis using ANOVA with p<0.05 designated as the level of significance.

Results:
Although the total cumulative weight of recovered antibiotic at 30 days did vary from one cement to another, no single mixing method was consistently different from another or the premixed preparation for either cumulative weight of recovered antibiotic at 30 days or homogeneity of antibiotic distribution throughout the AL-PMMA.

The COV, Graph 1, was greatest (less homogeneous) for the mixing bowl method (p<.05), but was inconsistent with respect to relative magnitude, in some cements it out performed the average, and in some it underperformed.

Graph 1

Discussion:
We found that antibiotic powder distribution in bone cement based on elution of antibiotic from specimens of AL-PMMA throughout an individual mix was not meaningfully different between surgeon mixing methods or premixed preparations. Consistency between mixes is dependent on the skill of execution for the surgeon mixing methods. We made considerable effort to standardize the mixing method across cements and for prepare the test specimens. It is expected that this is more consistent than would be expected by operating room personnel but may be less consistent than conditions achieved in highly controlled commercial developmental and quality control testing. To avoid technology bias a commercial mixing bowl was not used for the polymerization mixing and this variable may have hidden some small differences. We believe that if present these differences in preparation between batches of cement are small.

We chose surgeon mixing methods that were expected to cover the spectrum of possibilities in the operating room. Suspension in the monomer caused completely even distribution prior to adding to the polymer and this was expected to be the best possible homogeneity but it turned out to be the most inconsistent. The only explanation apparent to us is that the polymer powder acted as a filter concentrating the antibiotic in a focal location in the AL-PMMA which then was not secondarily distributed well during the polymerization mixing. Interestingly when no attempt was made to mix the antibiotic powder into the polymer before the monomer was added, the result was not worse than the other mixing methods. Simply mixing the monomer in the polymer is sufficient to distribute the antibiotic load. ANOVA for Graph 1 indicates that mixing type is not a significant factor in determining the COV between cements (p>.05). Post Hoc t-testing for Graph 1 indicates that none of the mixes COV is statistically different from pre-mixed cement, with (p>.05). Hand stirring and using a commercial mixing bowl are the two methods mostly commonly used in clinical application. Our data show neither significantly improved release nor significantly less variability between commercially mixed cement and the surgeon mixed alternatives.

In conclusion the elution of antibiotic from surgeon-mixed antibiotic loaded bone cement is not inferior to commercially pre-mixed preparations for either total release or homogeneity of distribution.