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Dual Antibiotic Prophylaxis is Associated with Acute Kidney Injury after Primary Joint Arthroplasty

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Introduction

With increasing prevalence of MRSA in patients undergoing hip and knee replacement procedures, some have advocated a dual antibiotic prophylactic regimen including Vancomycin to minimize the risk of surgical site infections.[1,2,3,4] Orthopaedic surgeons have studied several methods to reduce the infection rate following primary TJA. While preventing prosthetic joint infection is multifactorial, administration of prophylactic antibiotics one hour prior to surgical incision has become the standard of care in preventing SSI in primary TJA.[5,6,7,8] The American Academy of Orthopaedic Surgeons (AAOS) currently recommends the use of cefazolin or cefuroxime prior to patients undergoing any orthopaedic procedure.[9] With the increasing prevalence of methicillin-resistant staphylococcus aureus (MRSA), recent studies have suggested the addition of vancomycin to the prophylactic antibiotic regimen.[1,10,11] While vancomycin has proven pharmacologic efficacy against gram-positive bacteria and particularly MRSA, its superiority over cefazolin or cefuroxime in reducing SSI after primary TJA continues to be debated in the literature.[1,2,3,4] Administration of vancomycin is also not without adverse effects. Exposure to vancomycin has been shown to be a risk factor for development of vancomycin resistant enterococcus (VRE) and acute kidney injury (AKI).[10,12,13] The purpose of this study is to determine if patients receiving antibiotic prophylaxis with Cefazolin and Vancomycin have a higher rate of postoperative acute kidney injury (AKI) compared to patients receiving Cefazolin alone prior to elective primary hip and knee replacement surgery.

Materials and Methods

We retrospectively reviewed a consecutive series of patients who underwent primary TKA or THA at a single high-volume academic institution between September 2008 and December 2012. The study was conducted according to guidelines set forth by our hospital's Institutional Review Board (IRB). We included all patients who received cefazolin alone or cefazolin plus vancomycin as perioperative antibiotic prophylaxis prior to TJA. Patients were excluded from the study if they had a documented allergy to penicillins, cephalosporins, or vancomycin or if they received an antibiotic other than cefazolin or vancomycin prior to surgery. A SSI was defined according to Centers for Disease Control and Prevention (CDC) guidelines as an infection occurring at the surgical site within 30 days of the operation or up to 1 year if an implant was inserted and the infection appears related to the surgery.[14] The SSI rate of both groups was previously published.[2]

We recorded patient variables that could impact postoperative renal function including American Society of Anesthesiologists (ASA) classification, age, surgical procedure, estimated blood loss (EBL), intraoperative fluid resuscitation, and preoperative kidney function. Each patient's preoperative creatinine was documented in addition to creatinine on post-operative days 1 and 2 as per our hospital's protocol. Preoperative kidney disease was defined as if the patient's preoperative GFR was less than 60 mL/min/1.73 m^2. We defined and classified postoperative AKI according to the published, validated Acute Kidney Injury Network (AKIN) criteria.[15] We first performed an *a priori* power analysis to identify an adequately powered sample size for our study. Univariate logistic regression analysis of all variables was performed to identify risk factors for postoperative AKI. To control for confounding variables, we analyzed the data using a multivariate logistic regression model to identify independent risk factors for acute kidney injury following primary joint arthroplasty.

Of the 2215 consecutive primary TJA patients during the study period, 1828 patients met inclusion criteria and were included in the final analysis. There were 500 patients in the cefazolin group and 1328 patients in the cefazolin plus vancomycin group. Complete demographic details of the patient population are shown in table 1.

Results

The overall incidence of patients with AKI following surgery was 11.3% (207 patients). Patients in the dual antibiotic prophylaxis

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Table 1. Comparison of outcomes between patients receiving cefazolin alone and cefazolin plus vancomycin perioperatively.

