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Original research

Clinical outcome evaluation of intraosseous vancomycin in total knee arthroplasty

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ABSTRACT

Background: Vancomycin is a commonly used prophylactic antibiotic for total joint replacement surgery to protect against methicillin-resistant *Staphylococcus aureus*. Studies have suggested intraosseous (IO) infusions provide superior local tissue antibiotic concentration compared with intravenous (IV) access in total knee arthroplasty (TKA). We reviewed patients receiving IO vancomycin before TKA, comparing complication rates to a matched group receiving IV prophylactic vancomycin.
Methods: Retrospective review of TKA patients administered IO vancomycin (500 mg vancomycin in 200 mL normal saline), September 1, 2018 to March 1, 2019, was compared with TKAs performed with prophylactic IV vancomycin, January 1, 2018 to August 31, 2018. Before incision, an IO needle was inserted into the tibial tubercle region, delivering 100 mL of the mixed vancomycin solution. The needle was then removed and inserted into the distal femur, delivering 100 mL of the solution. Evaluation included preoperative and postoperative creatinine values, tourniquet time, and knee-related 30-day and 90-day complications. Data for primary and revision TKA surgery cases were analyzed independently.
Results: There were 100 primary and 29 revision TKA cases in the control (IV) arm and 100 primary and 19 revision TKA cases in the intervention (IO) arm, comprising a study group of 248 cases. There were fifteen 30-day complications and eighteen 90-day complications overall. No significant differences in the complication rate or creatinine values were identified between IO and IV groups.
Conclusions: IO vancomycin has an adequate safety profile in primary and revision TKA, eliminating the logistical challenge of timely prophylactic antibiotic administration.

Introduction

Vancomycin is a commonly used prophylactic antibiotic for total joint replacement with bactericidal activity against methicillin-resistant *Staphylococcus aureus*. Literature has suggested that intraosseous (IO) infusions are capable of providing equivalent plasma antibiotic concentrations to those administered via the intravenous (IV) access [1,2]. In total knee arthroplasty (TKA), IO infusions administered after tourniquet inflation have demonstrated improved local vancomycin concentrations with decreased systemic absorption [3]. IO infusion of prophylactic surgical antibiotics therefore may be more effective than IV administration, with potential for reduction in surgical site infections (SSIs). The purpose of this study was to evaluate patients who were administered IO vancomycin before TKA and to determine if administration via the IO route provided equivalent or improved clinical outcomes.

Material and methods

This was a retrospective cohort study at an urban, tertiary referral center. Institutional review board approval was acquired through our institution. Patients of the senior author who received IO vancomycin (500 mg vancomycin in 200 mL normal saline) before TKA from September 1, 2018 to March 1, 2019, were retrospectively evaluated. A control cohort of patients who underwent TKA with IV vancomycin (15 mg/kg dose) from January 1, 2018 to August 31, 2018, were used for comparison. Exclusion criteria included additional procedures at time of TKA (n = 3),

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intraoperative technical challenges which would lead to prolonged tourniquet time including severe deformity correction requiring augment (n = 1) and intraoperative instability (n = 1), and missing data from the electronic medical record (n = 1).

Administration of IO vancomycin followed a standard protocol. After the operative extremity had been prepped and draped in the usual sterile fashion, the limb was elevated and the tourniquet inflated to 300 mm Hg. Before incision, an IO vascular access system (Teleflex Arrow EZ-IO, Morrisville, NC) was inserted with a power driver into the tibial tubercle region. There was 100 mL of the vancomycin solution administered via syringe. The device was then removed and inserted into the anterior distal femur, centrally just proximal to the patella for administration of the remaining 100 mL of the mixed solution. The device was removed and the TKA proceeded according to the surgeon's standard technique.

Evaluation included preoperative and postoperative creatinine values, tourniquet time, and knee-related 30-day and 90-day complications. Demographic, body mass index and medical comorbidity data were also collected. Wound complications were recorded including cellulitis of the operative extremity, erythema or skin reaction, delayed healing, and drainage. Data for primary and revision TKA surgery cases were analyzed independently from one another, whereas the control and intervention groups were compared within each surgical type (primary or revision).

