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AAHKS Award Paper

# The AAHKS Clinical Research Award: Intraosseous Regional Prophylaxis Provides Higher Tissue Concentrations in High BMI Patients in Total Knee Arthroplasty: A Randomized Trial

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ABSTRACT

*Background:* Obesity is an established risk factor for periprosthetic joint infections after total knee arthroplasty (TKA). In obese patients, a larger dose of prophylactic vancomycin based on actual body weight is required to reach therapeutic concentrations. It is unclear how tissue concentrations are affected when intraosseous regional administration (IORA) is used in this population. This study compared tissue concentrations of low-dose vancomycin via IORA vs actual body weight–adjusted systemic intravenous (IV) dose in primary TKA.

*Methods:* Twenty-two patients with a body mass index (BMI) >35 undergoing TKA were randomized into 2 groups. The IV group received 15 mg/kg (maximum of 2 g) of systemic IV vancomycin and the IORA group received 500 mg vancomycin into the tibia. Subcutaneous fat and bone samples were taken at regular intervals. Tissue antibiotic concentrations were measured using liquid chromatography coupled with tandem mass spectrometry. A blood sample was taken 1 to 2 hours after tourniquet deflation to measure systemic concentration.

*Results:* The mean BMI was 41.1 in the IORA group and 40.1 in the IV systemic group. The overall mean tissue concentration in subcutaneous fat was 39.3 μg/g in the IORA group and 4.4 μg/g in the IV systemic group ($P < .01$). Mean tissue concentrations in bones were 34.4 μg/g in the IORA group and 6.1 μg/g in the IV systemic group ($P < .01$).

*Conclusion:* Low-dose IORA was effective in the high-BMI population group, providing tissue concentrations of vancomycin 5-9 times higher than systemic administration. IORA optimizes timing of vancomycin administration and provides high tissue antibiotic concentrations during TKA in this high-risk patient group.



Obesity is considered a global epidemic [1]. Through biomechanical and physiological mechanisms, it is a risk factor for both the incidence and progression of knee osteoarthritis [2–4]. As such, obese patients are over-represented in patients presenting for total knee arthroplasty (TKA) [5], and the obesity epidemic is a factor in the significant increase in the number of TKAs performed each year [6].

Obesity is also an important risk factor for periprosthetic joint infection (PJI) after TKA [7], a devastating complication for the patient [8] and the health-care system [9]. In a meta-analysis of 83,001 patients, obesity was associated with an odds ratio of 2.2 for superficial infections and 2.4 for deep infections [10]. Furthermore, registry data show a 7% increase in risk per unit of body mass index (BMI) above a threshold of 35 [11]. A number of potential mechanisms are implicated. Obese patients have disrupted microcirculation and macrocirculation [12], decreased wound healing [12], and impaired immune function [13]. Surgically, they are associated with

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**Table 1**
Patient Demographics.

| Variable | Intraosseous Group | Systemic Group |
|---|---|---|
| Number of males | 7 | 6 |
| Number of females | 4 | 5 |
| Age (years) | 66 | 63 |
| BMI | 41 | 40 |
| Procedure length (minutes skin to skin) | 80 | 85 |
| Estimated glomerular filtration rate | 65 | 76 |
| ASA score | 3 | 3 |

ASA, American Society of Anaesthesiologists; BMI, body mass index.

greater difficulty [14] and a longer surgical time [15], prolonging exposure to microorganisms [16]. The higher risk of PJI has led some authors to suggest refusing TKA in patients above a certain BMI threshold [17]. However, obese patients benefit from TKA at least as much as patients with a normal BMI [5], and therefore, strategies to reduce PJI risk in high-BMI patients are needed.

In the nonobese TKA population, intraosseous regional administration (IORA) of prophylactic antibiotics provides tissue concentrations 5-8 times higher than systemic administration in TKA [18]. However, the physiology in the obese patient unpredictably alters pharmacokinetics for different drugs [19]. For vancomycin, there is a higher volume of distribution and a shorter elimination half-life in the morbidly obese to nonobese individuals [20]. Thus, vancomycin requires total body weight–based dosing to achieve ideal target steady-state concentrations when given systemically [21]. The importance of higher dose of vancomycin is emphasized with bony infections as it displays poor bone penetration in animal models [22]. We hypothesized that a non–weight-based low-dose of vancomycin via IORA could still achieve adequate tissue concentrations equal or superior to those of weight-based systemic administration of vancomycin before TKA. Hence, the purpose of this study was to compare tissue concentrations of intravenously and intraosseously administered vancomycin in the obese population undergoing TKA.

