Dual Antibiotic Prophylaxis in Primary Total Knee Arthroplasty—No Benefit for Extremely Obese Patients

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J Knee Surg 2022;35:1209–1213.

Abstract

We performed this study to assess the effectiveness of multimodal total knee arthroplasty prosthetic joint infection (TKA-PJI) prophylaxis including "on-time" dual-antibiotic prophylaxis, and the influence of body mass index (BMI) on prophylaxis effectiveness. After obtaining Institutional Review Board approval, we assessed 1,802 primary TKAs (1,496 patients) who received cefazolin alone or cefazolin combined with vancomycin for TKA-PJI prophylaxis. A detailed chart review was performed to determine patient demographic features (age, gender, BMI, American Society of Anesthesiologists Score), antibiotic selection, vancomycin administration timing, and 1-year PJI rates. Statistical assessment was accomplished using a two-sided Student's *t*-test or Fisher's exact test. Patients who received dual-antibiotic prophylaxis with "on time" vancomycin infusion (Group CVt) had significantly lower infection rates than other TKA patients (0.8 vs. 2.7%, $p < 0.01$). "On Time" vancomycin administration was associated with a lower TKA-PJI rate for patients with a BMI $< 45\ kg/m^2$ (0.5 vs. 2.6%, $p < 0.01$) with no infections in 120 TKA patients with a BMI between 40 and $44.9\ kg/m^2$ ($p < 0.01$). No difference was noted for patients with a BMI $\geq 45\ kg/m^2$ (3.3 vs. 2.6%, $p = 0.71$). There were no infections in 150 TKA patients with a normal BMI ($18–25\ kg/m^2$) in any PJI-prophylaxis treatment group. Adoption of a dual-antibiotic prophylaxis approach can successfully reduce TKA-PJI rates among overweight and moderately obese patients. The approach does not appear to influence outcomes for low risk patients with a normal BMI ($18–25\ kg/m^2$) or for higher risk patients with a BMI $> 45\ kg/m^2$.

Keywords

- prosthetic joint infection
- vancomycin
- dual-antibiotic
- total knee arthroplasty
- total hip arthroplasty
- total joint arthroplasty

Complications from prosthetic joint infection (PJI) can be devastating with both social and economic costs to individual patients and healthcare systems. Parvizi et al estimated treatment costs of $68,053 and $107,624 for PJI caused by susceptible and resistant organisms.[1] With projected increases in primary total knee arthroplasty (TKA) above 3 million procedures per year by 2030, the economic burden of PJI treatment will likely be substantial.[2] Kurtz et al have projected that 1.62 billion dollars will be spent to treat PJI in the United States by the year 2020.[3]

The administration of antibiotic prophylaxis within 1 hour before surgical incision has been a long-standing accepted approach for decreasing surgical site infection (SSI) risk in primary total joint arthroplasty (TJA); and first-generation cephalosporins have been used most commonly used for PJI prophylaxis.[4–6] The complete infusion of intravenous antibiotics before tourniquet infusion has been considered an important part of TKA-PJI prophylaxis and included among TKA performance measures by the American Association of Hip and Knee Surgeons.[7] Vancomycin has generally been considered an acceptable alternative for patients with cephalosporin/penicillin allergy, for individual patients with methicillin-resistant *Staphylococcus aureus* (MRSA) colonization, and for institutions with a high prevalence of MRSA infections.[5] However, studies have reported higher infection rates when vancomycin is used

received
September 25, 2020
accepted after revision
November 12, 2020
published online
January 22, 2021

Thieme Medical Publishers, Inc.,
333 Seventh Avenue, 18th Floor,
New York, NY 10001, USA

DOI https://doi.org/10.1055/s-0040-1722350.
ISSN 1538-8506.

as a single PJI prophylaxis agent and vancomycin administration timing has been implicated as a factor in PJI prophylaxis success or failure.[8–12] Kheir et al suggested that inadequate infusion could be a factor in higher PJI infection rates with single-agent vancomycin PJI prophylaxis.[9]

