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Acute Kidney Injury With Tobramycin-Impregnated Bone Cement Spacers in Prosthetic Joint Infections

Elissa S. Y. Aeng, BSc (Pharm), ACPR[1], Karen F. Shalansky, PharmD, FCSHP[2], Tim T. Y. Lau, PharmD, ACPR, FCSHP[2], Nadia Zalunardo, MD, FRCP(C), SM (Epi)[2], Guiyun Li, MPH, MSc[2], William R. Bowie, MD, FRCP(C)[2], and Clive P. Duncan, MD, FRCS(C)[2]

Abstract

Background: Antibiotic-impregnated bone cement spacer (ACS) with tobramycin ± vancomycin is commonly used in a 2-stage replacement of infected prosthetic joints. This procedure has been associated with development of acute kidney injury (AKI). **Objective:** To determine the incidence and risk factors for AKI after implantation of tobramycin-impregnated ACS. **Methods:** This prospective, observational study evaluated 50 consecutive patients who received tobramycin ACS for first-stage revision of an infected hip or knee arthroplasty from August 2011 to February 2013. AKI was defined as 50% or greater rise in serum creatinine (SCr) from baseline within the first 7 postoperative days (PODs). **Results:** The incidence of AKI was 20%, with median onset occurring at POD 2 (interquartile range [IQR] = 1-3); patients with AKI had a longer median duration of hospital stay (16 days, IQR = 12-17, vs 10 days, IQR = 8-10; $P = 0.03$). Serum tobramycin concentrations were significantly higher in the AKI group, peaking on POD 1 (median 1.9 vs 0.9 µg/mL, $P = 0.01$). Risk factors for nephrotoxicity identified by multivariate analysis were use of bone cement premanufactured with gentamicin (OR = 8.2; 95% CI = 1.1-60; $P = 0.04$), administration of blood transfusions intraoperatively (OR = 32.5; 95% CI = 2.3-454.3; $P = 0.01$) and nonsteroidal anti-inflammatory drugs postoperatively (OR = 23.0; 95% CI = 1.3-397.7; $P = 0.03$). **Conclusions:** Tobramycin ACS is associated with a high risk of AKI. Measures to minimize AKI risk in the perioperative period include early detection through close monitoring of SCr, avoiding use of premanufactured bone cement containing gentamicin, and avoiding potential nephrotoxins within the first 72 hours postoperatively.

Keywords

aminoglycosides, vancomycin, bone/joint disorders, drug delivery, surgery, infectious diseases, nephrotoxicity, orthopedics

Introduction

Infection of prosthetic joint arthroplasties occurs at an incidence rate of 0.5% to 3%, with the majority of infections caused by *Staphylococcus* species.[1,2] Standard of care for treatment of an infected joint arthroplasty is a 2-stage replacement procedure.[1] In stage 1, an articulating antibiotic-impregnated bone cement spacer (ACS) is inserted into the joint space, followed by a 6-week course of systemic antibiotics; in stage 2, the spacer is replaced by permanent implants. ACS provides direct delivery of antibiotics with high local concentrations in the periprosthetic space and fluid while preserving patient mobility and facilitating reimplantation surgery by maintaining the soft-tissue planes after debridement.[1-3] An aminoglycoside and vancomycin together are commonly added to ACS, both of which have been shown to elute into joint spaces with minimal systemic concentrations.[2,4-6]

Whereas several studies have demonstrated the efficacy of ACS, there are few published reports regarding its safety.[1,2] A recent retrospective trial and several case reports have reported acute kidney injury (AKI) associated with the use of ACS.[7-9] An observational, retrospective study of 84 patients with infected knee arthroplasties reported a 17% incidence of AKI.[7] Spacers contained primarily tobramycin (94%) and vancomycin (82%), and serum antibiotic concentrations were not measured. Development of AKI has been associated with increased length of hospital stay,

[1]Surrey Memorial Hospital, Surrey, BC, Canada
[2]Vancouver General Hospital, Vancouver, BC, Canada