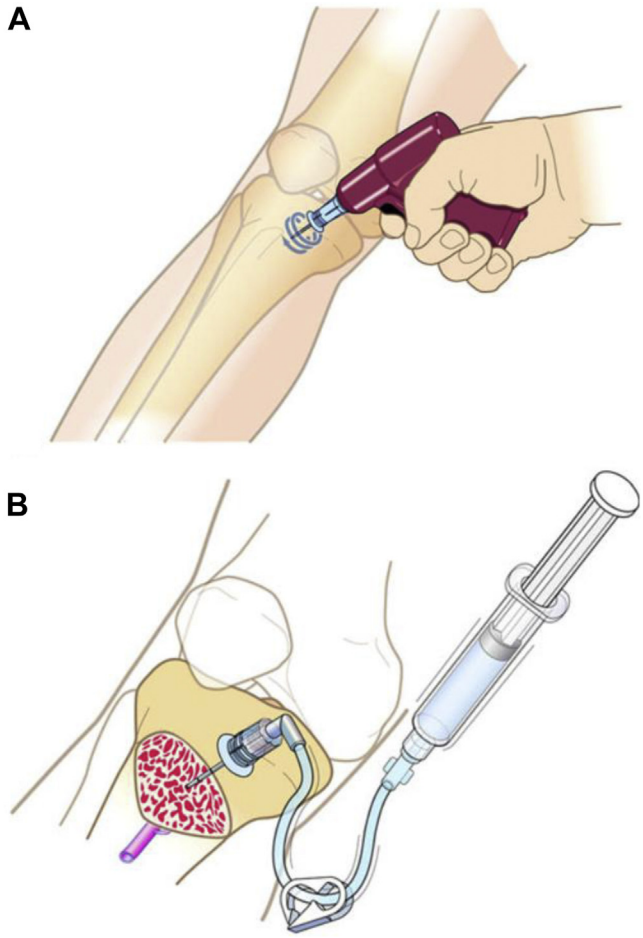


**Fig. 1.** Images show (A) insertion of the intraosseous needle using a sterilized driver and (B) the needle in situ allowing injection of the antibiotic, occurring after tourniquet inflation and before skin incision.
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## Patients and Methods

Patients undergoing primary TKA at a single institution were eligible for enrolment into this prospective, randomized controlled trial. Ethical approval was obtained from the national ethical review board, and the trial and protocol were registered with ClinicalTrials.gov (Identifier: NCT02527148). Inclusion criteria were patients with a BMI ≥35, age 55-85 years, and undergoing primary TKA for a diagnosis of osteoarthritis. Exclusion criteria were allergy to an antibiotic used in the study or abnormal cardiac or renal function or concurrent nephrotoxic medications or previous compartment syndrome. From May 2015 to May 2016, 22 patients were enrolled and randomized into 2 groups using computer-generated random allocations placed in numbered, opaque, sealed envelopes (Table 1). Patients were randomized in the preoperative area to allow time for systemic vancomycin infusion and appropriate setup in the operative room. Patients were followed up for 6 months for potential complications.

All patients received standard prophylaxis of systemic intravenous (IV) cefazolin 15 minutes before tourniquet inflation regardless of randomization—either 2 g for patients between 80 kg and 120 kg or 3 g for patients over 120 kg. All patients underwent limb exsanguination and inflation of an above-knee tourniquet to 300 mmHg before routine preparation and draping. The tourniquet remained inflated for the entire procedure.

The intervention group (500-mg IORA) received 500 mg of vancomycin in 150 mL of normal saline via IORA using an EZ-IO (Teleflex Corp, San Antonio, TX; Food and Drug Administration approved) intraosseous cannula, placed into the medial aspect of the proximal tibia approximately at the level of the tibial tubercle after draping and before skin incision (Fig. 1). The injection was administered as a bolus immediately after tourniquet inflation, and surgical incision occurred immediately (<1 minute) after this. The control group (systemic) was given 15 mg/kg vancomycin based on actual body weight (maximum of 2g) through a forearm vein over a 1-2 hour infusion (1g per hour), beginning 60 to 120 minutes before surgery.