The addition of vancomycin into a dual-antibiotic prophylaxis approach is controversial, with conflicting reports on effectiveness and concerns over unbalanced acute kidney injury (AKI) risk, or the potential for emerging antibiotic resistance.[10,11,13–16] Most previous studies comparing single- and dual-antibiotic prophylaxis have not specifically addressed vancomycin administration timing.[11,14,16,17] Burger et al reported safety and effectiveness of a dual-antibiotic protocol with "on time" vancomycin administration, noting significantly decreased infection rates without increase in AKI rate and no identified cases of antibiotic resistance.[18]

Morbid obesity is a risk factor for adverse outcomes of TKA, including implant revision and infection.[19,20] The best approaches for decreasing TKA-PJI risk in this patient cohort have not been well defined. Inabathula et al have reported successful reduction in 90-day postoperative infection rates among high risk patients who received an extended course of oral antibiotic treatment following either THA or TKA.[21] We performed this study to assess the effectiveness of "on time" vancomycin administration on total knee arthroplasty prosthetic joint infection (TKA-PJI) rates and the influence of patient body mass index (BMI) on multimodal, dual-antibiotic antibiotic prophylaxis that also included preoperative nasal MRSA decolonization and skin preparation with chlorhexidine. We hypothesized that the protocol would be equally effective among patients who were normal weight, overweight, obese, and morbidly obese.

Methods

Following approval from our institutional review board, we retrospectively reviewed 1,802 consecutive primary TKA procedures (1,496 patients) where a first-generation cephalosporin was used for TKA-PJI prophylaxis either alone, or in combination with a single preoperative dose of vancomycin. Procedures were performed at a single tertiary care academic hospital by fellowship trained arthroplasty surgeons between January 1, 2012 and May 31, 2017. All TKA procedures were performed as an inpatient admission. Patients 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 (Chlora-Prep). All patients were treated with nasal mupirocin ointment as well on their day of surgery. Patients received a weight-based cephalosporin antibiotic (cefazolin) in the operating room prior to the surgical incision, and antibiotic administration was continued for 23 hours after surgery (3 postoperative 1 g cefazolin doses). Venous thromboembolism (VTE) prophylaxis was performed using a risk-stratification approach with low/standard risk patients receiving aspirin and higher risk patients receiving warfarin, fondaparinux, or rivaroxaban, based on surgeon preference. Perioperative autologous and allogeneic blood transfusions were minimized using more selective transfusion guidelines, including a lower hemoglobin level (7 mg/dL) for asymptomatic patients. Tranexamic acid was not utilized during the initial time interval (2012–2013), but was incorporated into operative protocols beginning in 2014.

Between January 1, 2012 and January 31, 2015, antibiotic prophylaxis was selected independently by the operating surgeon. One surgeon primarily used a dual-antibiotic approach for all patients, but did not standardize vancomycin administration timing. A second surgeon primarily used cefazolin alone but added a single preoperative vancomycin dose (1 g intravenous) for higher PJI risk patients. The third surgeon primarily used cefazolin alone, but added a single preoperative dose of gentamicin (120 mg intravenous) for patients considered higher infection risk. All three surgeons utilized commercially premixed antibiotic cement during their procedures. Between February 1, 2015 and May 31, 2017, a standardized protocol for dual-antibiotic administration was adopted by the surgical group. Procedures were performed by five surgeons using TKA-PJI prophylaxis with a multimodal approach including an intended dual-antibiotic approach with vancomycin administration prior to the surgical incision. A single preoperative dose of vancomycin (1 gm) was started in the preoperative holding area, with cefazolin administration (2 gm for patients with a BMI $<$ 100 kg and 3 gm for patients with a BMI $>$ 100 kg) in the operating room within 30 minutes of the surgical incision. Four of the surgeons utilized commercially premixed antibiotic cement during their procedures. One surgeon utilized a risk-based approach for antibiotic cement selective for high-risk patients with morbid obesity, diabetes mellitus, inflammatory arthritis, or immune system compromise.