Corresponding Author:
Dr. Karen F. Shalansky, Department of Pharmaceutical Sciences, Vancouver General Hospital, 855 West 12th Avenue, Vancouver, BC V5Z 1M9, Canada.
Email: karen.shalansky@vch.ca

mortality, and cost and is a risk factor for progression to chronic kidney disease (CKD).[10,11]

Our hospital is a tertiary referral centre for treatment of infected prosthetic joints. Anecdotally, we had observed cases of AKI associated with surgeries involving ACS with tobramycin. The purpose of this study was to 1) determine incidence of AKI in the immediate 7-day post-operative period among patients with infected knee or hip arthroplasties receiving a first-stage ACS revision with tobramycin; 2) assess tobramycin serum concentrations after implantation of ACS; and 3) evaluate risk factors associated with AKI.

Methods

Study Population

This was a prospective, observational study of 50 consecutive patients ≥18 years old who received insertion of ACS with tobramycin powder (SteriMax, Mississauga, Ontario, Canada) ± vancomycin powder (PPC, Richmond Hill, Ontario, Canada) in polymethylmethacrylate (PMMA) bone cement for first-stage revision of an infected hip or knee arthroplasty from August 2011 to February 2013. Exclusion criteria were hemodialysis dependence or development of AKI prior to surgery. This study was approved by our institutional ethics board and research institute.

Data Collection

Baseline serum creatinine (SCr) and hemoglobin (Hgb) were collected preoperatively, on postoperative day 1 (POD 1; 24 hours postoperatively), and on PODs 3, 5, and 7 (mornings). Baseline SCr was calculated by averaging the 2 most recent values within 1 year preoperatively; the corresponding estimated glomerular filtration rate (eGFR) was determined using the Modification of Diet in Renal Disease (MDRD) equation: $175 \times (SCr)^{-1.154} \times (Age)^{-0.203} \times (0.742$ if female) $\times (1.210$ if black).[12] A 1-year time frame was chosen for determining baseline SCr because SCr was not assessed routinely preoperatively. Of note, median baseline SCr values were the same whether assessed at 3, 6, or 12 months from baseline (0.86 mg/dL). Tobramycin and vancomycin serum concentrations were drawn similarly to SCr on PODs 1, 3, 5, and 7 for quality assurance. Patients were allowed to receive systemic antibiotics postoperatively based on culture results. When patients received vancomycin in their bone cement, serial vancomycin concentrations were only recorded if concomitant intravenous (IV) vancomycin was not received. SCr was also recorded 2 to 6 months later, prior to the stage-2 procedure. Drug concentrations were determined on the Siemens Vista analyzer using PETINA (enhanced turbidometric immunoassay); the lowest level of detection for tobramycin is 0.3 ± 0.1 μg/mL and for vancomycin is 0.8 ± 0.24 μg/mL.

AKI was defined as an increase in SCr ≥50% from baseline within 7 days postoperatively.[13] Staging of AKI was determined from the peak postoperative SCr value using Acute Kidney Injury Network (AKIN) criteria[13]:

AKIN stage 1: SCr increase to ≥150% to 200% from baseline
AKIN stage 2: SCr increase to >200 to 300% from baseline
AKIN stage 3: SCr increase to >300% from baseline

Other baseline data included patient demographics, use of nephrotoxic drugs, systemic antibiotics given within 2 months preoperatively, and comorbidities (hypertension, sepsis, diabetes mellitus, congestive heart failure, Hgb <10 g/dL, and eGFR <60 mL/min/1.73 m^2). Length of hospital stay, complications, blood transfusions, and administration of potentially nephrotoxic drugs and systemic antibiotics were recorded postoperatively. Culture results from blood, tissue, and joint fluid were collected up to 6 months prior to surgery.

Outcome Measures

Primary outcomes were to (1) determine the incidence of AKI at POD 7 and (2) determine whether tobramycin serum concentrations reached values above 2 μg/mL between PODs 1 and 7.