Samples of subcutaneous fat and femoral cancellous bone (approximately 0.5 $cm^3$) were taken at 4 points during the procedure. The first subcutaneous fat sample was taken immediately after skin incision, and subsequently, both bone and fat samples were taken at the time of the distal femoral cut, at the time of trialling components, and immediately before closure. Bone samples were taken from the distal femur using a curette. Collection times were recorded for each sample (Table 2). In addition, systemic blood samples were taken 1-2 hours after tourniquet deflation. In our previous study of IORA vancomycin, peak systemic concentration in the intraosseous group occurred 60 to 70 minutes after tourniquet deflation [18].

Tissue samples were rinsed in saline to remove excess blood and stored at −80°C until analyzed. Vancomycin concentrations were analyzed using our previously published liquid chromatography coupled with tandem mass spectrometry method [18,23]. All

**Table 2**
Mean Tissue Concentrations of Vancomycin at Each Sample Point.

| Sample | Systemic | | 500-mg IORA | |
|---|---|---|---|---|
| | Time | Concentration[a] | Time | Concentration[a] |
| | Minutes (±SD) | μg/g (±SD) | Minutes (±SD) | μg/g (±SD) |
| Subcutaneous fat 1 | 2 (1) | 5 (5.8) | 2 (1) | 82 (80) |
| Subcutaneous fat 2 | 19 (10) | 5.1 (2.9) | 18 (6) | 16 (18.7) |
| Subcutaneous fat 3 | 47 (14) | 4.8 (3.1) | 44 (10) | 27.7 (30.3) |
| Subcutaneous fat 4 | 72 (15) | 2.6 (1.3) | 65 (15) | 17 (16.1) |
| Bone sample 1 | 19 (10) | 7.7 (7.8) | 18 (6) | 16 (18.7) |
| Bone sample 2 | 47 (14) | 5.5 (4.5) | 44 (10) | 66.2 (120.3) |
| Bone sample 3 | 72 (15) | 5.1 (3.6) | 65 (15) | 20.9 (25.3) |

ASA, American Society of Anaesthesiologists; SD, standard deviation
[a] Differences in the mean tissue concentrations on the log scale between the 2 groups were statistically significant ($P < .001$) adjusted for age, sex, BMI, and ASA score.

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 controlled trial comparing IORA vs systemic administration of vancomycin [18] showed mean (±standard deviation) tissue concentrations of vancomycin in subcutaneous fat at different collection intervals ranged from 32 (±18) to 52.3 (±67) μg/g in the IORA group and from 2.4 (±1.5) to 4.4 (±2.0) μg/g in the systemic group. The mean tissue concentration in bone ranged from 20.7 (±7.0) to 81 (±11.1) μg/g in the IORA group and from 3.3 (±2.4) to 5.3 (±2.7) μg/g in the systemic group. Using these data, a priori power analysis calculated 11 patients in each arm would provide greater than 90% statistical power to detect the expected fold difference in subcutaneous fat and bone concentrations between the 2 groups at the 5% significance level.

### *Statistical Analysis*

Means, standard deviations, 95% confidence intervals, and median and interquartile ranges were calculated for the concentrations in the different samples. Different tissue samples were pooled according to the surgical steps at which they were taken. A mixed-effect repeated-measure analysis of variance was used to compare the average level of log concentration across time among groups adjusted by sex, age, BMI, American Society of Anaesthesiologists score, and time from incision. The interaction between time from incision and group was also assessed. For those with serum blood sample concentrations of less than 2 μg/mL, a random imputation was applied according to the available information and assumed the missing data are left-censored normally distributed on the log scale.

## Results

The overall mean tissue concentration of vancomycin was higher in the IORA group than in the systemic group in subcutaneous fat (39.3 μg/g vs 4.4 μg/g $P < .001$) and bone (34.3 μg/g vs 6.1 μg/g) (Table 2). There was a significant difference between the groups across all samples in fat (Fig. 2) and bone (Fig. 3). Of tissue samples in the systemic group, 12% (9 of 77) were less than 2.0 μg/g, the minimum inhibitory concentration (MIC) for certain strains of methicillin-resistant *Staphylococcus aureus* (MRSA) [24]. In comparison, 1% (1 of 77) of IORA samples was below this level.

In both groups, we found no significant association between body weight and bone or fat concentration. Systemic vancomycin plasma concentrations were obtained 47-91 minutes after tourniquet deflation. The mean plasma concentration was lower in the IORA group (1.8 μg/ml) than in the systemic group (16.6 μg/ml) ($P < .001$).

