Effect of hand mixing tobramycin on the fatigue strength of Simplex P

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In a recent study, we showed that the presence of gentamicin in Palacos R or erythromycin plus colistin in Simplex P bone cement did not significantly decrease the fatigue strength of the cement. [J. P. Davies, D.O. O'Connor, D.W. Burke, and W. H. Harris, "Influence of antibiotic impregnation on the fatigue life of Simplex P and Palacos R acrylic bone cements, with and without centrifugation," *J. Biomed. Mater. Res.*, **23**, 379–397 (1989)] However, the commercially prepared Palacos R with Gentamicin and AKZ (Simplex P with colistin and erythromycin) which were tested are not approved by the FDA for use in the United States. Because of this, many surgeons in the United States hand mix tobramycin with the cement in the operating room if a case calls for the use of antibiotic-impregnated cement. In this study, we determined the effect of adding 1.2 g of tobramycin to one pack (40 g) of Simplex P powder on the fatigue strength of the cement. The effect of centrifugation on the fatigue strength of Simplex P with the tobramycin added was also assessed. Simplex P was prepared according to the manufacturer's instructions with and without the addition of 1.2 g tobramycin per 40-g pack and with and without centrifugation. Fifteen specimens of each of the four cement preparations were tested in fully reversed tension-compression fatigue at ±15 MPa, 2 Hz. The fatigue strength of the uncentrifuged and centrifuged Simplex P was not significantly reduced by the tobramycin. Centrifugation significantly increased the fatigue life of Simplex P both with and without the addition of tobramycin. The fatigue life of the Simplex P with tobramycin was increased by a factor of 8 by centrifugation.

INTRODUCTION

The use of antibiotic-impregnated bone cements in the United States has not been approved by the FDA. However, many surgeons use bone cement containing tobramycin powder for revision surgery in septic or potentially septic total joint replacements.

There have been a number of studies which report the effect of antibiotic addition on the static mechanical properties of bone cement.[1-5] In one study, Bargar et al. found that the addition of tobramycin significantly reduced the three-point bending strength of bone cement.[6] Several studies from our laboratory have shown the importance of studying the fatigue rather than static mechanical properties of bone cement.[7-10] Clinically, the cement is cyclically

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loaded and would most likely fail in fatigue. Previously we studied the effect of antibiotic addition on the fatigue strength of Palacos R and Simplex P by testing Palacos Gentamicin (0.5 g per 40-g pack) and AKZ (Simplex P with 0.4 g colistin and 0.5 g erythromycin), both of which are commercially available in Europe.[10] The effect of porosity reduction by centrifugation on the fatigue properties of these cements was also assessed. These antibiotics did not significantly reduce the fatigue strength of the Palacos R or Simplex P. Centrifugation significantly increased the fatigue strength of Simplex P and AKZ but did not significantly increase the fatigue strength of Palacos R or Palacos Gentamicin.

This study examined the effect of adding tobramycin, which is commonly hand mixed with the cement at the time of surgery, on the fatigue life of Simplex P. The effect of centrifugation on this cement preparation was also assessed.

METHODS AND MATERIALS

One dose (1.2 g) of tobramycin powder (Nebcin)* was added to 40 g of Simplex P bone cement powder and carefully mixed by hand. When two packs of cement were to be prepared at the same time, the contents of two previously mixed bowls of 1.2 g. tobramycin/40 g cement powder were combined and the two packs were again carefully mixed together.

The uncentrifuged Simplex P cement was prepared following the manufacturer's instructions. One pack of cement, with or without the tobramycin, was mixed with the monomer at room temperature until the cement no longer adhered to the surgical glove (dough stage). The cement was then introduced into the Miller cement syringe.† In contrast, those batches of Simplex P, with and without the antibiotics, which were to be centrifuged were prepared by mixing with the monomer at 0°C for 75 s. The cement was then poured into the Miller cement syringe. The syringe was spun in an IEC HNS-II centrifuge‡ at 2400 rpm for 1 min. The uncentrifuged and centrifuged cements were then injected into a cylindrical Teflon mold which was open at both ends, using a Miller cement gun. One end of the mold was then capped to prevent leakage and the molds were placed into a 37°C water bath and allowed to cure for 20 min. No external pressure was applied during the molding or curing of the specimens. Five molds were filled per 40-g pack of cement. After curing, the specimens were machined on a computer-controlled lathe (Light Machines Corp.) into a fatigue test specimen. The machined specimen contained a waisted central portion with a gage length of 10 mm and 5 mm in diameter (Fig. 1). The fatigue test specimens were then soaked in a 37°C water bath for a minimum of 7 days before testing.

