



Dual Antibiotic Therapy with Vancomycin and Cefazolin for Surgical Prophylaxis in Total Knee Arthroplasty

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Abstract

Background: Perioperative administration of intravenous antibiotics is a routine part of total knee arthroplasty. Antibiotic selection is a matter of controversy, and the potential risks and benefits associated with each antibiotic selection need to be considered. The objective of this study is to examine the effects of routine dual antibiotic prophylaxis with both cefazolin and vancomycin on infection and renal failure after primary total knee arthroplasty (TKA) compared with cefazolin alone.

Methods: We performed a retrospective review of primary TKA patients for two years before and two years after routine dual antibiotic prophylaxis was implemented at our institution. 1502 patients were included (567 cefazolin-only and 935 dual prophylaxis).

Results: 2 patients (0.4%) in the cefazolin-only group had a deep surgical site infection, compared with 13 patients (1.4%) in the dual prophylaxis group ($p=0.06$). 46 patients (8.1%) in the cefazolin-only group had postoperative renal failure, compared with 36 patients (3.9%) in the dual prophylaxis group ($p=0.0006$).

Discussion and Conclusion: Our results did not support the routine use of vancomycin in primary total joint arthroplasty to decrease periprosthetic joint infection. However, we also did not see any clear harm due to renal failure in the routine use of dual antibiotic prophylaxis.

Background

Since its controversial introduction over 50 years ago, perioperative administration of intravenous antibiotics has become a routine part of total joint arthroplasty and is proven to reduce the risk of infection [1-4]. The recommended number and combination of specific antibiotics continues to be a matter of debate. The 2013 Proceedings of the International Consensus on Periprosthetic Joint Infection found a strong consensus that a first or second-generation cephalosporin should be used for routine surgical prophylaxis, as well as strong consensus against the routine use of vancomycin given the lack of convincing evidence available [5]. However, with the increased prevalence of methicillin-resistant *Staphylococcus aureus* (MRSA) having emerged over the past 2 decades, vancomycin is increasingly used for prophylaxis in primary and revision total joint arthroplasty [6-9].

Vancomycin is a glycopeptide antibiotic that inhibits bacterial cell wall synthesis, and has been found to be effective in the prevention of MRSA surgical site infections [10]. It is commonly used for surgical prophylaxis for patients with a β -lactam allergy or MRSA colonization, either alone or in combination with another antibiotic with

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broader coverage such as clindamycin or an aminoglycoside [10-12]. However, vancomycin has relatively weak antibacterial activity against methicillin-sensitive *Staphylococcus aureus* (MSSA). Vancomycin is also associated with nephrotoxicity and ototoxicity, as well as the development of vancomycin-resistant enterococci [13,14]. A 2015 study found that total joint arthroplasty patients receiving dual antibiotic prophylaxis with vancomycin and cefazolin had a higher incidence of acute kidney injury than those treated with cefazolin only [15].

There are relatively few studies comparing antibiotic prophylaxis with cefazolin alone with routine dual prophylaxis with cefazolin and vancomycin in total joint arthroplasty. A 2012 retrospective review by Sewick et al. of almost 2000 primary total joint arthroplasty patients found no reduction in surgical site infections after the addition of vancomycin to cefazolin for surgical prophylaxis [16]. A 2018 retrospective review of nearly 1900 patients by Burger et al. found that the addition of vancomycin to cefazolin at least 45 minutes prior to skin incision reduced deep infection rates in primary hip and knee arthroplasty with a low risk of renal impairment [17].

Given the potential risks of vancomycin administration and the relative paucity of comparative data, the purpose of this study was to investigate infection rates and nephrotoxicity in total knee arthroplasty patients before and after the adoption of routine dual-antibiotic prophylaxis by our institution. Our hypothesis was that there would be a decrease in periprosthetic joint infection and an increase in acute kidney injury during the dual prophylaxis period.

Materials and Methods

Following Institutional Review Board approval, we retrospectively reviewed all patients who had undergone primary total knee replacements performed from January 2010 to June 2014. In July 2012 our institutional protocol switched from using cefazolin alone to dual-antibiotic prophylaxis with cefazolin and vancomycin for total joint arthroplasty, allowing the division into two groups: 1) cefazolin only and 2) vancomycin and cefazolin. Primary total knee arthroplasty patients from this time period receiving a different combination of antibiotics were excluded. Prior to incision, patients in the cefazolin-only group received a weight-based dose of cefazolin, with patients less than 70kg receiving 1g, 70-120kg receiving 2g, and over 120kg receiving 3g. Those in the dual prophylaxis group received a weight-based dose of cefazolin and 1 gram of vancomycin. Both groups received 2 additional doses of intravenous cefazolin in a 24-hour period starting 8 hours

after the procedure. No additional postoperative dose of vancomycin was given to patients in the dual prophylaxis group.