We performed a detailed medical chart review to obtain patient demographic features (age, gender, BMI, American Society of Anesthesiologists [ASA] class), antibiotic selection, vancomycin administration timing, and PJI rate within 2 years of the surgical procedure. We excluded patients who had received vancomycin alone or clindamycin in the setting of a penicillin allergy and patients who had received gentamicin as a part of a dual-antibiotic prophylaxis approach. Antibiotic administration groups were subclassified into three groups: (1) Group C patients had received a first-generation cephalosporin alone, (2) Group CVt patients had received a dual-antibiotic approach with "on time" vancomycin administration either in the preoperative holding area or started in the operating room with at least 45 minutes prior to the skin incision, and (3) Group CVx patients had received a dual-antibiotic approach with vancomycin administration "not on time" with initiation in the operating room less than 45 minutes prior to the surgical incision.[18]

The presence of a deep SSI was considered possible for all cases where surgical treatment was undertaken for the treatment of a presumed acute or chronic PJI: debridement with implant retention, single stage revision surgery, or staged surgical reconstruction. The diagnosis of a PJI was confirmed by documentation of criteria established by the Musculoskeletal Infection Society: (1) presence of a draining sinus tract, (2) positive cultures obtained from joint fluid

Table 1 Patient demographics based on antibiotic prophylaxis group

	Cefazolin alone	Vancomycin on time (Group CVt)	Vancomycin not on time (Group CVx)
TKAs (n =)	686	739	377
Mean age	61.0 y	61.2 y	59.8 y[a]
Gender (% male)	39.4%	37.7%	36.2%
Mean BMI	35.0 kg/m^2	35.4 kg/m^2	39.9 kg/m^2[a]
Mean ASA	2.44	2.40	2.69[a]

Abbreviations: ASA, American Society of Anesthesiologists; BMI, body mass index; TKA, total knee arthroplasty.
[a]$p < 0.01$.

and/or surgical tissues, or (3) a combination of at least four other factors (elevated serum erythrocyte sedimentation rate, elevated C-reactive protein, elevated synovial leukocyte count, elevated synovial neutrophil percentage).[22] Frozen sections were not routinely performed.

We assessed comparative rates of infection based on the antibiotic treatment groups for the entire cohort and in the preprotocol and postprotocol groups. We also assessed patients using six BMI subgroups: normal (18–25 kg/m^2), overweight (26–30 kg/m^2), obese (31–35 kg/m^2), moderately obese (36–39 kg/m^2), morbidly obese (40–44 kg/m^2), extremely obese ($\geq$ 45 kg/m^2).

Statistical analysis was accomplished using a two-tailed Student's *t*-test for continuous variables (age, BMI, ASA class) and a two-tailed Fisher's exact test or chi-squared analysis for categorical variables (gender, infection cases). We accepted a p-value < 0.05 for significance.

Results

Patient demographic features were slightly different between the different treatment groups. (►**Table 1**) Compared with patients receiving dual-agent prophylaxis "on time," patients who did not have preoperative vancomycin infusion completed before their surgical incision were younger (mean age 59.8 vs. 61.2 years, $p < 0.001$), heavier (mean BMI: 39.9 kg/m^2 vs. 35.4 kg/m^2, $p < 0.001$), and less healthy (ASA 2.69 vs. 2.40 points, $p < 0.001$). The proportion of patients with a BMI > 45 kg/m^2 in the "on time" dual antibiotic protocol after surgery was significantly lower than in postprotocol cohort (2015–2017) than in the historical patient cohort (10.1 vs. 20.5%, $p < 0.01$).

Across all study years (2012–2017), patients with dual-antibiotic prophylaxis with "on time" vancomycin (Group CVt) had significantly lower infection rates when compared with patients who had received another antibiotic approach (0.8 vs. 2.7%, $p < 0.01$). This included patients in both Group C (0.8 vs. 2.5%, $p = 0.02$) and Group CVx (0.8 vs. 3.2%, $p < 0.01$). After incorporation of the TKA-PJI dual-antibiotic protocol, there was an improvement compared with the historical rate (0.9 vs. 2.4%, $p = 0.05$) and a trend toward a lower rate when considering patients who had not received the dual-antibiotic protocol after February 1, 2015 (0.9 vs. 2.7%, $p = 0.07$). When comparing patients across the preprotocol and postprotocol time intervals, the TKA-PJI rate was not statistically different with the different antibiotic prophylaxis approaches: Group C (2.6 vs. 1.3%, $p = 0.71$), Group CVt (0.4 vs. 0.9%, $p = 0.67$), and Group CVx (2.9 vs. 3.8%, $p = 0.74$).

