

Antibiotic Impregnated Bone Cement in Total Hip Arthroplasty

An *In Vivo* Comparison of the Elution Properties
of Tobramycin and Vancomycin

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A prospective *in vivo* quantification was performed to measure the elution of tobramycin and vancomycin antibiotics from two commonly used bone cements. Forty patients were divided into four groups: Group I, tobramycin-Simplex; Group II, tobramycin-Palacos-R; Group III, vancomycin-Simplex; and Group IV, vancomycin-Palacos-R. Antibiotic levels were measured from hemovac wound drainage, urine, and serum and compared with control groups who received either intravenous tobramycin or vancomycin. There were no significant differences in daily mean tobramycin levels in hemovac samples between Groups I and II. Tobramycin hemovac levels from Groups I and II were significantly higher than the tobramycin control group. Similarly, no differences were seen in daily mean vancomycin levels of the hemovac samples between Group III and IV; however, the intravenous vancomycin control group had significantly higher levels in the hemovac fluid than Groups III or IV. Tobramycin in the hemovac fluid from Groups I and II was highly bioactive against the control organism. Vancomycin in the hemovac fluid from Groups III and IV had variable bioactivity against the control organism. In 30% of the cases, no vancomycin was detected in the hemovac fluid, and in these cases, the hemovac fluid had no

effect on the control organism. Tobramycin elutes to give adequate local tissue levels and releases antibiotic effects when used in an antibiotic bone cement combination. Vancomycin has variable elution properties and is not a predictable additive for the bone cements tested.

Infection after total joint arthroplasty remains one of the most significant and difficult complications to treat with variable functional results.^{3-7,9,13,15,16,23,30} Although new antibiotics have improved the treatment of infectious diseases in general, the emergence of resistant strains of gram-positive organisms, such as methicillin-resistant *staphylococcus aureus*, and gram-negative organisms continues to provide a challenge in management.

The efficacy and safety of gentamicin-impregnated cement has been reported in the European^{1,2,8,11,24,32,33} and the American literature.^{5,10,12,18,21,26,29,34} The Food and Drug Administration's nonapproval of manufactured antibiotic-cement mixtures leaves the surgeon to decide which antibiotic to mix with cement. Furthermore, the surgeon must decide on one of several types of cement, each with its own physical and mechanical properties. Therefore, it is important that the orthopaedic surgeon and infectious disease colleagues know which individual antibiotic will have adequate elution from a specific cement with retention of its bioactivity.

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The purpose of this prospective *in vivo* study was to quantitatively measure the elution of tobramycin and vancomycin antibiotics from two commonly used bone cements after cemented total hip arthroplasty (THA).

MATERIALS AND METHODS

Forty patients treated by cemented THA were divided into four groups. Two commercially available bone cements were used, Simplex with barium (Howmedica, Rutherford, New Jersey) and radiopaque Palacos-R (Richards, Memphis, Tennessee). The two antibiotic preparations were tobramycin powder and vancomycin powder.

Ten consecutive patients were in each group, and the groups were as follows: Group I, tobramycin-Simplex cement; Group II, tobramycin-Palacos-R cement; Group III, vancomycin-Simplex cement; and Group IV, vancomycin-Palacos-R cement. No patients in these groups received intravenous tobramycin or vancomycin.

Two control groups consisting of five patients per group received intravenous tobramycin (Control A) and intravenous vancomycin (Control B) alone. No patients in the control groups had antibiotics added to the bone cement.

The antibiotic-cement preparation was prepared by mixing the antibiotic powder (tobramycin or vancomycin) with the powdered methylmethacrylate. They were mixed in a bowl with a spatula. After thorough mixing of the powders for a minimum of two minutes, the liquid monomer was added and mixed in a standard fashion. The tobramycin and vancomycin dosage used was 1.2 g and 500 mg per 40-g package of cement, respectively.

A protocol was established to measure the following laboratory toxicity monitoring parameters preoperatively and on postoperative Day 7 in all patients: hematocrit, hemoglobin, white blood cell count, and differential cell count; prothrombin time; serum electrolytes, liver function tests (serum glutamic oxaloacetic transaminase, and serum glutamic pyruvic transaminase, alkaline phosphatase and lactic dehydrogenase); and renal function tests (serum creatinine and blood urea nitrogen), and urinalysis.