Secondary outcomes were to assess (1) vancomycin serum concentrations postimplantation of vancomycin-impregnated bone cement; (2) risk factors associated with AKI; (3) time course for the development of AKI; (4) causative pathogens associated with prosthetic joint infections; and (5) length of hospital stay.

Statistical Methods

Quantitative variables were reported as medians and interquartile ranges (IQRs), other than age and weight, which were summarized as means and SDs. Categorical variables were reported as frequencies and percentages. Univariate analysis comparing patients with and without AKI were performed using the *t* test or Wilcoxon signed-rank test, as appropriate, for quantitative variables and Fisher's exact test for categorical variables. Results from the univariate analysis were used to identify variables for a stepwise multivariate logistic model. Variables with *P* values ≤0.1 between patients with or without AKI in the univariate analysis were included in the multiple logistic regression. Patients with serum concentrations of tobramycin <0.3 μg/mL and vancomycin <0.8 μg/mL were assigned a value of 0.3 and 0.8 μg/mL, respectively, for analysis.

All statistical tests were 2 tailed, and *P* values <0.05 were considered significant. SAS version 9.3 was used for statistical analysis (SAS Institute Inc, NC, USA).

Table 1. Baseline Patient Demographics.

Characteristic	n = 50
Age, years, mean ± SD	66.0 ± 13.0
Weight, kg, mean ± SD	82.8 ± 18.4
Gender, male, n (%)	27 (54)
Comorbidity, n (%)	27 (54)
Hypertension	19 (38)
Congestive heart failure	1 (2)
Diabetes	7 (14)
eGFR < 60 mL/min/1.73 m^2	12 (24)
Hemoglobin < 10 g/dL	4 (8)
Nephrotoxin preoperative, n (%)	25 (50)
ACE inhibitor or ARB	16 (32)
NSAID	10 (20)
Sulfamethoxazole and Trimethoprim	3 (6)
SCr, mg/dL, median (IQR)	0.86 (0.79-1.01)
eGFR, mL/min/1.73 m^2, median (IQR)	76.1 (60.9-91.9)
Hemoglobin, g/dL, mean ± SD	11.9 ± 1.8
Blood transfusion intraoperative, n (%)	10 (20)

Abbreviations: ACE, angiotensin-converting-enzyme; ARB, angiotensin II receptor blocker; eGFR, estimated glomerular filtration rate; IQR, interquartile range; NSAID, nonsteroidal anti-inflammatory drug; SCr, serum creatinine.

Results

A total of 54 consecutive patients were screened: 4 were excluded because they received a modified procedure (n = 2), developed AKI prior to the procedure (n = 1), and were hemodialysis dependent (n = 1). This resulted in 50 enrolled patients: 32 hip revisions and 18 knee revisions. At POD 7, 45 (90%) patients remained in the study.

Baseline characteristics are shown in Table 1. Two preoperative SCr concentrations were available in 70% of patients. The mean percentage difference between the preoperative and the next most recent value was −1.69% ± 8.4%. Of 12 patients with eGFR <60mL/min/1.73 m^2, only one had an eGFR <30 mL/min/1.73 m^2. Prior to admission, one-third of patients were taking an angiotensin-converting enzyme (ACE) inhibitor or angiotensin-II receptor blocker (ARB), and 20% received a nonsteroidal anti-inflammatory drug (NSAID). Blood transfusions were required intraoperatively in 20% of patients.

The PMMA bone cement used was either plain Palacos (Palacos R or Palacos LV, Heraeus Medical, Germany, n = 34) or Palacos premanufactured with gentamicin 0.5 g/40 g cement (n = 16, Palacos R+G, Heraeus Medical, Germany). The median dose of tobramycin added was 3.6 g (range = 2.4-4.8 g) per 40 g PMMA cement, and 92% of patients also received vancomycin at a median dose of 1.5 g (range = 1.5-3g) per 40 g PMMA; patients received a median of 2 packages of cement (range = 1-4) per operation. There were no differences in doses of tobramycin, vancomycin, or gentamicin in bone cement administered to AKI versus non-AKI patients.