Electronic medical records were reviewed for age, sex, ethnicity, body mass index (BMI), American Society of Anesthesiologists (ASA) class, pre and post-operative creatinine, readmission within 90 days, return to the operating room for another procedure, and occurrence of superficial or deep surgical site infection. Surgical site infection was defined according to the World Health Organization definition as “infections anatomically associated with a surgical procedure performed in an operating room and not present prior to the operation” [18]. Superficial surgical site infection (SSI) was considered to have occurred in any patient with abnormal superficial incisional signs such as redness or swelling, prolonged drainage, or for whom the surgeon administered any postoperative oral antibiotics. This diagnosis of SSI was made by the individual attending surgeon based upon clinical experience. Deep infection was considered to have occurred in any patient returned to the operating room in the 90-day postoperative period for hematoma, drainage, wound dehiscence, or purulence. A culture-negative deep infection was defined as a periprosthetic infection that had met Musculoskeletal Infection Society criteria for periprosthetic joint infection without positive cultures [19]. Patients with an elevation in postoperative creatinine were subcategorized into different stages of renal failure according to the Acute Kidney Injury Network staging system from 1 to 3 [20].

Statistical analysis of the two groups was performed using Pearson’s chi-square test. In addition, logistic regression was used to control for demographic differences between groups. Power analysis showed that we needed at least 435 patients in each group to be able to detect a 50% difference in infection rates between groups (combining superficial and deep infections) with 80% power.

Results

1502 primary total knee arthroplasty patients were included in the study, with 567 patients in the cefazolin-only group (65.4% female) and 935 patients (63.0% female) in the cefazolin and vancomycin group. Complete demographic data is shown in Table 1. 58 patients (10.2%) in the cefazolin-only group had a superficial surgical site infection, compared with 86 patients (9.2%) in the cefazolin and vancomycin group ($p=0.53$). 2 patients (0.4%) in the cefazolin-only group had a deep surgical site infection, compared with 13 patients (1.4%) in the cefazolin and vancomycin group ($p=0.06$). The 2 deep infections in the ce-

Table 1. Group Characteristics of TKA Patients, 2010-2014

	Cefazolin Only (n=567)		Cefazolin and Vancomycin (n=935)		p-value
	n	(%)	n	(%)	
Gender					
Male	196	(34.6)	346	(37.0)	p = 0.347
Female	371	(65.4)	589	(63.0)	
Ethnicity					
White	436	(76.9)	766	(81.9)	p = 0.021
Black	89	(15.7)	135	(14.4)	
Other	42	(7.4)	34	(3.6)	
ASA class					
1	3	(0.5)	7	(0.7)	p = 0.000
2	426	(75.1)	591	(63.2)	
3	137	(24.2)	332	(35.5)	
4	1	(0.2)	5	(0.5)	
BMI					
<18.0	3	(0.5)	1	(0.1)	p = 0.020
18.0-24.99	44	(7.8)	121	(12.9)	
25.00 to 29.99	157	(27.9)	259	(27.7)	
30.00 and higher	359	(63.8)	554	(59.3)	
BMI					
Average BMI \pm SD (standard deviation)	33.8 \pm 7.5		32.3 \pm 6.7		p = 0.000
Age					
Average age (years) \pm SD	62.5 \pm 10.5		64.4 \pm 10.2		p = 0.572

fazolin-only group were culture negative. Of the 13 deep infections in the cefazolin and vancomycin group, 4 were culture negative, while the remaining specimens grew positive cultures for methicillin-sensitive *Staphylococcus aureus* (MSSA) (4 patients), MRSA (2 patients), *Streptococcus agalactiae* (2 patients), *Enterobacter cloacae* (1 patient), and *Escheria coli* (1 patient, coinfecting with MRSA).

46 patients (8.1%) in the cefazolin-only group had postoperative renal failure, compared with 36 patients (3.9%) in the cefazolin and vancomycin group (p=0.0006). There were no statistically significant differences in 90-day readmission or return to operating room for further procedures (Table 2). Logistic regression analysis revealed an association between BMI and deep infection (p=0.0146), and that female sex, ASA class 1 and 2, and being in the vancomy-

Table 2. Adverse Outcomes of TKA Patients, 2010-2014

	Cefazolin Only (n=567)		Cefazolin and Vancomycin (n=935)		p-value
	n	(%)	n	(%)	
Superficial infection	58	(10.2)	86	(9.2)	0.5275
Deep infection	2	(0.4)	13	(1.4)	0.0606
Readmission within 90 days	22	(3.9)	25	(2.7)	0.2215
Return to surgery	13	(2.3)	16	(1.7)	0.4435
Renal failure (stages merged)	46	(8.1)	36	(3.9)	0.0006
Stage 1	43	(7.6)	33	(3.5)	-
Stage 2	2	(0.4)	2	(0.2)	-
Stage 3	1	(0.2)	1	(0.1)	-

cin and cefazolin group were protective against postoperative renal failure. Complete results of logistic regression analysis are found in Tables 3 and 4.

Discussion

We hypothesized that the group receiving dual antibiotic prophylaxis with vancomycin and cefazolin would have a decreased incidence of periprosthetic joint infection and an increase in acute kidney injury compared with the cefazolin group. In fact, somewhat counterintuitively, our data showed a trend towards deep infection in patients receiving dual antibiotic prophylaxis that did not reach statistical significance, as well as a statistically significant decrease in postoperative renal failure.