For tourniquet time, data were analyzed using an independent samples *t*-test between the intervention and control groups. For comparison of creatinine levels from the preoperative to postoperative time points, a 2 (group) by 2 (time point) mixed model analysis of covariance with repeated measures (covaried on baseline creatinine concentration) was used. A two-tailed independent sample *t*-test was used to compare age (years) and body mass index (kg/m^2) between the control and intervention groups within the primary and revision cases, respectively. The chi-square analysis was used to compare frequencies of comorbidities as well as proportions of males and females per group (control vs intervention) within primary and revision cases, respectively. For cases in which the number of observations within each category was below 5, a Fisher's exact test was used to confirm the conclusion. Type I error was set at $P < .05$ for all analyses.

Results

Patient demographics and comorbidity frequencies are shown in Table 1. No significant differences were detected between the control and intervention groups in both the primary and revision cases. Therefore, for final analysis of infection rates, data were collapsed to compare control and intervention cases within primary and revision cases, respectively.

There were 100 primary and 29 revision TKA cases in the control (IV) arm. In the intervention (IO) arm, there were 100 primary and 19 revision cases for a total of 248 cases. Refer to Figure 1 (CONSORT diagram) for complete breakdown of enrollment. Baseline medical comorbidities were similar and are shown in Table 1. There were fifteen 30-day complications and eighteen 90-day complications in total. Thirty- or 90-day complications were not significantly different in primary cases (30-day: control = 4.0%, intervention = 4.0%, 90-day: control = 7.0%, intervention = 3.0%), whereas 30-day complications for revisions were decreased but not significantly (control = 17.2%, intervention = 10.5%). The 90-day complications were decreased in the revision group receiving IO (control = 27.6%, intervention = 0%; $P = .015$). Overall, there were 33 (13.3%) separate complications recorded through the full 90-day follow-up. No complications directly related to the IO insertion device were identified.

Complications are summarized in Table 2. There were no deep infections in either primary TKA group. One deep infection occurred in each revision group, both in the setting of reimplantation as part of a two-stage protocol. In the revision control group (IV vancomycin), the infection was managed with explanation and insertion of a spacer. The infection occurring in the revision IO vancomycin group was managed with irrigation and debridement with polyethylene exchange.

No cases of red man syndrome were identified in any group. No increase in postoperative creatinine values occurred (primary: control = −0.08 ± 0.15 mg/dL, intervention = −0.03 ± 0.17 mg/dL; and revision: control = −0.10 ± 0.22 mg/dL, intervention = −0.02 ± 0.09 mg/dL). No incidences of acute kidney injury (AKI) were identified. Tourniquet time was increased by 1.87 minutes in the primary intervention vs control arm (on average), but this was not statistically significant ($P = .10$). Tourniquet time for revision cases was not evaluated because of a large variability in the procedures.

Discussion

The present study indicates that prophylactic IO vancomycin is a safe and effective alternative to using preoperative IV vancomycin in primary and revision TKA. This is the largest series to date evaluating the clinical outcomes of using IO administration of antibiotics preoperatively in TKA. A prospective, randomized study by Young et al [3] evaluated the local and systemic concentrations of

Table 1
Patient demographics and comorbidity frequencies.

Independent variable	Primary			Revision		
	Control (n = 100)	Intervention (n = 100)	Sig. (*P*-value)	Control (n = 29)	Intervention (n = 19)	Sig. (*P*-value)
Demographics						
Males (n)	40%	47%	0.318 (ns)	41%	47%	0.682 (ns)
Females (n)	60%	53%		59%	53%	
Age (yr)	67 ± 9	67 ± 10	0.833 (ns)	69 ± 10	66 ± 10	0.266 (ns)
BMI (kg/m^2)	32 ± 7	32 ± 7	0.486 (ns)	32 ± 6	32 ± 7	0.939 (ns)
Comorbidities						
%Obesity (BMI > 30)	60%	57%	0.667 (ns)	62%	68%	0.653 (ns)
Smoking	4%	6%	0.871 (ns)	3%	15%	0.130 (ns)
Diabetes	20%	26%	0.313 (ns)	24%	26%	0.864 (ns)
Rheumatoid arthritis	3%	2%	0.651 (ns)	6%	0%	0.534 (ns)
End-stage renal disease	2%	7%	0.090 (ns)	14%	11%	0.647 (ns)
HIV	0%	0%	1.000 (ns)	0%	0%	1.000 (ns)
Liver disease	1%	3%	0.312 (ns)	10%	5%	0.533 (ns)

Values are presented as means ± SD for age (years) and body mass index (BMI, kg/m^2), proportions of males and females in each group, and frequencies of known comorbidities for postoperative infection. No significant interactions were observed between groups within either primary or revision cases at $\alpha = 0.05$.