Table 2. Major Outcomes.

	AKI (n = 10)	Non-AKI (n = 40)	*P* Value
AKIN stage, n (%)			
1	5 (50)	—	
2	2 (20)	—	
3	3 (30)	—	
Day AKI first occurred, median (IQR)	2 (1-3)	—	
Length of hospital stay, days, median (IQR)	16.0 (12-17)	10 (8-10)	0.03
Tobramycin serum levels, µg/mL, median (IQR)			
POD 1	1.9 (1.3-2.8)	0.9 (0.4-1.6)	0.01
POD 3	1.4 (0.8-1.9)	<0.3 (<0.3-0.6)	0.001
POD 5	1.0 (0.7-1.2)	<0.3 (<0.3-0.5)	0.004
POD 7	0.8 (0.4-1)	<0.3 (<0.3-0.4)	0.02
Vancomycin serum levels, µg/mL, median (IQR)			
POD 1	<0.8 (<0.8-1.1)	<0.8 (<0.8-1)	0.19
POD 3	<0.8 (<0.8-0.9)	<0.8 (<0.8)	0.27
POD 5	<0.8 (<0.8)	<0.8 (<0.8)	0.74
POD 7	<0.8 (<0.8)	<0.8 (<0.8)	0.58

Abbreviations: AKI, acute kidney injury; AKIN, Acute Kidney Injury Network Classification; IQR, interquartile range; POD, postoperative day.

Patient outcomes are listed in Table 2. In all, 10 patients (20%) developed AKI. All cases occurred within the first 72 hours postoperatively, with a median onset of 2 days. Three AKI patients had stage 3 AKIN scores, of whom one required hemodialysis from PODs 5 to 13. This patient was switched from IV cloxacillin to vancomycin on POD 3 because of the possibility of cloxacillin-induced acute interstitial nephritis. Renal biopsy was not performed to confirm diagnosis. AKI patients had longer median length of hospital stay when compared with non-AKI patients (16 vs 9.5 days, $P = 0.03$).

Median baseline SCrs were similar in the AKI and non-AKI groups (0.89 vs 0.85 mg/dL, $P = 0.98$). Figure 1 illustrates the median percentage change of SCr from baseline. For AKI patients, median SCr peaked on POD 5 at 1.86 mg/dL (IQR = 1.26-3.12). Median SCr taken prior to the stage 2 procedure (2-6 months later, n = 45) was similar to baseline (0.95 vs 0.87 mg/dL baseline, $P = 0.2$). For patients who developed AKI and had follow-up SCr available (n = 8, 80%), median percentage change in SCr from baseline was 12.6% (IQR = 4.9-28.3) compared with 7.2% (IQR = 0-17.2) for non-AKI patients (n = 36). In the patient who required hemodialysis, SCr decreased from a peak of 8.26 mg/dL on POD 5 to 1.08 mg/dL 12 weeks later (similar to his baseline value).

Antibiotic Serum Concentrations

Tobramycin serum concentrations reached >2 µg/mL in 40% of AKI and 17.5% of non-AKI patients. Concentrations were significantly higher in patients experiencing AKI, with peak concentrations occurring on POD 1 (median = 1.9 µg/

