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The John N. Insall Award: Higher Tissue Concentrations of Vancomycin Achieved With Intraosseous Regional Prophylaxis in Revision TKA: A Randomized Controlled Trial

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Abstract

Background In primary TKA, prophylaxis with low-dose vancomycin through intraosseous regional administration (IORA) achieves tissue concentrations six to 10 times higher than systemic administration and was shown to provide more effective prophylaxis in an animal model. However, in revision TKA, the presence of a tibial implant may compromise IORA injection, and tourniquet deflation during a prolonged procedure may lower tissue concentrations.

Questions/purposes (1) Does low-dose IORA reliably provide equal or higher tissue concentrations of vancomycin compared with systemic IV administration in revision TKA? (2) Are tissue concentrations of vancomycin after IORA maintained for the duration of the revision TKA despite a period of tourniquet deflation? (3) Is there any difference in early postoperative (< 6 weeks) complications between IORA and systemic IV administration in revision TKA?

Methods Twenty patients undergoing aseptic revision TKA were randomized to two groups. The IV group received 1 g systemic IV prophylactic vancomycin. The IORA group received 500 mg vancomycin as a bolus injection into a tibial intraosseous cannula below an

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Each author certifies that his or her institution approved the human protocol for this investigation, that all investigations were conducted in conformity with ethical principles of research, and that informed consent for participation in the study was obtained.
Procedures and sample collection performed at Mayo Clinic, AZ, USA. Sample analysis performed at Canterbury Health Laboratories, Christchurch, New Zealand.
Clinical Trial Registration: NCT02020031.

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inflated thigh tourniquet before skin incision. In all patients receiving IORA, intraosseous tibial injection was technically possible despite the presence of a tibial implant. Mean procedure length was 3.5 hours in both groups. Mean initial tourniquet inflation was 1.5 hours with a second inflation for a mean of 35 minutes during cementation. During the procedure, subcutaneous fat and bone samples were taken at regular intervals. Tissue vancomycin concentrations were measured using high-performance liquid chromatography.

Results Overall geometric mean tissue concentration of vancomycin in fat samples was 3.7 μg/g (95% confidence interval [CI], 2.6-5.2) in the IV group versus 49.3 μg/g in the IORA group (95% CI, 33.2-73.4; ratio between means 13.5; 95% CI, 8.2-22.0; $p < 0.001$); mean tissue concentrations in femoral bone were 6.4 μg/g (95% CI, 4.5-9.2) in the IV group versus 77.1 μg/g (95% CI, 42.4-140) in the IORA group (ratio between means 12.0; 95% CI, 6.2-23.2; $p < 0.001$). Vancomycin concentrations in the final subcutaneous fat sample taken before closure were 5.3 times higher in the IORA group versus the IV group (mean ± SD, 18.2 ± 11.6 μg/g IORA versus 3.6 ± 2.5 μg/g; $p < 0.001$). The intraarticular concentration of vancomycin on postoperative Day 1 drain samples was not different between the two groups with the numbers available (mean 4.6 μg/L in the IV group versus 6.6 μg/g in the IORA group; mean difference 2.0 μg/g; 95% CI, 6.2-23.2; $p = 0.08$).

Conclusions IORA administration of vancomycin in patients undergoing revision TKA resulted in tissue concentrations of vancomycin five to 20 times higher than systemic IV administration despite the lower dose. High tissue concentrations were maintained throughout the procedure despite a period of tourniquet deflation. These preliminary results justify prospective cohort studies, which might focus on broader safety endpoints in more diverse patient populations. We believe that these studies should evaluate patients undergoing revision TKA in particular, because the risk of infection is greater than in patients undergoing primary TKA.

Level of Evidence Level I, therapeutic study.

Introduction

Periprosthetic joint infection (PJI) is more common after revision TKA with reported rates as high as 9% [18]. Such PJIs are more challenging to treat, because revision implants often involve the use of stems, cones, and augments, making thorough débridement or removal difficult. Prophylactic antibiotics reduce the risk of developing PJI [11, 14]; however, bacterial resistance to common prophylactic antibiotics such as cephalosporins is increasing [19, 27, 30]. Vancomycin has been proposed as an alternative [26]; however, it requires a prolonged administration time, can cause systemic toxicity, and risks promoting further antibiotic resistance. Low-dose prophylactic vancomycin through intraosseous regional administration (IORA) may mitigate these issues and in primary TKA achieves tissue concentrations six to 10 times higher than systemic administration [32]. In an animal model of TKA, IORA was also shown to provide more effective prophylaxis against PJI [31].