Samples were obtained from hemovac drainage, serum, and urine, six, 24, and 48 hours after surgery. Additionally, serum and urine samples were obtained on postoperative Day 7. These specimens were analyzed using fluorescence polarization immunoassay and were measured against control samples to assure accuracy. The results were recorded for the quantity of antibiotic pres-

ent in micrograms per milliliter. The low-end sensitivity of this technique was 0.18 $\mu\text{g/ml}$.

Control Group A received intravenous tobramycin with a loading dose of 1.5 mg per kilogram body weight followed by 1 mg per kilogram body weight every eight hours for 48 hours as prophylaxis. Control Group B received intravenous vancomycin in a dose of 500 mg every six hours for 48 hours as prophylaxis. Antibiotic levels (one hour after the intravenous antibiotic was infused) from the hemovac drainage, urine, and peak serum levels were obtained 24 hours postoperatively.

To determine the bioactivity of tobramycin and vancomycin, five samples at each period of collection from each of the four groups were analyzed simultaneously by a standardized bioassay and radioimmunoassay. The tube dilution bioassay was employed with twofold fluid dilutions using a selected *S. epidermidis* as a test organism (minimum inhibitory concentration, 0.2 $\mu\text{g/ml}$).

Antibiotic elution levels were measured in micrograms per milliliter ($\mu\text{g/ml}$). The mean \pm the standard error of the mean (SEM) is calculated. Statistical analysis was performed using the unpaired Student's *t*-test. Statistical significance was considered $p < 0.05$.

RESULTS

ANTIBIOTIC ELUTION TOBRAMYCIN

The mean (\pm SEM) tobramycin hemovac drainage levels in Group I (Simplex cement) versus Group II (Palacos-R cement) at six hours were 34.27 $\mu\text{g/ml} \pm 5.09$ versus 22.16 $\mu\text{g/ml} \pm 4.75$; at 24 hours, 14.27 $\mu\text{g/ml} \pm 4.03$ versus 10.80 $\mu\text{g/ml} \pm 1.60$; and at 48 hours, 3.84 $\mu\text{g/ml} \pm 1.66$ versus 8.12 $\mu\text{g/ml} \pm 1.85$ (Fig. 1). The hemovac drainage levels were approximately six and four times greater in Groups I and II, respectively, than the level of tobramycin in Control Group A (intravenous tobramycin) at 24 hours (average, 2.61 $\mu\text{g/ml} \pm 0.71$).

The mean tobramycin urine levels in Group I versus Group II at six hours were 17.59 $\mu\text{g/ml} \pm 6.56$ versus 14.76 $\mu\text{g/ml} \pm 3.35$; at 24 hours, 2.83 $\mu\text{g/ml} \pm 0.95$ versus 6.52 $\mu\text{g/ml} \pm 1.88$; at 48 hours, 2.58 $\mu\text{g/ml} \pm 0.54$ versus 1.55 $\mu\text{g/ml} \pm 0.36$; and at seven days, 1.24 $\mu\text{g/ml} \pm 0.46$ versus 0.70 $\mu\text{g/ml} \pm 0.24$ (Fig. 2). The mean urine tobramycin

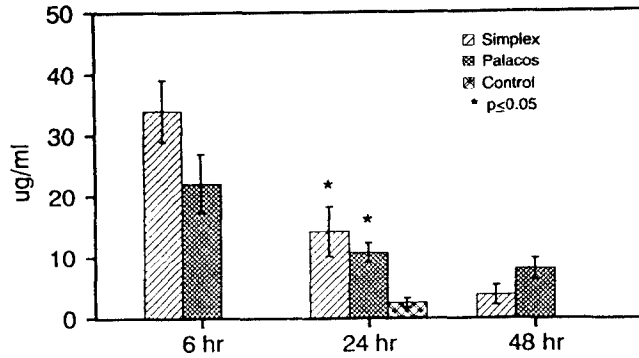


FIG. 1. Tobramycin levels in the hemovac drainage at specified postoperative intervals. Each value represents the mean \pm SD of the antibiotic level.

level in Control Group A at 24 hours was $44.1 \mu\text{g/ml} \pm 10.2$.