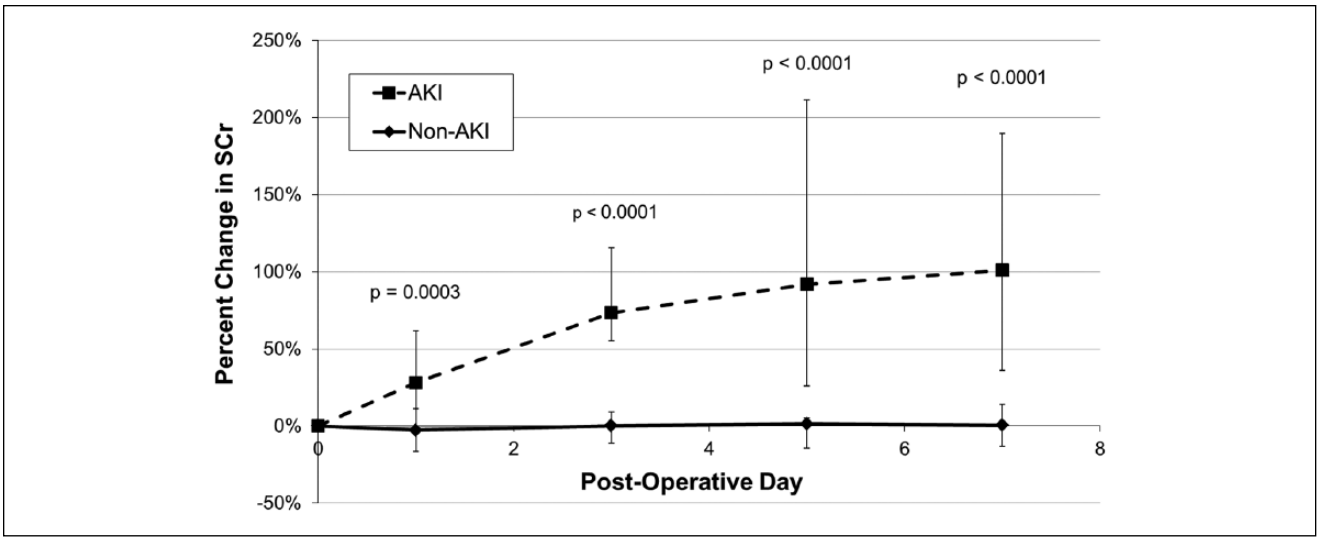

Figure 1. Median percentage change of SCr from baseline.
Abbreviations: AKI, acute kidney injury; SCr, serum creatinine.

mL in AKI vs 0.9 µg/mL non-AKI patients; $P = 0.01$; Table 2). The highest value recorded was 9.5 µg/mL on POD 1 in the patient who developed AKI and required hemodialysis. In non-AKI patients, median tobramycin concentrations were undetectable following POD 1. Of 46 patients who had vancomycin added to their bone cement, vancomycin concentrations were collected for 24 patients who were not concomitantly on IV vancomycin. All serum vancomycin concentrations were low, with the majority reported as <0.8 µg/mL. The highest value recorded was 2.7 µg/mL in an AKI patient on POD 1. There was no difference between serum vancomycin concentrations in patients with or without AKI.

Risk Factors for AKI

Univariate analysis (Table 3) revealed that patients who experienced nephrotoxicity were more likely to receive premanufactured bone cement containing gentamicin ($P = 0.06$), blood transfusions intraoperatively ($P = 0.09$), and NSAIDs postoperatively ($P = 0.08$). The dose of antibiotics (tobramycin, vancomycin, and gentamicin) in bone cement was not predictive of AKI; neither was preoperative administration of potential nephrotoxins (ie, ACE inhibitor/ARBs, NSAIDs), nor postoperative administration of IV vancomycin or ACE inhibitors/ARBs. A multivariate analysis controlling for baseline eGFR confirmed that gentamicin in premanufactured bone cement (OR = 8.2; 95% CI = 1.1-60; $P = 0.04$), intraoperative blood transfusions (OR = 32.5; 95% CI = 2.3-454.3; $P = 0.01$), and administration of postoperative NSAIDs (OR = 23.0; 95% CI = 1.3-397.7; $P = 0.03$) were risk factors for nephrotoxicity.