### *Complications*

Minor transient systolic blood pressure drops (>10 mmHg) was observed after tourniquet deflation in 2 patients in the IORA group and 6 in the systemic group. There were no clinical signs of red man syndrome in any patients from either group. One patient in the IORA group developed a right-sided subsegmental pulmonary embolus on day 3 postoperatively, treated with anticoagulation. Two patients in the systemic group developed superficial infections; one patient was treated with a course of oral cefaclor, and the other patient required a superficial wound debridement and closure of a stitch abscess with a course of IV flucloxacillin and *Staphylococcus dysgalactiae* was cultured. No deep infections occurred in either group.

## Discussion

Obesity is a growing problem in the TKA population, and these patients are at increased risk of PJI [7]. Inadequate tissue concentrations of prophylactic antibiotics in the obese patient have been implicated in the increased PJI risk [25]. This study found a fixed smaller dose IORA of prophylactic vancomycin resulted in a 5- to 9-fold increase in tissue concentrations in both fat and bone compared to a weight-based systemic administration in the obese population. These higher concentrations have the potential to provide more effective prophylaxis in this high-risk population group [26].

The average BMI of our IORA and systemic groups was 41 and 40, respectively. Although PJI risk increases with a BMI greater than 30 [10], the risk is more pronounced for BMI greater than 35 [11]. As over 50% of bacteria causing early PJI are resistant to cefazolin, vancomycin has been suggested as an additional prophylactic agent in high-risk patients [27]. Early PJI is commonly caused by coagulase-negative staphylococcus [28], and as many as 90% of

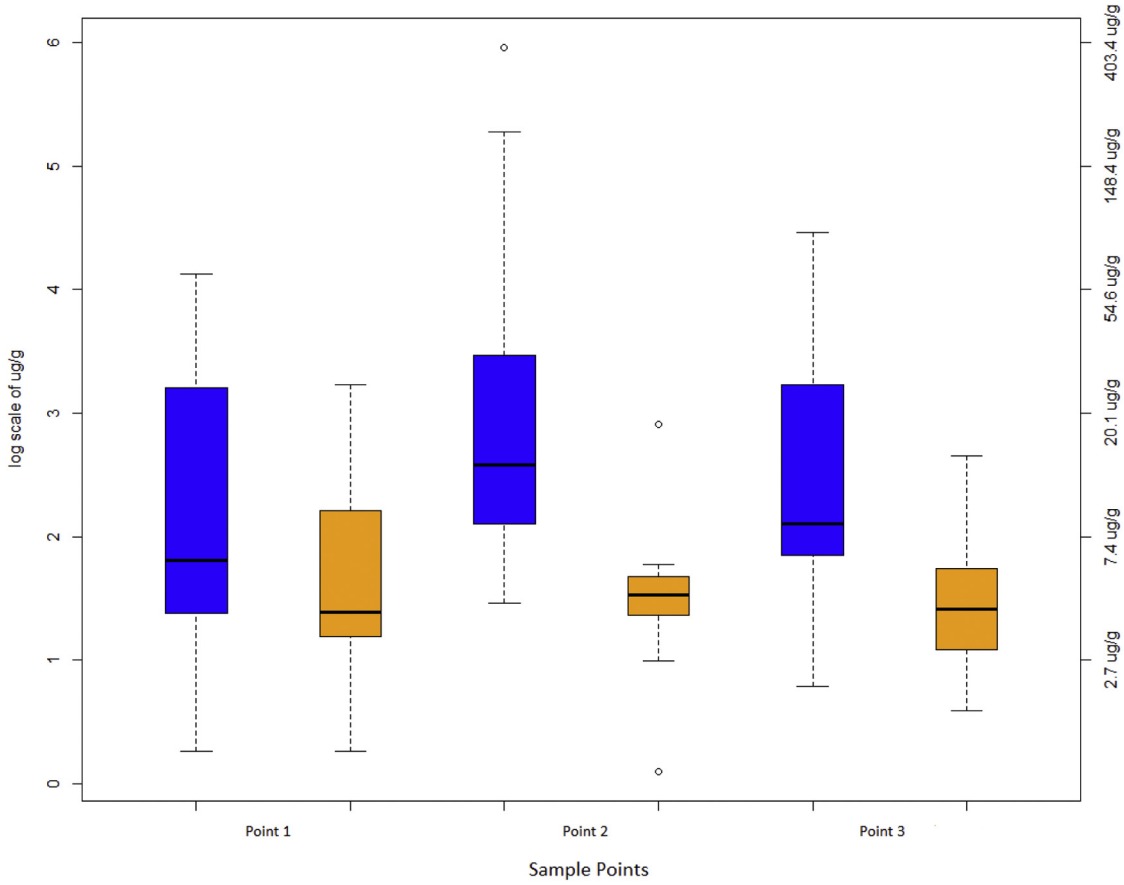


**Fig. 2.** A graph shows the tissue concentrations of vancomycin in bone at each sample point. The 500-mg IORA group is in blue and the systemic group is in orange. Box represents the median; horizontal line in box represents the 25% and 75% quartiles; whiskers represent 1.5 times the interquartile range from the box.