Table 2 Infection rate as a function of antibiotic protocol and patient body mass index

	Cefazolin alone	Vancomycin on time (Group CVt)	Vancomycin not on time (Group CVx)
TKAs (n =)	646	739	377
ALL TKAs	(2.48%)[a]	(0.81%)[ab]	(3.18%)[b]
BMI $\leq$25	0.00%	0.00%	0.00%
BMI 26–30	2.50%	0.64%	2.08%
BMI 31–35	2.94%	1.09%[b]	10.25%[b]
BMI 36–39	0.87%	0.00%	0.00%
BMI 40–44	6.58%[b]	0.00%[b]	0.00%
BMI $\geq$ 45	2.83%	3.30%	2.32%
BMI < 40	1.98%[a]	0.60%[ab]	4.55%[b]
BMI $\geq$ 40	4.39%	1.36%	1.68%
BMI < 45	2.59%[b]	0.46%[b]	3.63%
BMI $\geq$ 45	2.83%	3.30%	2.32%

Abbreviations: BMI, body mass index; TKA, total knee arthroplasty.
[a]$p \leq 0.05$.
[b]$p < 0.01$.

BMI had a measurable influence on the effectiveness of each antibiotic approach (►**Table 2**). TKA patients with a BMI < 40 kg/m^2 who had received the dual-antibiotic prophylaxis had a significantly lower infection risk than patients who had received cefazolin alone (0.6 vs. 1.98%, $p = 0.05$) or who were engaged with a dual-antibiotic approach without vancomycin being adequately infused at the time of the surgical incision (0.6 vs. 4.6%, $p < 0.001$). The lowest risk for infection was noted among patients with a normal BMI (18–25 kg/m^2), with no infections identified in any antibiotic prophylaxis group. The greatest potential for infection reduction was noted among overweight (BMI: 26–30 kg/m^2) and mildly obese (BMI: 31–35 kg/m^2) patients (0.9 vs. 4.0%, $p < 0.01$). None of the 120 TKA who were morbidly obese, but not extremely obese (BMI: 40–44.9 kg/m^2), and had received on-time dual antibiotic administration were identified with an infection. This was significantly different when compared with 76 TKA patients who received cefazolin alone (0.0 vs. 6.6%, $p < 0.01$). In contrast, the infection rate among patients who were extremely obese (BMI: $\geq$ 45 kg/m^2) and received on-time dual antibiotic prophylaxis had infection rates that remained high compared with patients receiving cefazolin alone (3.4 vs. 3.1%, $p = 1.0$).

Discussion

PJI is a devastating complication of primary or revision total joint arthroplasty surgery. Minimizing infection risk is an

important goal as long as these efforts do not introduce unacceptably high complication risks. Institutional concerns driving coverage against high resistance (MRSA) or low virulence gram positive organisms have led to some surgeons adopting dual-agent antibiotic prophylaxis regimens. Burger et al have previously reported a lower PJI rate for primary THA and TKA procedures using a dual-agent prophylaxis approach with a single preoperative vancomycin dose along with first-generation cephalosporin coverage. Vancomycin administration timing was identified as an important factor in reducing PJI rate with prophylaxis success dependent on at least 80% of preoperative vancomycin being infused prior to the surgical incision.[18] In the present study, we noted that "on time" administration of vancomycin in a dual-antibiotic, multimodal PJI prophylaxis protocol resulted in a significant reduction in institutional PJI rates when compared with both a historical control group and patients targeted for a dual-antibiotic approach but did not receive an adequate vancomycin dose prior to their incision (Group CVx). However, the on-time administration of vancomycin ahead of surgery did not impact the extremely low risk that was noted in healthy patients with a normal BMI and did not impact infection rates patients with a BMI $\geq$ 45 kg/m^2.