The mean tobramycin serum levels in Group I versus Group II at six hours were $0.60 \mu\text{g/ml} \pm 0.09$ versus $0.32 \mu\text{g/ml} \pm 0.07$; at 24 hours, $0.43 \mu\text{g/ml} \pm 0.04$ versus $0.21 \mu\text{g/ml} \pm 0.03$; at 48 hours, $0.40 \mu\text{g/ml} \pm 0.04$ versus $<0.18 \mu\text{g/ml}$; and at seven days, $0.39 \mu\text{g/ml} \pm 0.04$ versus $<0.18 \mu\text{g/ml}$ (Fig. 3). The mean serum level was $4.30 \mu\text{g/ml} \pm 0.54$ in Control Group A at 24 hours.

No significant differences were noted within each group for the serum or urine laboratory toxicity monitoring parameters measured preoperatively and at one week postoperatively.

ANTIBIOTIC ELUTION VANCOMYCIN

The mean vancomycin hemovac drainage levels in Group III (Simplex cement) versus Group IV (Palacos-R cement) at six hours

were $5.71 \mu\text{g/ml} \pm 2.07$ versus $5.48 \mu\text{g/ml} \pm 1.07$; at 24 hours, $2.46 \mu\text{g/ml} \pm 1.22$ versus $2.29 \mu\text{g/ml} \pm 0.64$; and at 48 hours, $2.31 \mu\text{g/ml} \pm 1.53$ versus $1.62 \mu\text{g/ml} \pm 0.59$ (Fig. 4). Vancomycin was below the detectable limits in 30% of the samples at 24 and 48 hours. The hemovac drainage levels in Groups III and IV were approximately one third the level of vancomycin in Control Group B (intravenous vancomycin) at 24 hours, which averaged $6.20 \mu\text{g/ml} \pm 1.31$.

The mean vancomycin urine levels in Group III versus Group IV at six hours were $2.43 \mu\text{g/ml} \pm 1.06$ versus $2.36 \mu\text{g/ml} \pm 0.87$; at 24 hours, $1.89 \mu\text{g/ml} \pm 0.76$ versus $1.49 \mu\text{g/ml} \pm 0.63$; at 48 hours, $1.33 \mu\text{g/ml} \pm 0.61$ versus $1.07 \mu\text{g/ml} \pm 0.44$; and at seven days, $<0.18 \mu\text{g/ml}$ versus $<0.18 \mu\text{g/ml}$ (Fig. 5). The mean urine vancomycin level in Control Group B at 24 hours was greater than $50 \mu\text{g/ml}$.

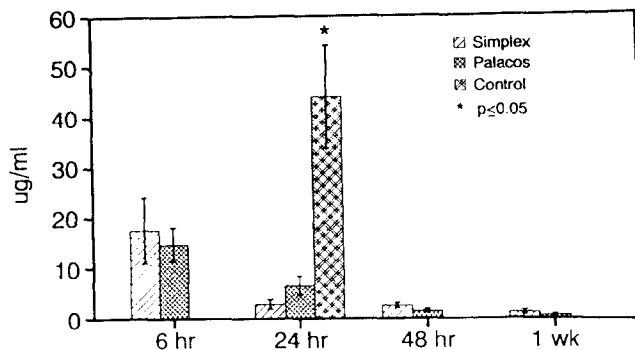
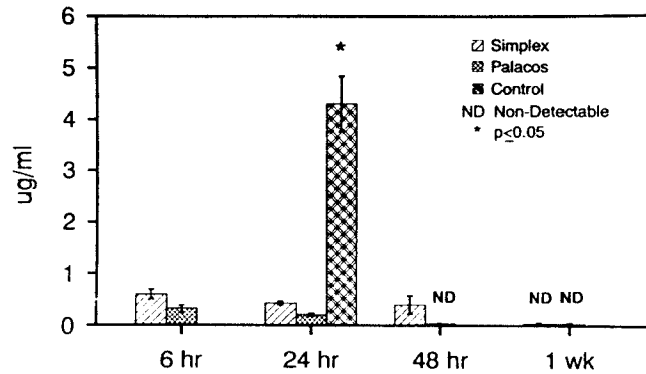


FIG. 2. Tobramycin levels (mean \pm SD) in the urine at specified postoperative levels.

FIG. 3. Tobramycin levels (mean \pm SD) in the serum at specified postoperative intervals.