In TKA prophylaxis, IORA involves intraosseous injection of antibiotics into the proximal tibia after tourniquet inflation and before skin incision. Even in adults, intraosseous injection is equivalent to IV administration [29] and is reliably successful in primary TKA [32, 33]. However, in revision TKA, it is unclear if intraosseous injection into the proximal tibia will be technically possible in the presence of a tibial implant. Additionally, revision TKA is often prolonged and the tourniquet may be deflated during the procedure. This removes the circulatory restriction of the antibiotic to the affected limb, potentially lowering tissue concentrations at the surgical site after deflation. Because the goal of prophylaxis is to provide adequate concentrations of antibiotic "from the time of incision to the time of closure" [2], this may decrease the effectiveness of IORA in revision TKA.

This study was performed to compare tissue concentrations of vancomycin through systemic IV administration versus IORA in revision TKA, in which the risk of PJI is higher. We aimed to answer the following questions: (1) Does low-dose IORA reliably provide equal or higher tissue concentrations of vancomycin compared with systemic IV administration in revision TKA? (2) Are tissue concentrations of vancomycin after IORA maintained for the duration of the revision TKA despite a period of tourniquet deflation? (3) Is there any difference in early postoperative (< 6 weeks) complications between IORA and systemic IV administration in revision TKA?

Patients and Methods

Patients undergoing unilateral revision TKA at a single tertiary institution were eligible for enrollment in this prospective, randomized controlled trial. Ethical approval was obtained from the institutional ethical review board, and the trial and protocol were

registered with ClinicalTrials.gov (Identifier: NCT02020031). Inclusion criteria were patients undergoing single-stage aseptic revision TKA with exchange of both tibial and femoral components. Exclusion criteria were previous or current PJI, known hypersensitivity to vancomycin, and major cardiac or respiratory disease. All procedures were performed by one of two fellowship-trained arthroplasty surgeons (HDC, MJS).

Between January 2014 and April 2015, 22 patients were enrolled by a trained research nurse (DLR) in an outpatient setting. Patients were, using computer-generated random allocations placed in numbered, opaque, sealed envelopes, in two groups. The IV group received 1 g systemic IV prophylactic vancomycin over a 1-hour infusion into an arm vein, timed to finish immediately before tourniquet inflation. The IORA group received 500 mg vancomycin in 150 mL saline as a bolus injection through a tibial intraosseous cannula, below an inflated thigh tourniquet, immediately (< 2 minutes) before skin incision. No further postoperative doses of vancomycin were administered in either group, but cefazolin was continued for 24 hours. In all patients receiving IORA, intraosseous tibial injection was technically possible despite the presence of a tibial implant. Although no patients in either group had large cortical perforations or massive osteolysis of the proximal tibia, in this situation, intraosseous injection into the medial malleolus was the planned alternative option. Randomization occurred at the time of consent (typically the day before surgery) to allow the appropriate order to be placed to allow the IV vancomycin to be infused at least 1 hour preoperatively or the IO vancomycin to be delivered to the operating room for IO administration. Both groups received 2 g systemic cefazolin 15 minutes before tourniquet inflation to ensure all patients received effective antibiotic prophylaxis regardless of randomization. Two patients (one from the IORA group and one from the IV group) were withdrawn from the study without samples being taken after an intraoperative decision not to proceed with full revision of both components, leaving 20 patients for analysis (10 in the IV group and 10 in the IORA group). Despite randomization, there were more females in the IORA group (seven versus five IORA) and the mean time between the first and second tourniquet inflations was longer in the IORA group (61 minutes versus 37 minutes IORA). There were no other major differences between groups (Table 1). Intention-to-treat analysis of complications did not alter results (no complications occurred in the withdrawn patients), and the per-protocol analysis is presented. All patients in both groups had estimated glomerular filtration rates > 50 preoperatively and at the time of discharge. All patients received a general anesthetic combined

Table 1. Patient demographics

Demographic	1 g systemic (n = 10)	500 mg IORA (n = 10)
Males	5	3
Females	5	7
Age (years)	68 (54-82)	69 (43-83)
BMI (kg/m^2)	33 (22-42)	32 (26-42)
Indication for revision† (n)		
Aseptic loosening	5	5
Polyethylene wear	0	2
Instability	4	4
Malrotation/malalignment	4	3
First tourniquet time (minutes)*	94 (85-108)	91 (89-96)
Tourniquet deflation time (minutes)*	37 (15-88)	61 (18-109)
Second tourniquet time (cementation; minutes)*	35 (25-48)	35 (21-52)
Total procedure time (minutes skin to skin)	212 (177-282)	219 (167-263)
ASA score (range)	2.4 (2-3)	2.7 (2-3)

Values given as mean with range in parentheses.
*excludes three patients (one systemic, two IORA) in whom a tourniquet was used for 120 minutes and not reinflated.
†some patients had more than one indication.
IORA = Intraosseous Regional Administration; BMI = Body Mass Index; ASA = American Society of Anesthesiologists.

with a periarticular injection of local anesthetic; eight patients (four in each group) also received a peripheral nerve block. Revision TKA was performed using components from one of two suppliers (Stryker Inc, Mahwah, NJ, USA; Zimmer, Warsaw, IN, USA). Three intraoperative tissue cultures were taken in all patients to exclude PJI.