Antibiotics/Cultures

In all, 28% of patients received one or more systemic antibiotics within 2 months prior to surgery. Preoperative antibiotics included β-lactams (n = 5), vancomycin (n = 5), quinolones (n = 4), rifampin (n = 3), sulfamethoxazole and trimethoprim (n = 2), and clindamycin (n = 2). Postoperatively, all patients were administered one or more systemic antibiotics (primarily cephalosporins, vancomycin, and rifampin). Positive cultures were identified in 72% of patients. Five patients grew 2 organisms. Pathogens included coagulase-negative staphylococci (CNS, n = 10), methicillin-sensitive *Staphylococcus aureus* (MSSA, n = 11), *Enterococcus* sp. (n = 4), methicillin-resistant *Staphylococcus aureus* (MRSA, n = 2), other Gram-positive organisms (n = 9), and Gram-negative organisms (n = 5). Of 14 patients who received antibiotics within 2 months prior to surgery, 8 had positive intraoperative cultures that were sensitive to their preoperative antibiotic, and 6 had no documented growth.

Other Adverse Outcomes

Three adverse events occurred. One patient experienced a myocardial infarction postoperatively. One patient had an above-knee amputation of the infected joint on POD 10, prolonging length of stay to 26 days. There was also 1 death in a patient who developed AKI. This patient's renal function, however, normalized to baseline by POD 11, and cause of death was attributable to multiorgan failure with sepsis on POD 62.

Discussion

In this prospective, observational study, the incidence of AKI in patients undergoing ACS insertion for infected hip

Table 3. Univariate Analysis for Nephrotoxicity.

Variable	AKI (n = 10)	Non-AKI (n = 40)	*P* Value
Age, years, mean ± SD	68.9 ± 9.9	65.2 ± 13.6	0.43
Weight, kg, mean ± SD	81.8 ± 26.1	83.1 ± 16.4	0.85
Gender, male, n (%)	3 (30)	24 (60)	0.15
SCr, mg/dL, median (IQR)	0.90 (0.76-1.10)	0.86 (0.81-0.99)	0.98
eGFR, mL/min/1.73m2, median (IQR)	72.4 (66.7-79.5)	81.0 (60.0-92.9)	0.48
Hemoglobin, g/dL, mean ± SD	12.0 ± 1.5	11.8 ± 1.9	0.74
Comorbidity, n (%)	6 (60)	21 (52)	0.73
Hypertension	4 (40)	15 (38)	1.0
Congestive heart failure	0 (0)	1 (2)	1.0
Diabetes	0 (0)	7 (18)	0.32
eGFR < 60 mL/min/1.73 m^2	2 (20)	10 (25)	1.0
Hemoglobin < 10 g/dL	0 (0)	4 (10)	0.57
Blood transfusions, n (%)			
Intraoperative[a]	4 (40)	6 (15)	0.09
PODs 1-7	4 (40)	12 (30)	0.71
Potential nephrotoxins, n (%)			
ACE inhibitor or ARB preoperative	5 (50)	11 (28)	0.26
ACE inhibitor or ARB postoperative	4 (40)	10 (25)	0.44
NSAIDs preoperative	2 (20)	8 (20)	1.00
NSAIDs postoperative[a]	8 (80)	19 (48)	0.08
Vancomycin IV postoperative	7 (70)	18 (45)	0.29
Gentamicin in bone cement,[a] n (%)	6 (60)	10 (25)	0.06
Organisms identified, n (%) patients			
MRSA	0	2 (5)	1.0
MSSA	4 (40)	7 (17.5)	0.2
Coagulase-negative *Staphylococcus*	1 (10)	9 (22.5)	0.66
Other Gram positives	2 (20)	11 (27.5)	1.0
Gram negatives	1 (10)	4 (10)	1.0

Abbreviations: ACE, angiotensin-converting-enzyme; AKI, acute kidney injury; ARB, angiotensin II receptor blocker; eGFR, estimated glomerular filtration rate; IQR, interquartile range; IV, intravenous; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-sensitive *Staphylococcus aureus*; NSAID, nonsteroidal anti-inflammatory drug; POD, postoperative day; SCr, serum creatinine.
[a]Variables included in the multivariate logistic regression.

or knee arthroplasty was 20%. Patients with AKI had significantly longer median duration of hospital stay compared to non-AKI patients (16 vs 10 days, $P = 0.03$). Additionally, AKI patients had significantly higher tobramycin serum concentrations on all PODs, with median peak concentrations occurring on POD 1 (AKI 1.9 µg/mL vs non-AKI 0.9 µg/mL, $P = 0.01$). Independent risk factors for development of AKI were use of bone cement premanufactured with gentamicin ($P = 0.04$), administration of intraoperative blood transfusions ($P = 0.01$), and use of NSAIDs postoperatively ($P = 0.03$).