Patient Variable	Ancef Only (n = 500)	Ancef + Vancomycin (n = 1328)	p value
Acute Kidney Injury (%)	39 (7.8)	168 (12.6)	0.002
Surgical Site Infection (%)	7 (1.4)	15 (1.1)	0.636
Estimated Blood Loss in mL (SD)	277 (418)	223 (309)	0.476
Intraoperative Fluids in mL (SD)	1825 (890)	1837 (874)	0.576
Preoperative Kidney Disease (%)	128 (26)	283 (21)	0.050
Preoperative GFR in mL/min/1.73 m^2 (SD)	77.0 (26)	78.6 (26)	0.645
Preoperative Creatinine in mg/dL (SD)	1.00 (0.84)	0.92 (0.54)	0.844
Percent Change GFR	47.3	44	0.186

group were more likely to sustain AKI than patients receiving cefazolin alone (12.6% vs. 7.8%, $p = 0.002$). There was no statistical difference between the groups with respect to EBL, intraoperative fluid resuscitation, preoperative kidney function, or percent change in GFR postoperatively.

Patients returned to within 50 percent of baseline kidney function at an overall mean of 2.6 days (range 1-29 days). While there was no difference in the time to return to baseline kidney function (2.7 vs. 2.2 days, $p = 0.155$) between the dual antibiotic group and cefazolin alone (Figure 2), patients with dual antibiotic prophylaxis were more likely to have severe grade II or III kidney injury (3.1% vs. 0.0%, $p < 0.001$). Two patients required dialysis following joint replacement surgery, both in the cefazolin and vancomycin group, and both with multiorgan system complications in the intensive care unit.

Using multivariate logistic regression to controlling for confounding variables, we found that dual antibiotic prophylaxis is an independent risk factor for AKI after primary TJA (adjusted OR 1.82, 95% CI 1.25 − 2.64). ASA classification (adjusted OR 1.64, 95% CI 1.24 − 2.17) and preoperative kidney disease (adjusted OR 1.81, 95% CI 1.30 − 2.52) were also independent risk factors. Age, procedure, EBL, and intraoperative fluid resuscitation were not significant risk factors for development of AKI (Table 2).

Discussion

This study suggests no difference in SSI between patients receiving cefazolin alone and cefazolin plus vancomycin prior and is in keeping with published infection rates for primary TJA in the literature. The effect of the addition of vancomycin

Table 2. Univariate and multivariate logistic regression analysis of risk factors for AKI after primary hip and knee arthroplasty.

	Univariate Anaylsis			Multivariate Analysis		
Risk Factor	Odds Ratio	95% Confidence Interval	p value	Odds Ratio	95% Confidence Interval	p value
Age (years)	1.01	1.00-1.02	0.048	1.01	0.99-1.02	0.368
Knee Arthroplasty	1.03	0.76-1.38	0.871	1.23	0.84-1.80	0.278
EBL (per 100mL)	1.03	1.00-1.07	0.087	1.04	0.99-1.09	0.184
Intraoperative Fluids (per 100mL)	1.02	1.00-1.03	0.056	1.02	0.99-1.04	0.149
ASA	1.75	1.33-2.29	< 0.001	1.64	1.24-2.17	0.001
Dual Antibiotic Prophylaxis	1.71	1.89-2.47	0.003	1.82	1.25-2.64	0.002
Preoperative kidney disease	1.87	1.37-2.55	< 0.001	1.81	1.30-2.52	0.001