The revision TKA was performed with the tourniquet initially inflated for exposure and implant removal, deflated, and then reinflated for implant cementation. Tobramycin cement was used in all patients in both groups. Patients were monitored for clinical signs of red man syndrome, particularly after tourniquet deflation. An antihistamine was available for use if required. Mean procedure length was 3.5 hours in both groups. The mean initial tourniquet inflation was 1.5 hours with a second inflation for a mean of 35 minutes during implant cementation. In three patients (one systemic, two IORA), the tourniquet was used for 120 minutes and not reinflated. During the procedure, subcutaneous fat and bone samples (approximately 0.5 cm^3) were taken at regular intervals until skin closure; a total of six fat and four bone samples were taken for each patient at the same operative steps in both groups (see Appendix 1, Supplemental Digital Content 1). All bone samples were taken from the femur, distant from the tibial intraosseous injection site. Tissue samples were stored at -90° C until they were analyzed.

Vancomycin concentrations were determined by liquid chromatography coupled with tandem mass spectrometry using a validated technique that has been previously described [32, 34]. On postoperative Day 1, intraarticular vancomycin concentrations were determined from a sample taken from the drain. All patient samples were analyzed in duplicate, and laboratory analysis was carried out blinded as to the randomization group.

Power Calculation

Data from a previous randomized trial comparing IORA of 250 mg versus systemic administration of 1 g vancomycin [32] showed mean tissue concentrations of vancomycin in subcutaneous fat at different collection points ranged from 8.1 (SD 5.6) to 19.4 (SD 11.7) μg/g in the intraosseous group and from 2.4 (SD 1.5) to 4.4 (SD 2.0) μg/g in the IV systemic group; thus, the concentration of vancomycin was approximately 3.3 times higher in the IORA group. In bone samples, the difference in vancomycin concentration was 4.5-fold. Using these data, a priori power analysis calculated 10 patients in each arm would provide > 90% statistical power to detect the expected fold difference in subcutaneous fat and bone concentrations at a 5% significance level if IORA doses 25% (250 mg) of the systemic dose (1 g) were used. As a result of the longer nature of revision surgery, we chose to use a higher IORA dose of 500 mg; therefore, this power analysis represents a conservative estimate likely to overestimate the number of patients required.

There are limited data on the pharmacodynamics of vancomycin for surgical prophylaxis; however, in treatment models of infection, the pharmacokinetic-pharmacodynamic parameter most predictive of efficacy is the area under the concentration time curve divided by the minimum inhibitory concentration (MIC) [7]. Increased vancomycin tissue concentrations can therefore be expected to enhance effectiveness, especially in organisms with MICs of 1 g/L or more such as methicillin-resistant *Staphylococcus aureus* and coagulase-negative staphylococci [8]. An animal study of IORA vancomycin supports this [31]; therefore, the differences used in our power analysis are likely to be clinically relevant.

Statistical Analysis

Means, SDs, and the 95% confidence limits were calculated for the concentrations in the different samples. Different tissue samples were pooled according to surgical steps (Appendix 1). Coefficients of variation of concentration level were summarized at each surgical step for comparison between the two groups. Repeated-measures analysis of variance was used to compare the average level of concentration across time between groups adjusted by body mass index, age, and length of the surgical procedure; the Shapiro-Wilk test was used to assess the normality of the residuals. Adverse events were tallied for each group and reported descriptively.

Results

Higher tissue and bone concentrations consistently were achieved in patients treated with IORA. The overall geometric mean of average tissue concentrations of vancomycin in fat samples was 3.7 μg/g (95% confidence interval [CI], 2.6-5.2) in the IV group versus 49.3 μg/g in the IORA group (95% CI, 33.2-73.4; ratio between means 13.5; 95% CI, 8.2-22.0; $p < 0.001$; Table 2). Overall geometric mean of average tissue concentrations in femoral bone was 6.4 μg/g (95% CI, 4.5-9.2) in the IV group versus 77.1 μg/g (95% CI, 42.4-140) in the IORA

group (ratio between means 12.0; 95% CI, 6.2-23.2; p < 0.001; Fig. 1A-B; see Appendix 2, Supplemental Digital Content 2, and Appendix 3, Supplemental Digital Content 3).

