The Journal of Arthroplasty xxx (2018) 1–6

Contents lists available at ScienceDirect

The Journal of Arthroplasty

journal homepage: www.arthroplastyjournal.org

Dual-Agent Antibiotic Prophylaxis Using a Single Preoperative Vancomycin Dose Effectively Reduces Prosthetic Joint Infection Rates With Minimal Renal Toxicity Risk

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ARTICLE INFO

Article history:
Received 17 September 2017
Received in revised form
5 March 2018
Accepted 6 March 2018
Available online xxx

Keywords:
prosthetic joint infection
dual-agent antibiotic
vancomycin
renal toxicity
primary total knee arthroplasty
primary total hip arthroplasty

ABSTRACT

Background: We performed this study to compare prosthetic joint infection (PJI) and renal toxicity rates following hip and knee total joint arthroplasty (TJA) when a first-generation cephalosporin was administered either alone or in combination with a single preoperative vancomycin dose, whether vancomycin administration timing potentially influenced dual-antibiotic PJI prophylaxis approach effectiveness, and whether single-dose vancomycin use increased risk of renal impairment.
Methods: This was a retrospective study of 1977 consecutive primary TJAs (1871 patients) treated with cefazolin alone (1044 TJAs) or cefazolin with single-dose vancomycin (953 TJAs). The vancomycin group included 476 TJAs (450 patients) with infusion started at least 45 minutes before the skin incision and 477 TJAs (464 patients) with infusion started less than 45 minutes before the skin incision.
Results: The addition of a single dose of vancomycin did not significantly reduce PJI rates when compared with cefazolin alone (1.6% vs 2.1%, $P = .32$). However, the PJI rate was significantly lower following primary TJA when vancomycin administration was initiated at least 45 minutes before incision (0.2%) when compared with other TJA procedures performed using cefazolin and vancomycin (2.9%, $P < .01$) or cefazolin alone (2.1%, $P < .01$). We observed no difference in renal toxicity between treatment groups.
Conclusion: In our institution, the addition of vancomycin to cefazolin at least 45 minutes before incision reduced PJI infection rates in primary hip and knee TJA with a low risk of renal impairment.

Prosthetic joint infection (PJI) is an infrequent, but potentially devastating complication of total joint arthroplasty (TJA). Patients with chronic infection frequently require multiple surgical procedures and a prolonged course of treatment that contributes to high social and economic costs. Parvizi et al [1] have reported cost estimates of $68,053 and $107,624 for the treatment of susceptible and resistant organisms, respectively.

The administration of antibiotic prophylaxis within 1 hour of the surgical incision has been an accepted approach for decreasing surgical site infection (SSI) risk in primary TJA, with first-generation cephalosporins most commonly used for PJI prophylaxis [2–4]. Vancomycin may be considered for patients with cephalosporin/penicillin allergy or methicillin-resistant *Staphylococcus aureus* (MRSA) colonization, and for institutions with a high prevalence of MRSA [4]. However, several studies have reported higher infection rates when vancomycin is used as a single agent for PJI prophylaxis [5–8].

Multimodal PJI prophylaxis approaches have become widely engaged in lower-extremity joint arthroplasty. These initiatives may include MRSA screening, MRSA prophylaxis or decolonization, preoperative skin preparation, perioperative glycemic control, modification of venous thromboembolism protocols, operative environment controls, and antibiotic selection. While MRSA screening and skin decolonization have become more commonly used, this approach may not be fully effective [9]. Low-virulence organisms contribute substantially to infection rates and have been cultured from sonicated implants retrieved during aseptic revision arthroplasty procedures and revision cases with suspected infection [10,11]. Wimmer et al [12] have reported a high proportion of

One or more of the authors of this paper have disclosed potential or pertinent conflicts of interest, which may include receipt of payment, either direct or indirect, institutional support, or association with an entity in the biomedical field which may be perceived to have potential conflict of interest with this work. For full disclosure statements refer to https://doi.org/10.1016/j.arth.2018.03.009.

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https://doi.org/10.1016/j.arth.2018.03.009
0883-5403/

polymicrobial infections among patients presenting for management of PJI, with lower infection-free survival after revision surgery.

While the introduction of a secondary antibiotic may be appropriate to address institutional or regional patterns of infection, the benefits of dual-agent prophylaxis approaches are controversial. Studies have reported both potential benefits and risks associated with this approach [8,13–16]. The timing of antibiotic administration has been identified as an important factor in PJI prophylaxis success [17,18]. However, most studies comparing single-antibiotic and dual-antibiotic prophylaxis using a first-generation cephalosporin have not specifically addressed vancomycin administration timing [13–16]. Kheir et al [7] have proposed that inadequate infusion is a factor in higher PJI infection rates when vancomycin is used as a single agent. In addition, several studies have reported higher rates of acute kidney injury (AKI) after elective TJA when vancomycin was included in prophylaxis [8,14,19]. However, vancomycin dosing was extended after surgery for a period of 23 hours. These considerations highlight the importance of understanding the relationships between vancomycin administration timing and cumulative dose on PJI prophylaxis effectiveness and AKI risk. To our knowledge, no studies have assessed both infection and AKI rates for patients receiving dual-agent prophylaxis including a single preoperative dose of vancomycin, and no studies have assessed the role of vancomycin administration timing when it is incorporated in a dual-antibiotic PJI prophylaxis approach.