The mean vancomycin serum levels in Group III versus Group IV at six hours were $0.74 \mu\text{g/ml} \pm 0.31$ versus $<0.18 \mu\text{g/ml}$; at 24 hours, $0.79 \mu\text{g/ml} \pm 0.31$ versus <0.18 ; at 48 hours, $0.84 \mu\text{g/ml} \pm 0.36$ versus $<0.18 \mu\text{g/ml}$; and at seven days, $<0.18 \mu\text{g/ml}$ versus $<0.18 \mu\text{g/ml}$ (Fig. 6). The mean serum level was $19.3 \mu\text{g/ml} \pm 1.61$ in Control Group B at 24 hours.

No significant differences were noted within each group for the serum or urine laboratory toxicity monitoring parameters measured preoperatively and at one week postoperatively.

ANTIBIOTIC BIOACTIVITY

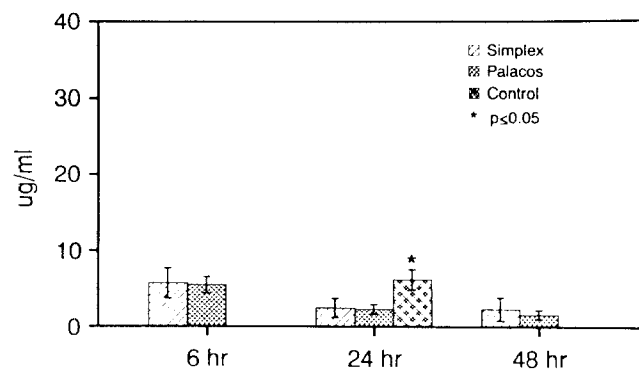
Tobramycin collected from the hemovac fluid retained its bioactivity against the *S. epidermidis* test organism in each sample tested. Vancomycin collected from the he-

movac fluid had variable bioactivity. Vancomycin was bioactive against the test organism from the six-hour samples; however, samples at 24 and 48 hours had vancomycin concentrations that were less than $4 \mu\text{g/ml}$ and were not bioactive.

DISCUSSION

For an antibiotic to be acceptable for mixing with bone cement in the operating room, it must be safe, thermostable, water-soluble, hypoallergenic, bactericidal with a broad spectrum of activity, and in powder form.²² The potential effects on the physical and mechanical properties of established antibiotic-cement mixtures have been well studied.^{11,14,17,18,20,28,31,36} The operative team must be cognizant of the need to thoroughly mix the powders to obtain as homogenous a mixture as possible to prevent alterations of the

FIG. 4. Vancomycin levels (mean \pm SD) in the hemovac drainage at specified postoperative intervals.



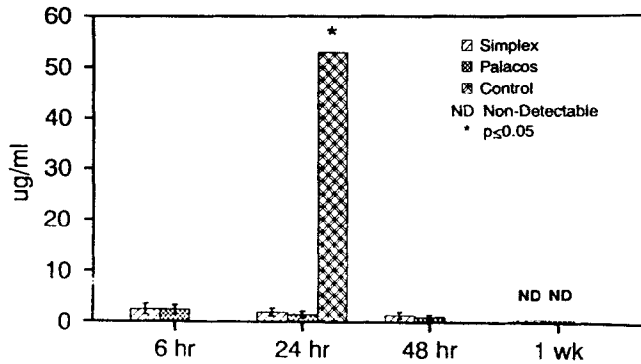


FIG. 5. Vancomycin levels (mean \pm SD) in the urine at specified postoperative intervals.

mechanical and elution properties. Tobramycin and vancomycin meet these criteria.

Some microorganisms are sensitive to tobramycin at minimum serum levels of 4 $\mu\text{g}/\text{ml}$ and to vancomycin at minimum serum levels of 4 $\mu\text{g}/\text{ml}$. In comparing the achieved mean hemovac drainage levels of tobramycin with those of vancomycin, effective tobramycin levels were achieved throughout the period of study and were achieved with vancomycin elution only at six hours.