Sustained levels of vancomycin remained higher throughout the procedures in patients treated with IORA. Vancomycin concentrations in the final subcutaneous fat sample taken before closure were 5.3 times higher in the IORA group versus the IV group (mean, 18.2 ± 11.6 μg/g IORA versus 3.6 ± 2.5 μg/g; p < 0.001; Fig. 2). The intra-articular concentration of vancomycin on postoperative Day 1 drain samples was not different between the two groups with the numbers available (mean 4.6 μg/L in the IV group versus 6.6 μg/g in the IORA group; mean difference 2.0 μg/g; 95% CI, 6.2-23.2; p = 0.08; Fig. 3).

No patient in either group developed symptoms of red man syndrome. There were no thromboembolic complications or deep or superficial infections in either group. One patient in the IORA group developed foot drop postoperatively and underwent exploration and decompression of the common peroneal nerve 3.5 months postoperatively. The etiology of the foot drop was unknown, although the patient was obese and surgical exposure was difficult. This complication has not previously been reported with IORA and was not thought to be related. There were no other reoperations in either group.

Discussion

PJI is more common in revision than primary TKA [18, 25] and has been reported to account for > 44% of rerevisions after revision TKA [17].

Table 2. Mean tissue concentrations of vancomycin at each sample point

	1 g systemic		500 mg IORA		
	Time (minutes; ± SD)	Mean concentration (μg/g; ± SD)	Time (minutes; ± SD)	Mean concentration (μg/g; ± SD)	p value
Subcutaneous fat 1 (S1)	2	3.2	3	94	< 0.001
	(1)	(1.8)	(4)	(69)	
Subcutaneous fat 2 (S2)	34	5.0	30	88	< 0.001
	(7)	(2.9)	(6)	(131)	
Subcutaneous fat 3 (S4)	50	4.2	48	69	< 0.001
	(10)	(2.5)	(12)	(50)	
Subcutaneous fat 4 (S6)	115	4.7	119	173	< 0.001
	(30)	(2.6)	(30)	(445)	
Subcutaneous fat 5 (S8)	145	4.0	151	249	< 0.001
	(34)	(2.2)	(36)	(639)	
Subcutaneous fat 6 (S10)	180	3.6	193	18	< 0.001
	(64)	(2.5)	(82)	(11.6)	
Bone sample 1 (S3)	34	7.9	30	91	< 0.001
	(7)	(5.7)	(6)	(77)	
Bone sample 2 (S5)	50	8.6	48	193	< 0.001
	(10)	(5.9)	(12)	(191)	
Bone sample 3 (S7)	115	5.0	119	60	< 0.001
	(30)	(2.3)	(30)	(63)	
Bone sample 4 (S9)	145	7.1	151	63	< 0.001
	(34)	(4.4)	(36)	(62)	

Times are given as minutes after surgical incision.
differences in mean tissue concentrations between the two groups were statistically significant (p < 0.0001) for all comparison points after adjustment by gender, age, body mass index, American Society of Anesthesiologists score, interaction between groups, and time from incision.
IORA = Intraosseous Regional Administration.

