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Systemic Absorption of Antibiotics From Antibiotic-Loaded Cement Spacers for the Treatment of Periprosthetic Joint Infection

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ABSTRACT

Background: Two-stage treatment of periprosthetic joint infections involves placement of high-dose antibiotic-loaded cement spacers (ACSs). Reports of ACS-induced nephrotoxicity have raised concern regarding systemic absorption of antibiotics after ACS placement. We sought to characterize the serum concentrations of antibiotics that occur after ACS placement.

Methods: We performed a prospective study of patients with an infected primary total hip (THA) or knee arthroplasty (TKA) treated with standardized ACSs with vancomycin, gentamicin, and tobramycin. Serum antibiotic levels were collected weekly for 8 weeks.

Results: Twenty-one patients (10 THA, 11 TKA) were included. Mean serum gentamicin levels ranged between 0.275±0.046 and 0.364±0.163 mg/L; mean serum tobramycin levels ranged from 0.313±0.207 to 0.527±0.424 mg/L; and mean serum vancomycin levels ranged from 5.46±6.6 to 15.34±9.6 mg/L. Serum antibiotic levels were detectable throughout the 8-week duration of ACS treatment. Regression analysis found that diabetes (coefficient 6.73, 95% CI 0.92-12.54, $P < .05$), blood urea nitrogen (coefficient 0.83, 95% CI 0.45-1.22, $P < .001$), number of cement doses (coefficient 3.71, 95% CI 0.76-6.66, $P < .05$), and use of systemic vancomycin (coefficient 6.24, 95% CI 2.72-9.75, $P < .001$) correlated with serum vancomycin levels. Patient age (coefficient −0.01, 95% CI −0.02 to 0, $P < .01$) and male sex (coefficient 0.20, 95% CI 0-0.41, $P < .05$) correlated with serum aminoglycoside level.

Conclusion: Systemic absorption of antibiotics from high-dose ACS persists for at least 8 weeks. Patients should be monitored closely for complications related to systemic absorption of antibiotics from ACS treatment.

Despite the advent of modern antisepsis protocols in total joint arthroplasty (TJA), the projected increase in TJA utilization will yield over 250,000 hip and knee periprosthetic joint infections (PJIs) annually by the year 2030 [1]. The projected PJI burden demands the development of safe and efficacious treatment protocols for PJI. Two-stage treatment of PJI, consisting of joint resection and insertion of a high-dose antibiotic-loaded cement spacer (ACS) followed by delayed reimplantation of components, is the current gold standard with reported failure occurring in <10% of cases in some series [2,3]. The delay between joint resection and reimplantation of components is typically at least 6 weeks [4]. Studies of antibiotic concentrations achieved within the joint from ACS treatment have shown high local concentrations that are often many times above the minimum inhibitory concentration and persist throughout the duration of ACS treatment [5–8].

Previous studies of systemic absorption of antibiotics from cement have found that systemic concentrations peak several

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hours after surgery and rapidly decrease within 1-2 days [9–11]. Several reports on use of antibiotic-impregnated cement in TJA have documented low rates of systemic toxicity [12–14]. The Infectious Diseases Society of America stated in published guidelines on the treatment of PJI that systemic toxicity from ACS treatment is rare [4].

More recently, reports have emerged of serious systemic toxicity related to use of ACS including acute kidney injury [15]. Menge et al [16] reported a 17% rate of nephrotoxicity after the placement of an ACS for the treatment of knee PJI. The high incidence of systemic toxicity in these series contradicts earlier reports of low systemic absorption of antibiotics from cement spacers. Moreover, a report by Aeng et al found that in the week after surgery, 22% of patients treated with ACS for PJI had serum tobramycin concentrations >2 mg/L, a known threshold for the risk of nephrotoxicity [17]. Given the conflicting evidence regarding systemic toxicity from use of ACS, we sought to investigate the systemic antibiotic concentrations that occur after the placement of an ACS for the treatment of PJI.

Materials and Methods

This study was a prospective study of patients with an infected primary hip or knee arthroplasty who underwent 2-stage treatment with joint resection and placement of an antibiotic-loaded polymethylmethacrylate spacer. Patients were recruited from a tertiary referral center between 2014 and 2016. ACSs were made using PALACOS R+G Bone Cement (Zimmer Biomet, Warsaw, IN), each pack of which contained 40 g of polymethylmethacrylate with 0.5 g of gentamicin. To each pack was admixed 3 g of vancomycin and 2.4 g of tobramycin. Cement spacers were made with between 2 and 4 packs of antibiotic cement; the exact amount used depended on patient size and the degree of bone loss. The decision to use a static or articulating spacer was based on the soft tissue status of the infected joint.