The incidence of AKI in this study is comparable to that in a recent retrospective study that found a 17% incidence in 84 patients who received ACS impregnated primarily with tobramycin and vancomycin for infected total knee arthroplasties.[7] Their definition of AKI was an increase of at least 50% in SCr from baseline to a level above 1.4 mg/dL within 90 days postoperatively. In this trial, SCr peaked on POD 30 and remained elevated until POD 90 in patients who developed AKI. The AKI criteria aligned closely with our definition, but the follow-up period was longer. We, however, found that in patients who developed AKI, SCr prior to stage 2 revision (measured 2-6 months later) fell to within baseline values in most patients. Kalil et al[14] observed a 35% incidence of AKI in 17 patients receiving tobramycin-impregnated ACS with follow-up until hospital discharge (mean 11.1 ± 6.9 days). AKI was defined as SCr increase from a baseline value of ≥0.3 mg/dL. This was a lower threshold definition of AKI than ours, and no patient in this trial had a ≥50% rise in SCr from baseline within the first 7 PODs (definition from our study). Of interest, as a quality assurance initiative, we prospectively followed 69 consecutive patients undergoing routine noninfected hip arthroplasty from August 2012 to February 2013. None of these patients received ACS. We found a significantly lower incidence of AKI in the routine noninfected arthroplasty

group compared with our ACS group (4.3% vs 20%, $P = 0.01$) as well as shorter hospital stay (median = 5 days, IQR = 4-8, vs 10.5 days, IQR = 8-16; $P = 0.0001$).

The purpose of adding antibiotics directly into bone cement is to obtain high local antibiotic concentrations at the site of infection, with minimal systemic concentrations.[4,6,14] Local implantation of tobramycin provides bactericidal activity against common Gram-negative organisms and methicillin-sensitive staphylococci and provides high periprosthetic concentrations that are effective against strains not susceptible to systemic antibiotics.[4,15] A pharmacokinetic study in 10 patients assessing release characteristics of tobramycin 1 to 2.2 g/40 g PMMA bone cement showed high mean tobramycin concentrations of 103 μg/mL in drainage fluid at 1 hour after insertion, declining to 15.1 μg/mL after 48 hours.[4] In contrast, mean serum tobramycin concentrations were consistently low, peaking at 0.94 μg/mL at 3 hours and decreasing to 0.2 μg/mL by 48 hours.

With traditional aminoglycoside dosing of 1.5 to 2 mg/kg IV every 8 hours, trough concentrations >2 μg/mL have been associated with a higher incidence of nephrotoxicity, and peak concentrations above 4 μg/mL are considered therapeutic.[16] In our study, we found elevated serum tobramycin concentrations >2 μg/mL primarily in patients who developed AKI. Tobramycin 3.6 g and vancomycin 1.5 g were most commonly added to 40 g of PMMA bone cement, which is consistent with current doses reported in the literature.[1,7,15] The highest tobramycin level detected was 9.5 μg/mL, occurring on POD 1, and levels remained above 4 μg/mL for the entire study period; this patient developed AKI and required hemodialysis. Whereas smaller studies using lower tobramycin doses in ACS reported minimal serum tobramycin concentrations following ACS implantation or no difference in concentrations in patients with or without renal dysfunction,[4,5] recent case reports have shown high aminoglycoside serum concentrations comparable to ours.[3,17] A recent case series of 10 patients experiencing AKI with placement of ACS containing a mean tobramycin dose of 8.2 g found detectable serum tobramycin concentrations in all patients, ranging from 0.1 to 19.6 μg/mL.[17] A possible explanation for higher serum tobramycin concentrations is the use of generic tobramycin. In 2009, our hospital formulary changed from proprietary to generic tobramycin. Generic forms of tobramycin may have different characteristics from the proprietary brand (Eli Lily, Canada) used in previous studies.[2] Generic tobramycin is composed of larger, less-compact particles, resulting in elution of generic tobramycin from the PMMA matrix at least twice as fast because of larger pores, greater permeability, and faster diffusion.[18] Thus, increased systemic tobramycin concentrations may occur, enhancing the risk of AKI.