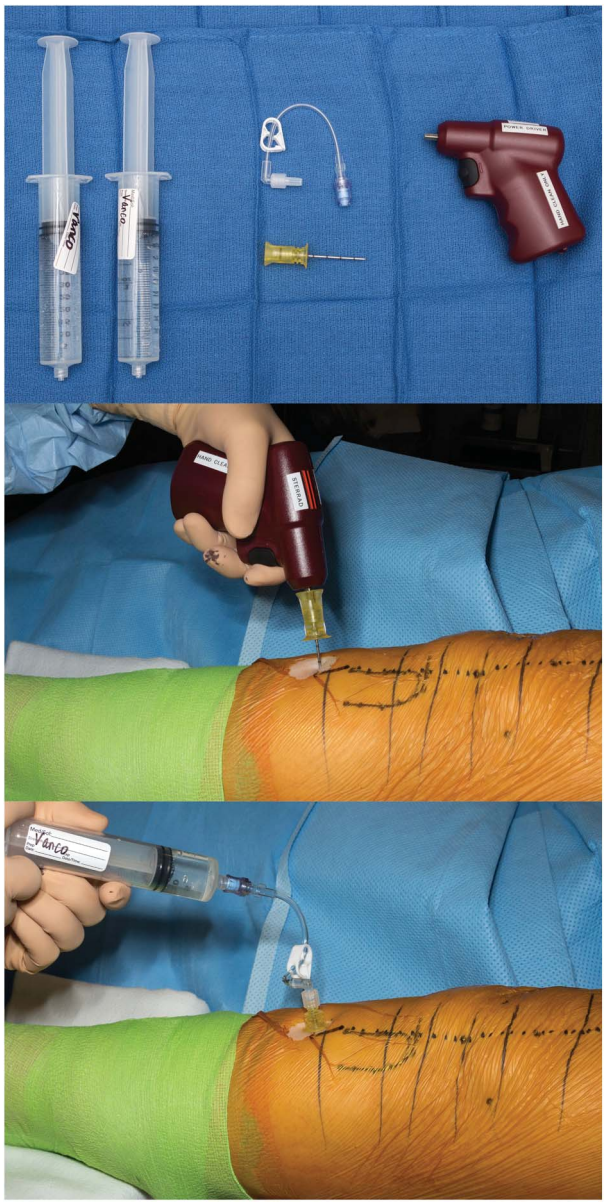

Fig. 1 Intraosseous injection was performed after tourniquet inflation. After injection, the needle is removed and the injection site covered with Ioban (3M, St Paul, MN, USA) before proceeding with the skin incision and surgery.

Measures aiming to reduce PJI therefore are particularly relevant in revision TKA given both the higher incidence and the difficultly in treatment in the presence of revision implants. This study found IORA of low-dose vancomycin to be effective in the setting of revision TKA, reliably providing tissue concentrations five to 20 times higher than systemic IV administration for the duration of the procedure.

A limitation of this study is that the power analysis was based on the tissue concentration of vancomycin and not the development of PJI, because the numbers required to detect a difference in PJI incidence between the two techniques would be prohibitive. However, the pharmacokinetic-pharmacodynamic parameter most predictive of efficacy of vancomycin is the area under the concentration time curve divided by the MIC [7]; therefore, higher vancomycin tissue concentrations are likely to enhance effectiveness. A recent animal study supports this, finding low-dose IORA vancomycin prophylaxis to be more effective than standard-dose systemic vancomycin in preventing PJI in a murine model of TKA [31]. Second, we used a standard 1-g dose of vancomycin, whereas some authors have advocated weight-based dosing (eg, 15 mg/L) to ensure adequate tissue concentrations are achieved [3]. However, a 1-g dose for orthopaedic prophylaxis is commonly reported [8, 22, 26] and given the magnitude of the difference seen, the use of a weight-based systemic dose would have been unlikely to alter the findings of this study. Third, randomization envelopes were opened the day before surgery to allow pharmacy preparation of the appropriate vancomycin administration method. To avoid potential subversion of randomization, the envelopes were opened by an independent researcher and surgeons were not informed of the randomization until the day of surgery. Also, although sample analysis was performed in a blinded fashion, the surgeon was not blinded to treatment group potentially biasing interpretation of short-term complications. This was not the primary outcome of the study, however, and there were few complications in either group. Finally, although we found no difference in complication rates between the two groups, the

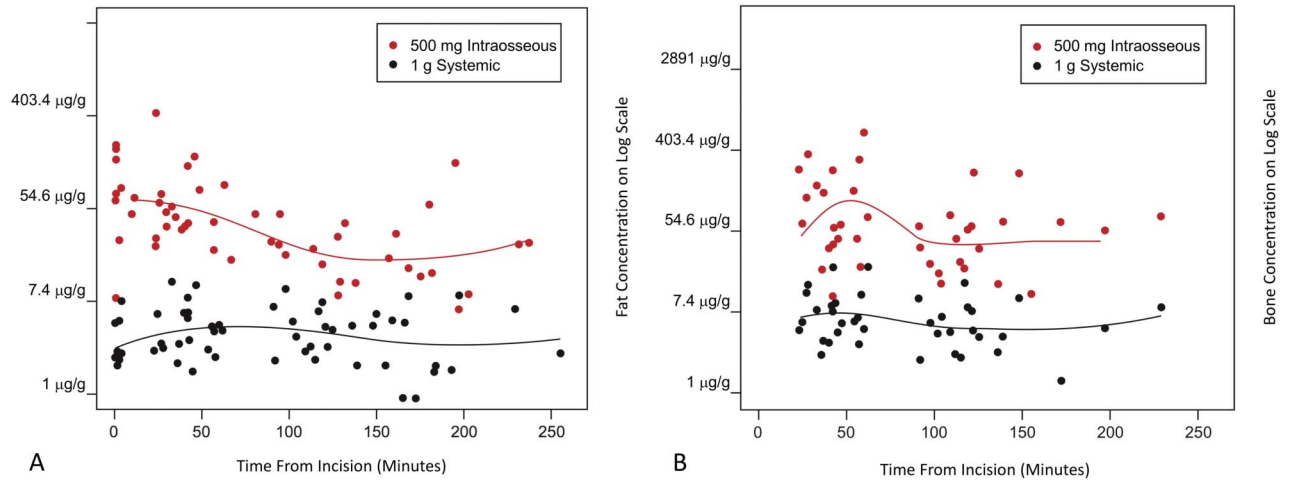

Fig. 2 A-B (**A**) Scatterplot showing tissue concentration of vancomycin in subcutaneous fat at various time points after incision. Note the scale is logarithmic. (**B**) Scatterplot showing tissue concentration of vancomycin in bone at various time points after incision. Note the scale is logarithmic.

number of patients was relatively small. Two previous studies of IORA in primary TKA have also found no increase in complications [32, 33], and in veterinary research, IORA of vancomycin and other antibiotics is well described for treatment of equine septic arthritis, again without reported complications [23, 24].