hospital coagulase-negative staphylococcus isolates are resistant to cephalosporins [29]. In addition, some centers have reported between 30% and 56% of *Staphylococcus aureus* cultured from infected joint arthroplasties as MRSA [30,31]. Obesity is an independent risk factor for MRSA colonization [32].

The major combined pharmacodynamic-pharmacokinetic parameter correlated with therapeutic efficacy for vancomycin is the area under the concentration-time curve (AUC) divided by the MIC, AUC/MIC [24]. The therapeutic target of AUC/MIC for vancomycin is 400 [33]. Greater tissue vancomycin concentrations increase efficacy and duration of action by increasing the AUC [34]. This is particularly important for treating MRSA strains with a higher MIC [24], which is associated with higher treatment failure [35]. Several centers have observed an increase in MIC among MRSA isolates [36,37]. In our systemic group, we found 9 of 77 samples in 4 patients (none of whom were limited by the 2 g ceiling dose for systemic vancomycin) were below this level, compared with one sample in the IORA group.

Reaching therapeutic concentration of vancomycin is more difficult in the obese population. In clinical practice, the AUC/MIC is impractical to measure. Thus, serum trough concentration, which is predictive of AUC/MIC [33], is used as its surrogate measurement. Catanzano et al [38] reported inadequate serum concentrations in 60% of 216 patients given systemic vancomycin prophylaxis. Kheir [25] reported appropriate vancomycin prophylaxis dosing in only 28% of 1828 arthroplasty patients, with underdosing more likely in obese patients. Further to treatment failure with inadequate serum concentrations, subtherapeutic concentration of vancomycin has been implicated in the development of resistant strains [39,40]. To mitigate this, we used a systemic vancomycin dose based on actual body weight as per the current recommended loading dose [20]. The IORA group received a fixed 500-mg dose, which has previously achieved higher tissue concentrations than both a fixed systemic 1 g dose and 250 mg intraosseous dose without adverse effects in a nonobese population [18].

Weight-based systemic dosing, especially in the large doses required in the obese population, necessitates an increase in infusion period to 1 to 2 hours to avoid red man syndrome [41]. This potentiates vancomycin's association with poor timing of prophylactic administration, reportedly as low as 22% in arthroplasty cases [42], possibly impairing its clinical efficacy [43]. It can also add additional operating room utilization time, which is already higher for the obese patient group [44]. By allowing a bolus injection, IORA ensures correct timing of vancomycin prophylaxis with minimal addition to operative time.

Higher vancomycin doses and trough concentrations are associated with nephrotoxicity [45,46] and high-frequency hearing loss in older patients [47]. Obese patients have a further increased likelihood of developing nephrotoxicity because of vancomycin [48]. We found patients in the systemic group had a significantly higher serum concentrations level (16.6 μg/ml) than in the IORA group (1.8 μg/ml) after tourniquet deflation. This suggests a protective effect of IORA to systemic toxicity from vancomycin. This finding is consistent with our previous study in the nonobese population [18]. Tourniquet's efficacy in preventing a rise in systemic plasma concentration of administered drugs is established in the practice of Bier blocks [49]. Specific to intraosseous administration of vancomycin, animal models have shown that it distributes out of the intravascular compartment with time [50].