Vancomycin is often combined with tobramycin in bone cement to provide broader Gram-positive coverage for MRSA, CNS, and *Enterococcus*.[1] Our study provides evidence that vancomycin elutes poorly into systemic circulation from PMMA cement, with almost undetectable serum concentrations, which is similar to other reports.[3,19] The majority of serum vancomycin concentrations were undetectable, and the highest level was 2.7 μg/mL, which is well below the recommended trough upper limit of 20 μg/mL.[20] Despite low serum levels of vancomycin, it has been shown to elute locally into joint fluid at therapeutic concentrations for prolonged periods.[21] Because of minimal systemic exposure, it is unlikely that vancomycin in bone cement would contribute significantly to the development of AKI.

Independent risk factors for AKI included use of bone cement premanufactured with gentamicin, administration of blood transfusions intraoperatively, and NSAIDs given postoperatively. Because we demonstrated that tobramycin elutes well from bone cement with measurable serum concentrations, it is not surprising that addition of tobramycin to bone cement already containing an aminoglycoside (gentamicin) was a risk factor for AKI. Although this practice appears to be unusual, based on earlier studies showing minimal elution of aminoglycosides from bone cement into systemic circulation,[4,5] some orthopedic surgeons at our institution chose to use gentamicin-impregnated bone cement as their base cement in select cases where they judged that the risk of ongoing infection was high. NSAIDs can cause AKI from glomerular hypoperfusion, especially in the presence of intravascular volume depletion (which may have occurred in our AKI group intraoperatively from excessive blood loss), or with concomitant medications that alter renal autoregulation (eg, ACE inhibitors/ARBs).[22] Alternatives to perioperative NSAIDs include administration of regional analgesia or opioids, and ACE inhibitors/ARBs can be substituted with hydralazine or calcium channel blockers, for example.

Several limitations were associated with this study. Although this was a prospective study, it was observational in nature. Two baseline creatinine values were unavailable within 1 year in 30% of patients; therefore, only their preoperative value was used. Five patients (10%) were discharged prior to POD 7, leading to incomplete follow-up data. Because SCr was collected on alternate days, there is a possibility that a mild acute rise in SCr was missed, and because this study was nonblinded, surgeons could have become cognizant of changes in SCr over time, which may have affected prescribing practices. It is unclear whether tobramycin concentrations were high as a result of AKI or if AKI was the cause of the high concentrations. The small sample size restricted the number of variables that could be included in the multivariate analysis, likely contributed to the wide confidence intervals, and also limited our ability to identify other potential factors that may have influenced AKI such as hemodynamic compromise, severity of illness, diabetes, or the use of ACE inhibitors/ARBs.

In conclusion, we found a 20% incidence of AKI in patients with infected hip or knee arthroplasties receiving

tobramycin-impregnated bone cement. Hence, these patients should be considered at high risk for this outcome from the outset. In addition, AKI was associated with longer hospital stay, and from other studies, it is known to be a risk factor for the development of CKD. Strategies that our hospital implemented to minimize AKI in this high-risk group included (1) early detection through close monitoring of SCr daily for 3 days postoperatively, (2) making sure that acrylic polymers utilized to carry tobramycin did not contain another aminoglycoside, and (3) avoidance of all potential nephrotoxins within the first 72 hours postoperatively, if possible, including NSAIDs and ACE inhibitors/ARBs.

Larger studies are needed to confirm AKI risk factors and to reevaluate elution of tobramycin from acrylic polymers, especially comparing elution rates from proprietary versus generic aminoglycosides.

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Declaration of Conflicting Interests

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