We found intraosseous injection to be successful in all patients despite the presence of a tibial implant. Rapid distribution through the limb circulation after injection was evident by the very high vancomycin concentrations seen in the first tissue sample taken within minutes of the IORA injection. Regional administration of prophylactic antibiotics in TKA has been previously investigated by de Lalla et al. [9] comparing IV regional administration (IVRA) of 400 mg teicoplanin given through a foot vein with 800 mg teicoplanin given systemically. They reported tissue concentrations two to 10 times higher in the IVRA group. They evaluated this IVRA protocol in 250 patients undergoing TKA, reporting a 0% PJI rate [10]. In this study, we used the intraosseous route to perform regional administration, and the main advantages of IORA over IVRA are reliability and speed. Cannulation of a foot vein can be difficult in obese patients and involves exposing an area typically covered in sterile drapes. In contrast, intraosseous injection using modern equipment is rapid and reproducible [5], and injections travel directly into the intravascular space in a manner equivalent to IV injection in both adults and children [29]. A small area of cancellous bone is all that is

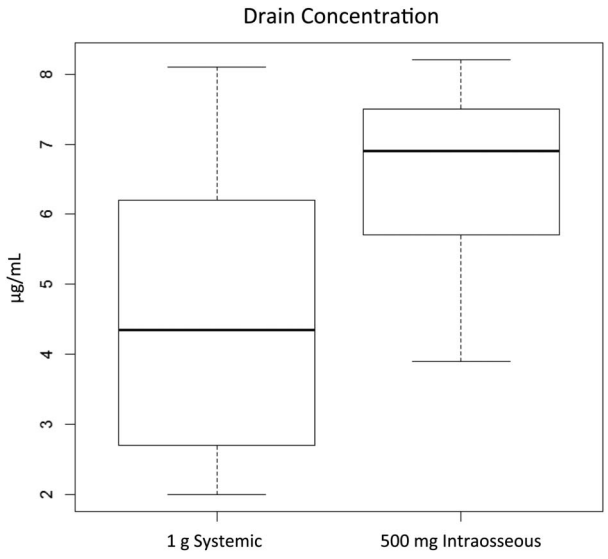

Fig. 3 Graph showing the intraarticular concentration of vancomycin in drain fluid drawn the morning after surgery. Central line represents the median; box represents the 25% and 75% quartiles; whiskers represent the range.

required, and the presence of tibial implants in this study did not alter the effectiveness of IORA. In the setting of severe proximal tibial bone loss, the IORA technique may not be feasible, although intraosseous injection can also be performed into the distal tibia, distal femur, or calcaneus [4, 15, 16].

We found higher tissue concentrations of vancomycin throughout the duration of the procedure in the IORA group, despite intraoperative tourniquet release. Revision TKAs are often prolonged, and inflation of the tourniquet for the entire procedure risks nerve or ischemic injury. Once the tourniquet is released, vancomycin levels at the operative site can be expected to decrease, although before this study, the rate at which they did so was unclear. We found intraarticular levels on postoperative Day 1 remained above the typical vancomycin MIC reported for methicillin-resistant *S aureus* (1.0 μg/mL) and coagulase-negative staphylococci (2.0 μg/mL) [28]. There is likely to be a depot effect of the initial high tissue concentrations, leading antibiotic to be released gradually into the systemic circulation after tourniquet deflation [23]. A potential weakness of the IORA technique is that many surgeons routinely continue antibiotics for 24 hours postoperatively, and further systemic vancomycin doses would thus still be required after IORA. However, randomized trials have shown no difference in infection rates between a single preoperative antibiotic dose and continuing antibiotics for 24 hours [12, 13]. This supports Burke's original theory of prophylaxis, which states adequate antibiotic tissue concentrations must be achieved from the time of incision to the time of closure, when contamination is occurring [2]. This outcome was clearly attained in the IORA group in this study despite the use of a lower vancomycin dose. The lower dose allows bolus administration instead of a prolonged systemic infusion and minimizes the risk of systemic complications such as red man syndrome [20] or nephrotoxicity [6]. This also avoids the need for preoperative coordination to ensure appropriate timing of prophylaxis administration, because most hospital protocols require vancomycin infusions of 1 g over 1 to 2 hours to avoid red man syndrome.