We performed this study to determine whether the addition of a single preoperative dose of vancomycin was effective in reducing primary total hip arthroplasty (THA) and total knee arthroplasty (TKA) PJI rates at our institution, to assess the effect of vancomycin administration timing on infection rates, and to assess the incidence of renal toxicity with the different antibiotic prophylaxis regimens. We hypothesized that TJA infection rates would be lower when a first-generation cephalosporin was augmented with a single preoperative dose of vancomycin, that late initiation of vancomycin administration would be associated with higher PJI rates, and that the use of a single dose of vancomycin in a dual-antibiotic prophylaxis approach would not adversely impact acute renal toxicity rates.

Methods

After obtaining institutional review board approval, we retrospectively identified a consecutive series of 2712 primary THA or TKA procedures performed at a tertiary care institution between January 1, 2012, and April 30, 2016. After excluding 346 patients who had received clindamycin as their primary antibiotic prophylaxis, 22 patients who had received vancomycin alone, and 472 patients who had received dual-antibiotic prophylaxis with a first-generation cephalosporin and gentamicin, we identified 1871 patients (1977 TJA procedures) who had received a first-generation cephalosporin as their primary antibiotic prophylaxis for their primary arthroplasty. This study population included 957 patients (1044 TJA procedures) treated with cefazolin alone (group C) and 914 patients (953 TJA procedures) who received cefazolin with a single preoperative dose of vancomycin (group CV). With vancomycin infusions typically occurring over a 60- to 90-minute time interval, we considered a minimum of 45 minutes to be necessary for at least 50%-75% of the total vancomycin dose to be delivered before the surgical incision. Among the dual-antibiotic prophylaxis group, we identified 450 patients (476 TJA procedures) where vancomycin dosing had been initiated in the preoperative holding area or in the operating room at least 45 minutes before the surgical incision (group CVt) and 464 patients (477 TJA procedures) where the vancomycin was initiated in the operating room less than 45 minutes before the surgical incision, at a mean 20.3 ± 12.4 minutes (group CVx). We performed a retrospective review of the electronic medical record to determine patient demographic characteristics at the time of surgery (age, gender, American Society of Anesthesiologists [ASA] class, body mass index) and each patient's physiological response to surgery (preoperative hemoglobin, preoperative creatinine, lowest postoperative hemoglobin, and highest postoperative creatinine levels).

All patients undergoing elective THA or TKA at our institution received standardized preoperative skin preparation including 2% Chlorhexidine wipes, hair removal with surgical clippers, and standard surgical skin preparation with isopropyl alcohol followed by a Chlorhexidine solution (Chlor-Prep). Cemented TKA procedures were commonly performed using antibiotic-incorporated cement, but the process was not standardized. Perioperative antibiotic prophylaxis was directed independently by 1 of 4 fellowship-trained arthroplasty surgeons. One surgeon primarily used cefazolin alone but added vancomycin (1 g) for patients considered to have a higher risk of infection. One surgeon primarily used cefazolin alone, but added a single preoperative dose of gentamicin (120 mg) for patients considered at a higher risk of infection. Two surgeons primarily used cefazolin with vancomycin (1 g) due to their perception of higher than anticipated infection rates in the collective practice and an intention to increase the effectiveness of coverage against a broader spectrum of gram-positive organisms including higher virulence

Table 1
Patient Demographic Features by Antibiotic Prophylaxis Approach and Procedures.

Procedure	Type	Cefazolin (C)	Cefazolin and Vancomycin (CV)	Test	*P* Value (Effect Size)	Cefazolin and Vancomycin (CVt)
All procedures	N (patients)	957	914	—	—	450
	Age (mean ± std)	60.31 ± 11.49	59.10 ± 11.55	*t*-Test	.02 (0.10)	58.64 ± 11.78
	Male, N (%)	400 (41.80)	393 (43.04)	Chi-square	.60 (0.01)	247 (43.87)
	BMI (mean ± std)	34.01 ± 8.15	35.58 ± 9.49	*t*-Test	.0001 (0.12)	36.85 ± 10.38
	ASA (mean ± std)	2.40 ± 0.58	2.52 ± 0.57	*t*-Test	.0001 (0.23)	2.64 ± 0.57
THA	N (patients)	362	343	—	—	160
	Age (mean ± std)	59.40 ± 12.85	57.96 ± 12.85	*t*-Test	.14 (0.11)	58.06 ± 12.90
	Male, N (%)	168 (46.41)	173 (50.44)	Chi-square	.29 (0.04)	120 (52.17)
	BMI (mean ± std)	32.04 ± 7.61	32.31 ± 8.34	*t*-Test	.66 (0.03)	32.93 ± 8.88
	ASA (mean ± std)	2.30 ± 0.60	2.48 ± 0.58	*t*-Test	.0001 (0.30)	2.58 ± 0.58
TKA	N (patients)	595	570	—	—	290
	Age (mean ± std)	60.86 ± 10.55	59.79 ± 10.64	*t*-Test	.09 (0.10)	59.05 ± 10.94
	Male, N (%)	232 (38.99)	220 (38.60)	Chi-square	.90 (0.00)	127 (38.14)
	BMI (mean ± std)	35.22 ± 8.23	37.55 ± 9.60	*t*-Test	.0001 (0.26)	39.55 ± 10.50
	ASA (mean ± std)	2.44 ± 0.56	2.54 ± 0.56	*t*-Test	.002 (0.18)	2.68 ± 0.56

The cefazolin and vancomycin timing group refers to a subgroup, which received vancomycin greater than 45 minutes before surgical incision or during preoperative holding. Effect size: Chi-square effect size used was Cramer's V (small: 0.07; medium: 0.21; large: 0.35). For *t*-test, the effect size used was Cohen's d (small: 0.2; medium: 0.5; large: 0.8). BMI, body mass index; std, standard deviation; ASA, American Society of Anesthesiologists; THA, total hip arthroplasty; TKA, total knee arthroplasty.