After surgery, patients underwent treatment for 6 weeks with culture-directed intravenous (IV) antibiotics under the direction of an infectious disease specialist. Patients were then given a 2-week antibiotic holiday followed by second-stage revision if laboratory and aspiration results were consistent with infection eradication. We excluded patients with allergies to vancomycin or aminoglycosides. We also excluded patients who received parenteral aminoglycoside therapy to allow for measurement of serum aminoglycoside levels attributable only to the ACS. We included patients who received parenteral vancomycin therapy, but tracked this variable to discern the impact of vancomycin in the ACS irrespective of systemic therapy.

Patients had weekly measurement of serum tobramycin, gentamycin, and vancomycin levels. For patients receiving systemic vancomycin, laboratory draws were performed as trough measurements. Patient characteristics including age, sex, race, body mass index, and diabetic status were documented. Mean serum concentrations of each antibiotic were calculated; vancomycin concentrations were calculated separately for the patients who did or did not receive systemic vancomycin treatment. At each weekly time point, the percentage of patients who had aminoglycoside or vancomycin levels above 2 mg/L or 15 mg/L, respectively, were calculated. These thresholds represent previously reported cutoffs above which the risk of nephrotoxicity increases [17,18]. In addition, regression models were fit to assess the relationship between patient characteristics, treatment variables, and the serum antibiotic levels. The level of significance was set at $P < .05$. Statistical analyses were performed using SAS statistical software (SAS Institute Inc, Cary, NC).

Table 1
Patient Characteristics.

Demographics	N = 21
Sex	
Male	13 (61.9)
Female	8 (38.1)
Race	
White	18 (85.7)
Other	3 (14.3)
Age, mean (SD), y	65.6 (13.6)
BMI, mean (SD), kg/m^2	32.2 (10.8)
Location	
Knee	11 (52.4)
Hip	10 (47.6)
Type of spacer	
Static	8 (38.1)
Articulating	13 (61.9)
Type of cement	
PALACOS R&G	21 (100)
Other	0
Number of doses of cement, mean (SD)	3.3 (0.6)
Discharged on IV antibiotics	
Vancomycin	9 (42.9)
Daptomycin	1 (4.8)
Penicillin G	1 (4.8)
Ceftriaxone	3 (14.3)
Cefazolin	5 (23.8)

BMI, body mass index; IV, intravenous; SD, standard deviation.

Results

We enrolled 22 patients in the study, and following application of exclusion criteria, the final analysis consisted of 21 patients (11 TKA and 10 THA). The mean age was 65.6 years and 62% were men. Eight received static spacers and 13 received articulating spacers. Patient characteristics are listed in Table 1. Mean weekly serum concentrations of gentamycin, tobramycin, and vancomycin were recorded for the 8-week duration of ACS treatment (Table 2 and Fig. 1). Mean serum gentamicin levels ranged between 0.275 ± 0.046 and 0.364 ± 0.163 mg/L; mean serum tobramycin levels ranged from 0.313 ± 0.207 to 0.527 ± 0.424 mg/L; and mean serum vancomycin levels ranged from 5.46 ± 6.6 to 15.34 ± 9.6 mg/L. Serum antibiotic levels were detectable throughout the 8-week duration of ACS treatment.

Vancomycin levels were also recorded separately for those who did or did not receive systemic vancomycin (Table 3 and Fig. 2). Serum vancomycin levels were higher in patients treated with systemic vancomycin (range 8.35-21.5 mg/L), but remained detectable in those without systemic treatment (range 1.8-14.38 mg/L).

The percentage of patients who reached nephrotoxicity threshold concentrations is reported in Table 4. No patients had recorded aminoglycoside levels above the nephrotoxicity threshold (2 mg/L) during the study. Depending on the week, between 14.3%

Table 2
Serum Antibiotic Concentrations.

	Vancomycin, Ug/mL, Mean (SD)	Tobramycin, Ug/mL, Mean (SD)	Gentamicin, Ug/mL, Mean (SD)
Week 1	16.97 (3.6)	0.27 (0.10)	0.30 (0)
Week 2	14.64 (9.5)	0.35 (0.08)	0.28 (0.05)
Week 3	11.80 (8.0)	0.41 (0.18)	0.33 (0.14)
Week 4	9.90 (8.3)	0.39 (0.14)	0.34 (0.14)
Week 5	10.11 (7.9)	0.32 (0.21)	0.40 (0.15)
Week 6	10.80 (8.5)	0.38 (0.15)	0.32 (0.16)
Week 7	5.54 (6.5)	0.30 (0.20)	0.38 (0.13)
Week 8	10.32 (10.2)	0.59 (0.58)	0.30 (0)

SD, standard deviation.