Fifteen specimens of each cement preparation were tested in fully reversed tension–compression fatigue on an MTS servohydraulic testing system. The

*Eli Lilly & Co., Indianapolis, IN.
†Zimmer Inc., Warsaw, IN.
‡International Equipment Co., Needham Heights, MA.

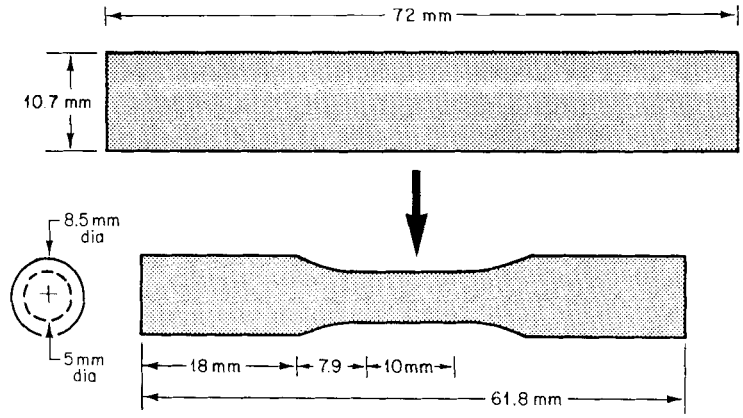

Figure 1. Schematic drawing of molded specimens and machined fatigue testing specimens.

specimens were tested under load control at ±15 MPa and a frequency of 2 Hz. The number of cycles to failure was recorded.

In addition to the Student's *t* test, Weibull distributions for survival probability were also used to analyze the data.[11] Survival probability of each specimen was determined from the failure order number (one is the shortest fatigue life, 15 is the longest). Fatigue life survival probability S (log N) was established using a two-parameter Weibull model of the form

$$S(\log N) = \exp\{-(\log N/\beta)^m\} \quad (1)$$

where N is the cycles to failure, and m and β are empirically determined constants. The values for m and β were obtained from a least-squares curve fit of the linearized form of Eq. (1).

RESULTS

Results of the fatigue tests are presented in Table I and the results of the Weibull analysis (Table II) are plotted in Figures 2 and 3. The *t*-test results show that when prepared in the standard fashion without centrifugation

TABLE I
Fatigue Test Results at ±15 MPa, 2 Hz

	Cycles to Failure (Mean ± SD)	
Uncentrifuged		
Without tobramycin	14,874 ± 32,024	NS
With tobramycin	7,890 ± 7,652	
Centrifuged		
Without tobramycin	75,768 ± 47,397	NS
With tobramycin	65,577 ± 51,441	

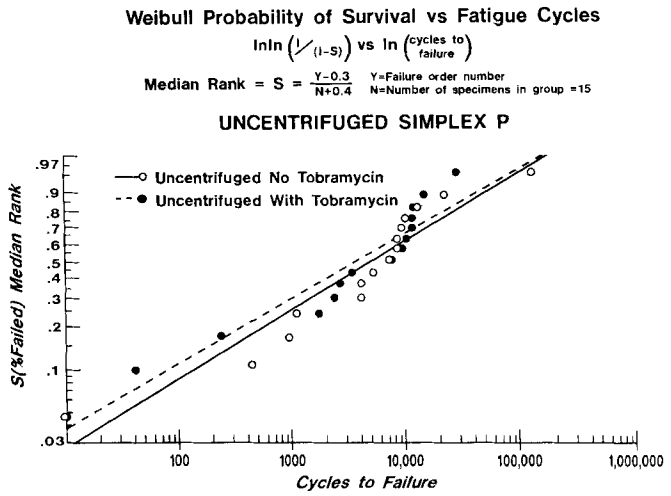

Figure 2. Diagram of fatigue life versus probability of survival for uncentrifuged Simplex P with and without tobramycin.

there was no significant decrease in the fatigue cycles to failure as a result of adding 1.2 g of tobramycin per 40-g pack of Simplex P.

While centrifugation of the cement immediately after mixing significantly increased the fatigue strength of the cement with and without the addition of antibiotics, there was no significant difference in fatigue cycles to failure of the centrifuged Simplex P with or without 1.2 g of tobramycin added per pack of cement.