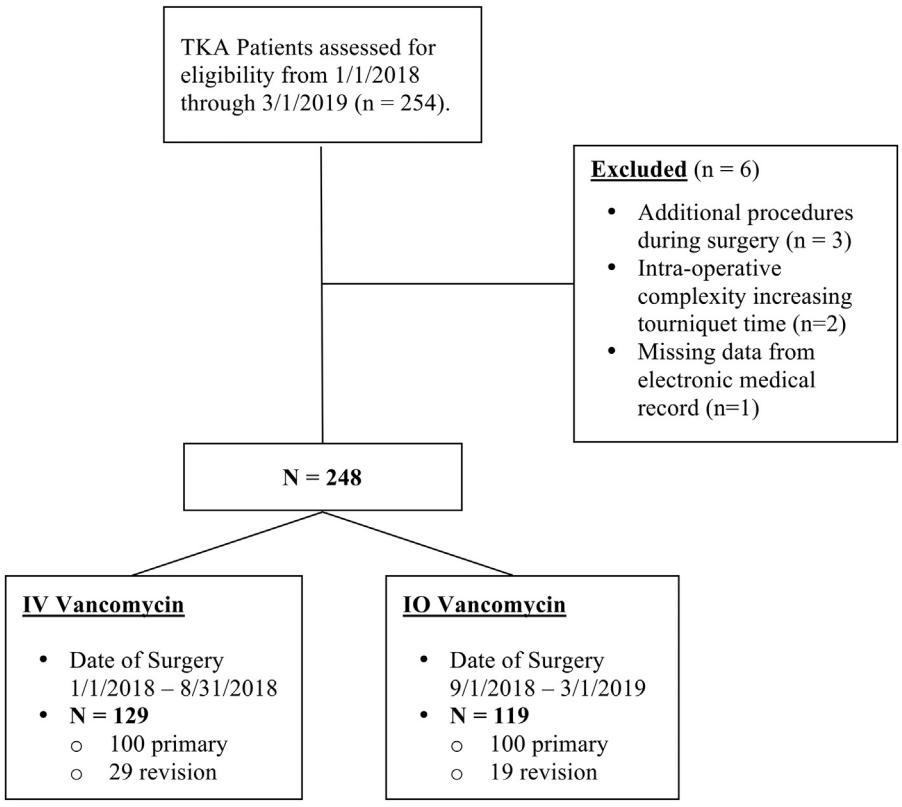

Figure 1. CONSORT diagram detailing breakdown of enrollment.

vancomycin after IO vs IV administration and found that low-dose IO vancomycin resulted in tissue concentrations equal or superior to those of systemic administration. They stated that IO administration by the surgeon optimizes timing of vancomycin administration and that the lower dose may reduce the risk of systemic side effects while providing equal or enhanced prophylaxis in TKA. Randomized trials performed by the same group have shown that this benefit remains intact for patients with a higher BMI [4] and that higher tissue concentrations can also be achieved in revision surgeries [5]. We have found that patients who receive IO vancomycin have equivalent 30- and 90-day complication rates in primary and revision TKA cases.

Infusion times for IV vancomycin are prolonged in an effort to minimize side effects, primarily that of red man syndrome [6]. The general recommendation for vancomycin is that infusions occur over a greater than 1-hour period [7]. In conjunction with this, it is also recommended that antibiotics be received within 60 minutes of incision to minimize the risk of SSIs [8], with some studies noting that within 30 minutes is ideal [9]. This leads to difficulty with timing the administration of vancomycin so that it has enough time to fully infuse and is completed within the 60 minutes prior-to-incision time period. A meta-analysis evaluating antibiotic prophylaxis times found that vancomycin was more likely to fall out of the recommended time range [8]. A study by Garey et al [10], who evaluated vancomycin use in cardiac procedures, concluded that SSIs were lowest in the group who received their antibiotics between 16 and 60 minutes before incision. Despite this, 2217 of the 2408 patients in their study (92%) received their antibiotics greater than 60 minutes before incision, with 55% receiving them greater than 120 minutes before incision [10]. In total hip and knee arthroplasty, patients who receive their preoperative antibiotics greater than 60 minutes before incision have been reported to have a 1.3 times increased risk of developing an SSI [11]. It is our belief that administering vancomycin via the IO route has the added benefit of improving preoperative antibiotic prophylaxis compliance.