The very high concentrations seen with IORA raises the question of potential local toxicity. The in vitro effect of high antibiotic concentrations on musculoskeletal cells has been investigated in the context of local delivery of antibiotic-impregnated cement for the treatment of infection. Antoci et al. reported minimal toxicity to osteoblastic and chondroblastic cell lines at vancomycin concentrations of 250 μg/mL with a reduction in cellular proliferation becoming apparent at concentrations > 2000 μg/mL [1]. Similarly, Rathbone et al. reported vancomycin to be the least toxic of 21 antibiotics tested with no effect on osteoblast survival or metabolic function until exposed to concentrations in excess of 2000 μg/mL for 10 to 14 days [21]. The IORA tissue concentrations in our study were well below these levels and the duration of exposure shorter, suggesting local toxicity is unlikely to occur.

In conclusion, IORA administration of vancomycin in patients undergoing revision TKA resulted in tissue concentrations of vancomycin five to 20 times higher than systemic IV administration despite the lower dose. The high tissue concentrations of vancomycin after IORA were maintained throughout the procedure and the first postoperative day despite a period of tourniquet deflation during surgery. These preliminary results justify prospective cohort studies, which might focus on broader safety endpoints in more diverse patient populations. We believe that these studies should evaluate patients undergoing revision TKA in particular, because the risk of infection is greater than in patients undergoing primary TKA.

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References

1. Antoci V, Adams CS, Hickok NJ, Shapiro IM, Parvizi J. Antibiotics for local delivery systems cause skeletal cell toxicity in vitro. *Clin Orthop Relat Res.* 2007;462:200–206.
2. Burke JF. The effective period of preventive antibiotic action in experimental incisions and dermal lesions. *Surgery*. 1961;50:161–168.
3. Catanzano A, Phillips M, Dubrovskaya Y, Hutzler L, Bosco J. The standard one gram dose of vancomycin is not adequate prophylaxis for MRSA. *Iowa Orthop J.* 2014;34:111–117.
4. Clem M, Tierney P. Intraosseous infusions via the calcaneus. *Resuscitation*. 2004;62:107–112.
5. Cooper BR, Mahoney PF, Hodgetts TJ, Mellor A. Intra-osseous access (EZ-IO) for resuscitation: UK military combat experience. *J R Army Med Corps*. 2007; 153:314–316.
6. Courtney PM, Melnic CM, Zimmer Z, Anari J, Lee G-C. Addition of vancomycin to cefazolin prophylaxis is associated with acute kidney injury after primary joint arthroplasty. *Clin Orthop Relat Res.* 2015;473:2197–2203.
7. Craig WA. Pharmacokinetic/pharmacodynamic parameters: rationale for antibacterial dosing of mice and men. *Clin Infect Dis*. 1998;26: 1–10; quiz 11–12.
8. Crawford T, Rodvold KA, Solomkin JS. Vancomycin for surgical prophylaxis? *Clin Infect Dis*. 2012;54:1474–1479.
9. de Lalla F, Novelli A, Pellizzer G, Milocchi F, Viola R, Rigon A, Stecca C, Dal Pizzol V, Fallani S, Periti P. Regional