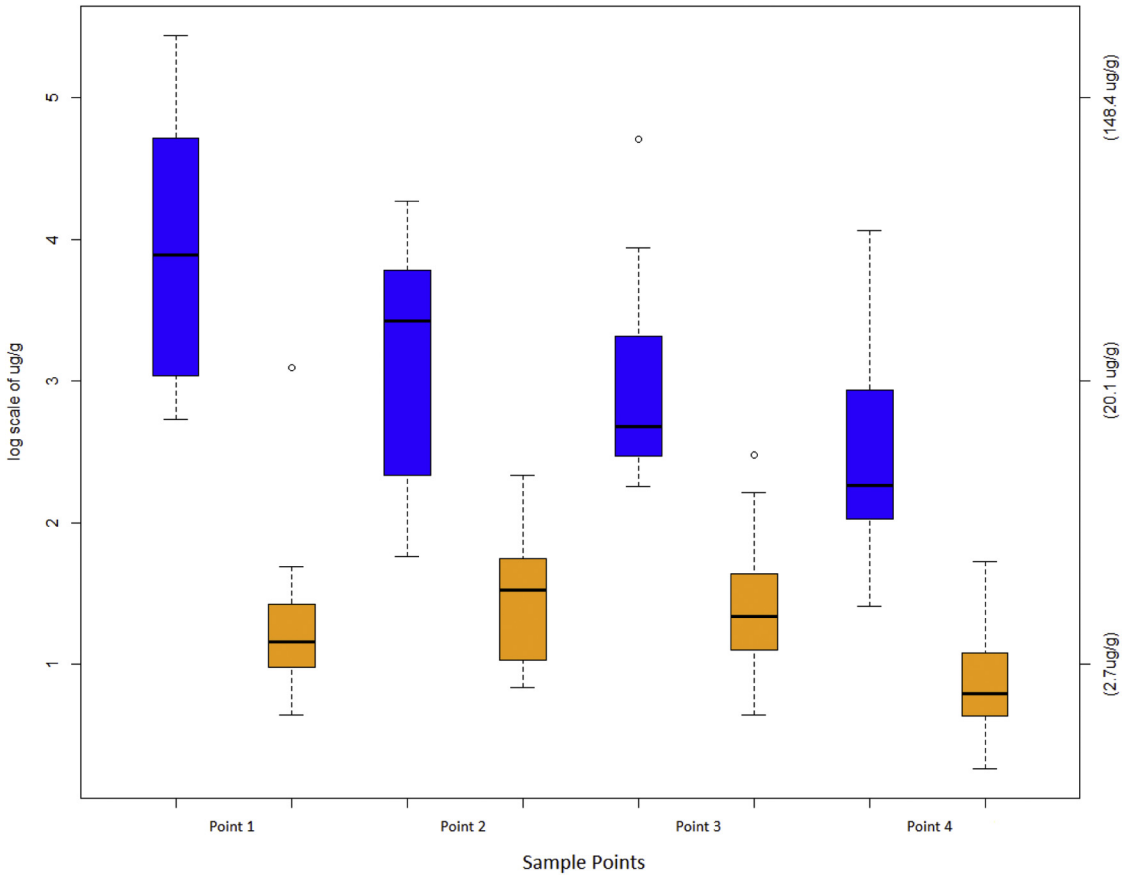


**Fig. 3.** A graph shows the tissue concentrations of vancomycin in subcutaneous fat at each sample point. The 500-mg IORA group is in blue and the systemic group is in orange. Box represents the median; horizontal line in box represents the 25% and 75% quartiles; whiskers represent 1.5 times the interquartile range from the box.

There are a number of limitations to our study. First, while we found higher tissue concentrations of vancomycin with IORA, this study design does not prove that this will result in a reduction in PJI. The rarity of PJI as a complication, even in high-BMI patients, makes powering a clinical study with PJI as the outcome difficult. However, in murine models of TKA, prophylaxis with IORA vancomycin was more effective than the same dose administered systemically in preventing PJI [26]. Limitations pertinent to intraosseous route of delivery include the potential for red man syndrome. This reaction is dependent on the dose administered and time of infusion [41]. Intraosseous delivery is as effective as IV delivery to the intravascular compartment [51]. Thus, as vancomycin was administered as a push bolus in our study, the patients were at potential risk of red man syndrome. However, we found a minimal increase in plasma vancomycin concentrations after tourniquet deflation, and a higher IORA dose in obese patients may be possible without causing red man syndrome.

## Conclusion

This study has found low-dose IORA effective in the high-BMI population group, providing tissue concentrations of vancomycin 5-9 times higher than systemic administration. This was despite an unadjusted IORA dose of 500 mg, compared with a weight-adjusted systemic dose. Systemic concentrations remained low after tourniquet deflation after IORA, and a higher IORA dose could be considered in the high-BMI patient. IORA optimizes timing of vancomycin administration and reduces the risk of systemic adverse effects, while providing high tissue antibiotic concentrations during TKA.

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