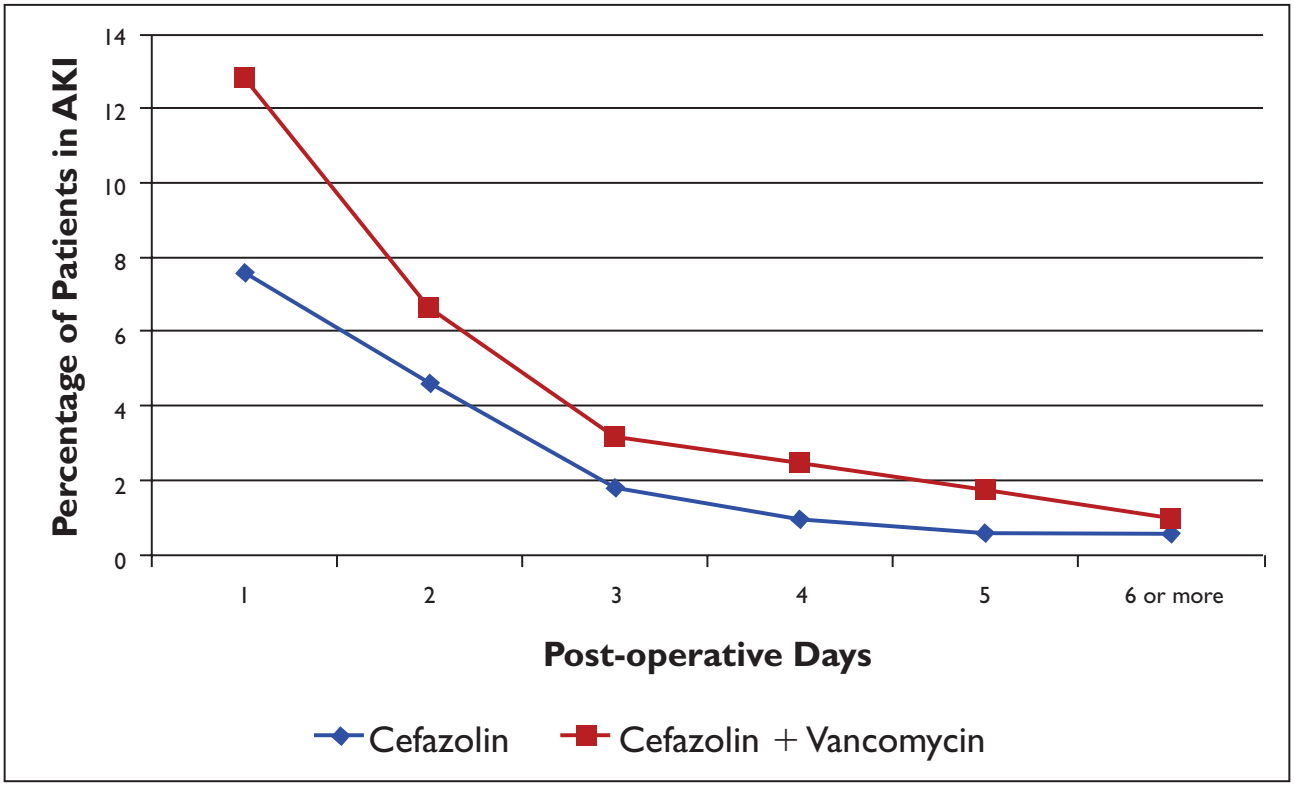

Figure 1. Graph plotting the number of patients meeting AKIN criteria for AKI against postoperative days. There was no statistical difference is the number of days to return to baseline between the two groups (2.7 vs. 2.2 days, p 0.155).

on renal function, however, appears to be transient, as there was no difference in the number of days to return to baseline creatinine (2.7 vs. 2.2 days, p = 0.155). Only 1% of all patients in both groups met criteria for AKI after post-operative day six (Figure 1). The impact of dual antibiotic prophylaxis on kidney function is limited to the immediate post-operative period. Whether or not this transient renal insult will limit patients' ability to deal with future renal injury is beyond the scope of this study.

There are several limitations to our study. Its retrospective design requiring a review of medical records has inherent limitations. A single surgeon treated the large majority of patients receiving cefazolin only for prophylaxis, leading to a potential selection bias, however there was no difference in age or ASA classification between the groups. While we controlled for multiple confounding variables such as age, medical comorbidities (ASA), preoperative kidney function, EBL, and intraoperative fluid resuscitation, we did not control for patients receiving other drugs with the potential for nephrotoxicity. Medications such as angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARB), or other non-steroidal anti-inflammatory drugs (NSAIDs) may have the potential to effect kidney function postoperatively.

Multivariate logistic regression analysis revealed dual antibiotic prophylaxis, ASA classification, and preoperative kidney disease to be independent predictors of AKI postoperatively. This finding agrees with data from Jafari *et al* who found that preoperative kidney disease and medical comorbidities predisposed patients to developing AKI after primary TJA.[16] In patients at low risk for MRSA, the authors suggest avoiding the addition of vancomycin in patients with pre-existing renal dysfunction and multiple medical comorbidities. We should be cautious about decolonizing patients and furthering drug resistant bacteria with the widespread use of vancomycin. Further studies should determine the value of selective preoperative screening for MRSA to determine perioperative antibiotic prophylaxis.

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