and systemic prophylaxis with teicoplanin in monolateral and bilateral total knee replacement procedures: study of pharmacokinetics and tissue penetration. *Antimicrob Agents Chemother*. 1993;37: 2693–2698.
10. de Lalla F, Viola R, Pellizzer G, Lazzarini L, Tramarin A, Fabris P. Regional prophylaxis with teicoplanin in monolateral or bilateral total knee replacement: an open study. *Antimicrob Agents Chemother*. 2000;44:316–319.
11. Doyon F, Evrard J, Mazas F, Hill C. Long-term results of prophylactic cefazolin versus placebo in total hip replacement. *Lancet*. 1987;1:860.
12. Garcia S, Lozano ML, Gatell JM, Soriano E, Ramon R, SanMiguel JG. Prophylaxis against infection. Single-dose cefonicid compared with multiple-dose cefamandole. *J Bone Joint Surg Am.* 1991;73: 1044–1048.
13. Heydemann JS, Nelson CL. Short-term preventive antibiotics. *Clin Orthop Relat Res.* 1986;205:184–187.
14. Hill C, Flamant R, Mazas F, Evrard J. Prophylactic cefazolin versus placebo in total hip replacement. Report of a multicentre double-blind randomised trial. *Lancet*. 1981;1:795–796.
15. Lairet J, Bebarta V, Lairet K, Kacprowicz R, Lawler C, Pitotti R, Bush A, King J. A comparison of proximal tibia, distal femur, and proximal humerus infusion rates using the EZ-IO intraosseous device on the adult swine (Sus scrofa) model. *Prehosp Emerg Care*. 2013;17:280–284.
16. McCarthy G, O'Donnell C, O'Brien M. Successful intraosseous infusion in the critically ill patient does not require a medullary cavity. *Resuscitation*. 2003; 56:183–186.
17. Mortazavi SMJ, Molligan J, Austin MS, Purtill JJ, Hozack WJ, Parvizi J. Failure following revision total knee arthroplasty: infection is the major cause. *Int Orthop*. 2011;35:1157–1164.
18. Mortazavi SMJ, Schwartzenberger J, Austin MS, Purtill JJ, Parvizi J. Revision total knee arthroplasty infection: incidence and predictors. *Clin Orthop Relat Res.* 2010;468:2052–2059.
19. Nickinson RSJ, Board TN, Gambhir AK, Porter ML, Kay PR. The microbiology of the infected knee arthroplasty. *Int Orthop*. 2010;34:505–510.
20. Polk RE, Healy DP, Schwartz LB, Rock DT, Garson ML, Roller K. Vancomycin and the red-man syndrome: pharmacodynamics of histamine release. *J Infect Dis*. 1988;157:502–507.
21. Rathbone CR, Cross JD, Brown KV, Murray CK, Wenke JC. Effect of various concentrations of antibiotics on osteogenic cell viability and activity. *J Orthop Res.* 2011;29:1070–1074.
22. Ritter MA, Barzilauskas CD, Faris PM, Keating EM. Vancomycin prophylaxis and elective total joint arthroplasty. *Orthopedics*. 1989;12:1333–1336.
23. Rubio-Martínez LM, López-Sanromán J, Cruz AM, Santos M, Andrés MS, Román FS. Evaluation of safety and pharmacokinetics of vancomycin after intravenous regional limb perfusion in horses. *Am J Vet Res.* 2005;66:2107–2113.
24. Scheuch BC, Van Hoogmoed LM, Wilson WD, Snyder JR, MacDonald MH, Watson ZE, Steffey EP. Comparison of intraosseous or intravenous infusion for delivery of amikacin sulfate to the tibiotarsal joint of horses. *Am J Vet Res.* 2002;63:374–380.
25. Sierra RJ, Cooney WP, Pagnano MW, Trousdale RT, Rand JA. Reoperations after 3200 revision TKAs: rates, etiology, and lessons learned. *Clin Orthop Relat Res.* 2004;425:200–206.
26. Smith EB, Wynne R, Joshi A, Liu H, Good RP. Is it time to include vancomycin for routine perioperative antibiotic prophylaxis in total joint arthroplasty patients? *J Arthroplasty*. 2012;27:55–60.
27. Stefánsdóttir A, Johansson D, Knutson K, Lidgren L, Robertsson O. Microbiology of the infected knee arthroplasty: report from the Swedish Knee Arthroplasty Register on 426 surgically revised cases. *Scand J Infect Dis.* 2009;41: 831–840.
28. Tenover FC, Moellering RCJ. The rationale for revising the Clinical and Laboratory Standards Institute vancomycin minimal inhibitory concentration interpretive criteria for *Staphylococcus aureus. Clin Infect Dis*. 2007;44: 1208–1215.
29. Tobias JD, Ross AK. Intraosseous infusions: a review for the anesthesiologist with a focus on pediatric use. *Anesth Analg*. 2010;110:391–401.
30. Yamada K, Matsumoto K, Tokimura F, Okazaki H, Tanaka S. Are bone and serum cefazolin concentrations adequate for antimicrobial prophylaxis? *Clin Orthop Relat Res.* 2011;469: 3486–3494.
31. Young SW, Roberts T, Johnson S, Dalton JP, Coleman B, Wiles S. Regional intraosseous administration of prophylactic antibiotics is more effective than systemic administration in a mouse model of TKA. *Clin Orthop Relat Res.* 2015;473: 3573–3584.
32. Young SW, Zhang M, Freeman JT, Mutu-Grigg J, Pavlou P, Moore GA. The Mark Coventry Award: Higher tissue concentrations of vancomycin with low-dose intraosseous regional versus systemic prophylaxis in TKA: a randomized trial. *Clin Orthop Relat Res.* 2014;472: 57–65.
33. Young SW, Zhang M, Freeman JT, Vince KG, Coleman B. Higher cefazolin concentrations with intraosseous regional prophylaxis in TKA. *Clin Orthop Relat Res.* 2013;471:244–249.
34. Zhang M, Moore GA, Young SW. Determination of vancomycin in human plasma, bone and fat by liquid chromatography/tandem mass spectrometry. *J Anal Bioanal Tech*. 2014;5:196.