These results were confirmed by the Weibull analysis. The data were plotted as S (probability of survival) versus log N in Figures 2 and 3. The regres-

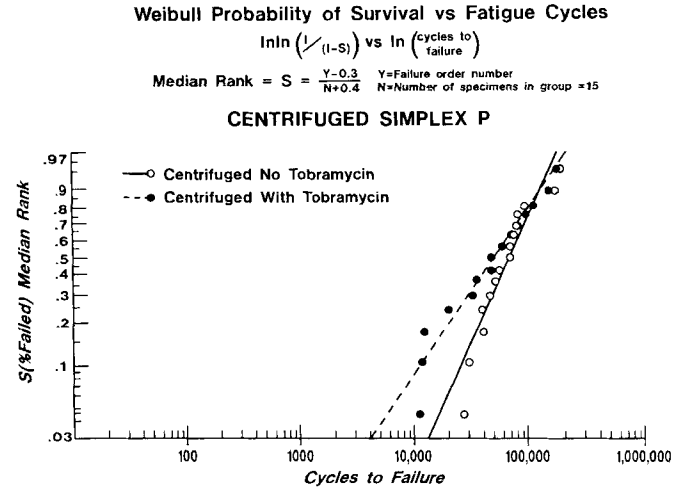

Figure 3. Diagram of fatigue life versus probability of survival for centrifuged Simplex P with and without tobramycin.

sion coefficients for lnln $(1/1 - S)$ versus ln N were at least 0.95 for all four cement preparations (Table II).

The Weibull mean fatigue life is dependent on the characteristic life (β) and the slope (m). The percentage failed at the mean is presented in Table II. The slope is a reflection of the amount of data scatter. The higher the slope, the less the data scatter. The Weibull analysis also gives the cycles at which 10% of the specimens have failed. This is important information because the objective of fatigue strength enhancing techniques is to selectively eliminate the very weak specimens.

Weibull statistical charts were used to determine significant differences. There was no significant difference ($p < 0.05$) in the Weibull mean fatigue lives of the uncentrifuged Simplex P with and without the addition of 1.2 g tobramycin added per 40 g of cement powder. The slope of the probability of survival versus cycles to failure for uncentrifuged Simplex P without tobramycin is just slightly higher than the Simplex P with tobramycin (Fig. 2). There was no significant difference in the two cement preparations for the number of the fatigue cycles that 10% of the specimens would fail.

All three of the Weibull parameters, the mean fatigue life, slope and 10% fatigue life were all significantly higher for the centrifuged Simplex P with and without tobramycin than the uncentrifuged Simplex P with and without tobramycin.

There was no significant difference in the Weibull mean fatigue life or the fatigue cycles that 10% of the specimens failed for the centrifuged Simplex P due to the addition of 1.2 g of tobramycin per 40-g pack. Also, the slope of the probability for survival versus cycles to failure was essentially unchanged for centrifuged Simplex P without the antibiotics compared to the centrifuged Simplex P containing the antibiotic (Fig. 3).

DISCUSSION

The fatigue test specimens were stored for a minimum of 7 days in a 37°C water bath. The actual storage time before testing ranged from 12 to 96 days

TABLE II
Weibull Analysis Results

	Slope	Regression Coefficient (R)	Percentage Failed at Mean (X100)	Weibull Mean Fatigue		10% Fatigue Life	
Uncentrifuged							
Without tobramycin	.51	.95	65	11814	NS	137	NS
With tobramycin	.48	.95	65	9193		72	
Centrifuged							
Without tobramycin	1.98	.95	54	82454	NS	27447	NS
With tobramycin	1.25	.97	60	67508		11849	

NS = not significantly different.

for the centrifuged specimens and 105–130 days for the uncentrifuged cement. Lawson et al. studied the elusion rate of tobramycin from bone cement after storage in 0.5*N* saline.[12] The antibiotic levels were 43.4 μg/mL on day 1, 0.5 μg/mL on day 7, and 0.4 μg/mL on day 28. Thus most of the tobramycin was eluded from the cement after 7 days. We do not believe the elusion rate would be seriously affected by storage in 37°C distilled water rather than 0.5*N* saline; therefore, the specimens in this study were tested after sufficient time for antibiotic elusion.

This study indicated that the fatigue life of Simplex P is not significantly reduced by adding 1.2 g of tobramycin per pack of Simplex P. This means that the surgeons in the USA have at their disposal a potent antibiotic which can be obtained in powder form and if mixed well with the Simplex P powder does not seriously compromise the fatigue strength of the cement.

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