The results of this study demonstrate that tobramycin is an excellent drug for addition to bone cement. High local levels of tobramycin with low systemic levels were achieved; therefore, this method of tobramycin delivery minimizes the risk of systemic effects from the antibiotic. Tobramycin levels were at least as high as other studies looking at the elution of gentamicin from bone cement and beads.^{19,26,27}

Organism sensitivity to an antimicrobial agent can vary widely even within the same antibiotic class. Tobramycin, for example, is more active *in vitro* against pseudomonas than gentamicin. Some gram-negative organisms may be resistant to tobramycin levels achieved in tissues and joint spaces when given intravenously. These same organisms may be sensitive to tobramycin at high local tissue concentrations. Therefore, the high local tobramycin levels delivered by using tobramycin impregnated cement result in a further need to reclassify organisms that were previously considered resistant and may further expand the indications for implantation after infected THA. It has previously been reported that recurrence of infection is higher with gram-negative bacteria than with gram-positive bacteria.^{2,4,6,16,27,35} The development of new antibiotics has extended the indications for reimplantation. The success or fail-

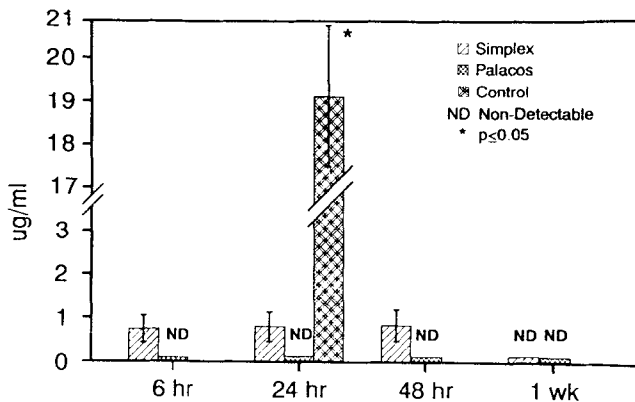


FIG. 6. Vancomycin levels (mean \pm SD) in the serum at specified postoperative intervals.

ure after reimplantation appears dependent to some degree on the organism's susceptibility to the antibiotic or antibiotic combinations. Sensitivity of bacteria is currently determined on the basis of effective serum levels. Most bacteria defined as resistant by this criteria might be sensitive when exposed to significantly high local tissue levels.²⁶ It might be more prudent not to base the prognosis for successful therapy on the gram-stain characteristics of the etiologic microorganism but rather to classify pathogens as sensitive or resistant based on the effectiveness of achievable local antibiotic tissue concentrations.^{25,26}

In contrast to other studies, which suggest that gentamicin elutes in greater concentrations from Palacos-R than Simplex cements,^{8,21,33} there is no statistical difference in the elution of tobramycin into the hip joint fluid from these two cements.¹⁷ Tobramycin is an excellent choice if the surgeon desires to use either cement. The critical factors in the treatment of any bone or joint infection are adequate surgical debridement, integrity of the host immune system, and adequate antibiotic levels. The use of antibiotic-impregnated cement does not replace the need for adequate surgical debridement in active infections.

Staphylococcus aureus and *S. epidermidis* remain the most frequent organisms infecting joint implants.²⁷ The development of resistant strains of *S. aureus* (including heterogeneous methicillin-resistant strains), *S. epidermidis*, and *Streptococcal* organisms (especially *Enterococcus*) is of concern and will continue to represent a significant problem in the future. Currently the drug of choice for many of these infections is intravenous vancomycin. Vancomycin alone is very active against these classes of bacteria, whereas aminoglycosides alone are not predictably effective.

Elution of vancomycin from Simplex and Palacos-R was suboptimal. The bioactivity of vancomycin was variable. In 30% of the cases, vancomycin levels were below the de-

tectable limits in each of the hemovac fluid samples. In these cases, the bioactivity was suboptimal. In a recent study by Lawson *et al.*,¹⁹ tobramycin and vancomycin showed similar elution properties *in vitro*. The disparity between the present *in vivo* study and their *in vitro* study is unclear; however, the laboratory is different from the *in vivo* setting where tissues, body fluids, bone, cement, and antibiotic must interact. Marks *et al.*²¹ employing *in vitro* methods demonstrated that oxacillin, gentamicin, and cefazolin diffused from Palacos in larger amounts and for a greater duration than from Simplex. However, in their *in vivo* study, there was no significant difference in the magnitude or duration of the concentrations of oxacillin in bone produced by a Palacos or Simplex composite. In the present study, vancomycin does not elute well *in vivo*.

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