A review of the existing data involving vancomycin and surgical site infection in total joint arthroplasty shows mixed results. As mentioned previously, the 2012 study by Sewick et al. directly comparing cefazolin monotherapy and dual prophylaxis with vancomycin and cefazolin found no significant change in surgical site infections (p=0.636) [16]. In contrast, the 2018 study by Burger et al. demonstrated a reduced rate of PJI with dual prophylaxis but only when the infusion of vancomycin was administered at least 45 minutes prior to skin incision [17]. Harold et al. and Lamplot et al. both noted a decrease in infection rates when a dual antibiotic approach was incorporated into a multifaceted aseptic protocol to reduce the rates of PJI which also included modified instrument care, preop-

Table 3: Results of Logistic Regression of TKA Patients with Deep Infection, 2010-2014

	p-value	OR Point Estimate	OR Confidence Interval
Vancomycin and cefazolin compared with cefazolin only	0.0634	4.221	(0.923, 19.306)
Female compared with male	0.6235	1.341	(0.415, 4.331)
Ethnicity compared with white			
Black	0.9359	1.055	(0.287, 3.877)
Other	0.9776	<0.001	(<0.001, >999.999)
ASA class 1&2 compared with 3&4	0.2037	0.493	(0.165, 1.468)
Age	0.8696	1.329	(0.044, 39.793)
BMI	0.0146	34.317	(2.011, 585.638)

erative nasal mupirocin and altered surgical skin preparation [21, 22].

Smith et al. retrospectively reviewed two groups of primary total joint arthroplasty patients who only received cefazolin and those who only received vancomycin for surgical prophylaxis, and found decreased rates of both periprosthetic joint infection overall and MRSA infection in the vancomycin only group [8]. Ponce et al. retrospectively reviewed over 18,000 primary total joint arthroplasties and found an increased rate of surgical site infection in patients without penicillin allergy receiving vancomycin only for prophylaxis compared with cefazolin only (2.6% vs. 1.3%, $p<0.01$). There was no statistically significant difference in the surgical site infection rates for patients receiving vancomycin only compared with vancomycin and cefazolin (2.6% vs. 1.6%, $p=0.17$) [23]. Tan et al. found a similar rate of deep infection in primary total joint arthroplasty patients treated with vancomycin monotherapy for β -lactam allergy compared with non-allergic patients receiving cefazolin, but a comparatively increased risk of Gram-negative infection [24].

Kheir et al. found a higher rate of periprosthetic joint infection in primary total joint arthroplasty patients receiving vancomycin only compared with cefazolin only, noting that only 28% of the patients in their vancomycin-only group received appropriate weight-based dosing of 15 mg/kg, and that the two periprosthetic infections that occurred in the underdosed group were both caused by MRSA [25]. In our study, all patients receiving dual antibiotic prophylaxis received 1g of vancomycin irrespective weight, which likely caused a portion likely caused a portion of patients to be underdosed. This could theoretically explain why the dual prophylaxis group did not have a lower rate

Table 4: Results of Logistic Regression of TKA Patients with Renal Failure, 2010-2014

	p-value	OR Point Estimate	OR Confidence Interval
Vancomycin and cefazolin compared with cefazolin only	0.0001	0.400	(0.250, 0.641)
Female compared with male	0.0001	0.381	(0.238, 0.610)
Ethnicity compared with white			
Black	0.2393	1.433	(0.787, 2.609)
Other	0.9504	1.035	(0.355, 3.019)
ASA class 1&2 compared with 3&4	0.0027	0.477	(0.294, 0.773)
Age	0.1248	3.345	(0.716, 15.636)
BMI	0.0025	6.625	(1.943, 22.581)

of infection compared with the cefazolin-only group. Vancomycin underdosing may also have contributed to the low rate of renal failure in the dual prophylaxis group, counter to our hypothesis that there would be an increase in renal failure in patients receiving a potential nephrotoxic medication. In addition, there may have been a selection bias in the dual prophylaxis group against patients at higher risk of renal failure for receiving vancomycin in the first place.

Limitations of this study include its retrospective design and the inclusion of only total knee arthroplasty patients. It is possible that our study is underpowered to show a difference in a relatively rare outcome such as postoperative infection. Also, we did not include close follow-up of postoperative renal failure patients with details such as rate of return to baseline renal function.

Conclusions

Our results, with the numbers available, did not support the routine use of vancomycin in primary total joint arthroplasty to decrease periprosthetic joint infection. However, we also did not see any clear harm due to renal failure in the routine use of dual antibiotic prophylaxis. Further research should be done to investigate whether routine dual antibiotic prophylaxis with vancomycin should continue to be used routinely for surgical prophylaxis in total joint arthroplasty, or if an algorithm-based antibiotic stewardship program should be adopted to restrict its use to selected subgroups of patients.

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AUTHOR DISCLOSURES

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