The utility of intrawound vancomycin powder (VP) was first established in spine literature [12,13], and its use is now common in joint arthroplasty. The literature on the efficacy of VP in arthroplasty remains inconclusive. Although some studies have shown a decrease in overall infection rates, incidence of periprosthetic joint infection and readmission rates for infection [14], others have shown no difference in reoperation rates or infection rates [15].

Table 2
Complications experienced by patients.

Type of complication	Total	30-Day complications				90-Day complications			
		Primary control	Primary intervention	Revision control	Revision intervention	Primary control	Primary intervention	Revision control	Revision intervention
Total	33	4	4	5	2	7	3	8	0
Wound	20	2	2	4	2	2	2	6	0
Other	13	2	2	1	0	5	1	2	0
MUA	10	0	2	1	0	4	1	2	0
DVT	3	2	0	0	0	1	0	0	0

MUA, manipulation under anesthesia; DVT, deep vein thrombosis.

Many surgeons continue to use VP, as most studies have determined no increased risk to the patient (ie, ototoxicity, nephrotoxicity) [14] or to implant longevity [16]. In prior studies examining soft tissue concentrations of vancomycin, IO vancomycin has reached levels of 44 μg/g in fat and 38 μg/g in bone [3], whereas intrawound VP has demonstrated 207 μg/mL concentrations within the drainage fluid at 24 hours [17]. There is no literature on bone concentrations of vancomycin after administration of intrawound VP in humans. However, it is unlikely that topical VP achieves measurable concentrations within the bone. Without bone concentration data, it is hard to directly compare the 2 administration modalities.

The rate of AKI after total joint arthroplasty is variable, with rates reported from 1% up to 20%. The rate of AKI has been associated with patient comorbidities [18,19]. A large contributor to that incidence is patients who have high serum concentrations of vancomycin [20], as well as in those who receive dual antibiotic prophylaxis (cefazolin and vancomycin) [21]. IO administration of vancomycin after tourniquet inflation has been shown to keep serum concentrations nondetectable during surgery [3]. This property of IO delivery is likely to contribute to a decreased incidence of AKI in total joint patients. Indeed, our study showed no incidence of AKI in patients receiving IO administration.

Limitations of the study include its retrospective nature and inclusion of data found in the electronic medical record. It is possible that data points were missed or misinterpreted. Our inclusion of all potential complications, beyond even those endorsed by the Knee Society [22], leads to a higher overall complication rate than those typically reported and therefore may skew our data. In addition, we used this broadened description to be able to quantify complications because standard infection rates are traditionally 0.5%-1% [23], and therefore, our study is underpowered to detect deep periprosthetic infections. Our revision data, which comprise a relatively small number of heterogeneous revision surgeries, are primarily included to demonstrate that this technique can deliver antibiotic safely even in the presence of an implant. A cost/benefit analysis would also have added to the value of our data.

Conclusions

Our study demonstrates that prophylactic IO vancomycin in primary and revision TKAs is a safe and effective alternative to IV administration. Further research, including large randomized studies comparing rates of periprosthetic joint infection between IV and IO vancomycin, is needed. IO infusion also eliminates the logistical challenges of timely prophylactic antibiotic administration before TKA.

Conflict of interest

Stephen J. Incavo, MD Paid consultant for Biomet, Kyocera Medical Corporation, Smith & Nephew, Microport.

All other authors declare no potential conflicts of interest.

For full disclosure statements refer to https://doi.org/10.1016/j.artd.2020.02.001

References

[1] Strandberg G, Larsson A, Lipcsey M, Michalek J, Eriksson M. Intraosseous and intravenous administration of antibiotics yields comparable plasma concentrations during experimental septic shock. Acta Anaesthesiol Scand 2015;59(3):346.

[2] Jaimovich DG, Kumar A, Francom S. Evaluation of intraosseous vs intravenous antibiotic levels in a porcine model. Am J Dis Child 1991;145(8):946.

[3] Young SW, Zhang M, Freeman JT, Mutu-Grigg J, Pavlou P, Moore GA. Higher tissue concentrations of vancomycin with low-dose intraosseous regional versus systemic prophylaxis in TKA: a randomized trial. Clin Orthop Relat Res 2014;472(1):57.

[4] Chin SJ, Moore GA, Zhang M, Clarke HD, Spangehl MJ, Young SW. Intraosseous regional prophylaxis provides higher tissue concentrations in high BMI patients in total knee arthroplasty: a randomized trial. J Arthroplasty 2018;33(7S):S13.