Multimodal PJI prophylaxis approaches have become widely utilized in lower extremity joint replacement surgery. These initiatives may include MRSA screening or prophylaxis, skin decolonization, perioperative glycemic control, modification of VTE protocols, operative environment controls, and antibiotic selection. Other previous studies have reported similar PJI reduction with the use of a dual-antibiotic protocol.[11,16–18] Sewick et al reported both a lower 1-year all-cause SSI rate and a 10-fold reduction in MRSA infections with the addition of vancomycin to a first-generation cephalosporin.[17] Lamplot et al reported more than a fourfold reduction in primary TKA SSI rates (0.49 vs. 2.24%) when a dual-agent PJI prophylaxis approach including 24 hours vancomycin dosing was introduced into their multimodal PJI reduction approach.[16]

Morbid obesity has been identified as a risk factor for in-hospital complications, postoperative complications, and increased revision risk for infection.[19,20] George et al have identified a higher risk for wound dehiscence, superficial infection, PJI, readmission, and reoperation among morbidly obese patients treated with TKA.[19] Electricwala et al reported a significant increase in early TKA revision for infection among patients with an elevated BMI compared with normal BMI patients.[20] Their study did not report a significant difference in TKA revision for other aseptic indications. The optimal approach for TKA-PJI reduction has not been defined. Our study suggests that patients with a BMI < 45 kg/m^2 can be successfully treated with a dual-antibiotic approach with vancomycin administered fully prior to the surgical incision. Other alternative approaches may be more appropriate for patients with a BMI $\geq$ 45 kg/m^2. Inabathula et al have reported on an extended 7-day oral antibiotic protocol for higher risk patients who had undergone either elective TKA or THA, with approximately two-third of their high-risk patients identified to have a BMI > 35 kg/m^2. While their study has reported low rates of infection at 90 days postoperative, a longer period of time may be needed to define the success of this approach.

This study has limitations that are expected from retrospective observation. While efforts were made to follow the antibiotic administration protocol, this was not always the case. Service protocols also included other approaches to patient optimization prior to surgery. These included movement toward a BMI threshold of 45 kg/m^2 for elective arthroplasty surgery, perioperative blood glucose management, and postsurgical wound containment with decreased frequency of dressing changes. There was a notable reduction in patients with a BMI $\geq$ 45 kg/m^2 in the postprotocol treatment group. Specific VTE medications and their potential influence on postoperative wound drainage were also not assessed, and these could have positively influenced lower rates of postoperative wound drainage and resulting PJI rates.

Conclusion

Reducing rates of PJI are important to reduce social, emotional, physical, and economic costs. While first-generation cephalosporins lower PJI infection rates, infections with low virulence and high resistance organisms may still occur. The use of a dual-antibiotic protocol including preoperative vancomycin with an intention for complete administration prior to surgical incision effectively reduced PJI rates following primary TKA procedures among overweight and obese patients with a BMI < 45 kg/m^2. Success with this approach appears to be dependent on adequate preoperative infusion of vancomycin. From a perspective of antibiotic stewardship, it may be more cost-effective to not engage normal weight, healthy patients with a BMI $\leq$25 kg/m^2. The protocol does not appear to be effective for extremely obese patients (BMI > 45 kg/m^2) and alternative measures should be considered to decrease their PJI risk. These alternatives may include medical optimization to achieve a lower BMI at the time of surgery, or extended oral antibiotic administration after discharge. Additional study is needed to identify optimal approaches to antibiotic prophylaxis in higher risk patients.

Conflict of Interest
J.A.K. reports personal fees from Depuy-Synthes, personal fees from Flexion Therapeutics, personal fees from Advance Medical, personal fees from Heron Pharmaceuticals, grants from ConforMIS, grants from Acelity/KCI, grants from Smith-Nephew, outside the submitted work. The other author declares no conflict of interest.

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