[5] Young SW, Zhang M, Moore GA, Pitto RP, Clarke HD, Spangehl MJ. Higher tissue concentrations of vancomycin achieved with intraosseus regional prophylaxis in revision TKA: a randomized controlled trial. Clin Orthop Relat Res 2018;476:66.

[6] Sivagnanam S, Deleu D. Red man syndrome. Crit Care 2003;7(2):119.

[7] Wilson APR. Comparative safety of teicoplanin and vancomycin. Int J Antimicrob Agents 1998;10:143.

[8] Willem de Jonge S, Gans SL, Atema JJ, Solomkin JS, Dellinger PE, Boermeester MA. Timing of preoperative antibiotic prophylaxis in 54,552 patients and the risk of surgical site infection: a systematic review and meta-analysis. Medicine (Baltimore) 2017;96(29):e6903.

[9] Koch CG, Nowicki ER, Rajeswaran J, et al. When the timing is right: antibiotic timing and infection after cardiac surgery. J Thorac Cardiovasc Surg 2012;144:931.

[10] Garey KW, Dao T, Chen H, et al. Timing of vancomycin prophylaxis for cardiac surgery patients and the risk of surgical site infections. J Antimicrob Chemother 2006;58:645.

[11] Van Kasteren MEE, Mannien J, Ott A, Kullberg BJ, de Boer AS, Gyssens IC. Antibiotic prophylaxis and the risk of surgical site infections following total hip arthroplasty: timely administration is the most important factor. Clin Infect Dis 2007;44(7):921.

[12] Bakhsheshian J, Dahdaleh NS, Lam SK, Savage JW, Smith ZA. The use of vancomycin powder in modern spine surgery: systematic review and meta-analysis of the clinical evidence. World Neurosurg 2015;83(5):816.

[13] Hey HW, Thiam DW, Koh ZS. Is intraoperative local vancomycin powder the answer to surgical site infections in spine surgery? Spine (Phila Pa 1976) 2017;42(4):267.

[14] Patel NN, Guild III GN, Kumar AR. Intrawound vancomycin in primary hip and knee arthroplasty: a safe and cost-effective means to decrease early periprosthetic joint infection. Arthroplast Today 2018;4(4):479.

[15] Lum Z, Ummel J, Coury J, Huff K, Cohen J, Casey J. No change in infection rates with inraoperative vancomycin powder in total joint arthroplasty. Orthopaedic Proc 2018;100-B(4 Suppl):53.

[16] Qadir R, Ochsner JL, Chimento GF, Meyer MS, Waddell B, Zavatsky JM. Establishing a role for vancomycin powder application for prosthetic joint infection prevention—results of a wear simulation study. J Arthroplasty 2014;29(7):1449.

[17] Johnson JD, Nessler JM, Horazdovsky RD, Vang S, Thomas AJ, Marston SB. Serum and wound vancomycin levels after intrawound administration in primary total joint arthroplasty. J Arthroplasty 2017;32(3):924.

[18] Ferguson KB, Winter A, Russo L, et al. Acute kidney injury following primary hip and knee arthroplasty surgery. Ann R Coll Surg Engl 2017;99(4):307.

[19] Gharaibeh KA, Hamadah AM, Sierra RJ, Leung N, Kremers WK, El-Zoghby ZM. The rate of acute kidney injury after total hip arthroplasty is low but increases significantly in patients with specific comorbidities. J Bone Joint Surg Am 2017;99(21):1819.

[20] Ma AH, Hoffman C, McNeil JI. Acute tubular necrosis associated with high serum vancomycin and tobramycin levels after revision of total knee arthroplasty with antibiotic-containing calcium sulfate beads. Open Forum Infect Dis 2019;6(4):ofz141.

[21] Courtney PM, Melnic CM, Zimmer Z, Anari J, Lee GC. Addition of vancomycin to cefazolin prophylaxis is associated with acute kidney injury after primary joint arthroplasty. Clin Orthop Relat Res 2015;473(7):2197.

[22] Healy WL, Della Valle CJ, Iorio R, et al. Complications of total knee arthroplasty: standardized list and definitions of the Knee Society. Clin Orthop Relat Res 2013;471(1):215.

[23] Spivey JC, Guild III GN, Scuderi GR. Use of articulating spacer technique in revision total knee arthroplasty complicated by sepsis: a systematic meta-analysis. Orthopedics 2017;40(4):212.