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2023 Hip Society Award

Otto Aufranc Award: Intraosseous Vancomycin in Total Hip Arthroplasty — Superior Tissue Concentrations and Improved Efficiency

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ABSTRACT

Background: Literature shows that intraosseous (IO) infusions are capable of providing increased local concentrations compared to those administered via intravenous (IV) access. Successes while using the technique for antibiotic prophylaxis administration in total knee arthroplasty (TKA) prompted consideration for use in total hip arthroplasty (THA) however; no study exists for the use of IO vancomycin in THA.

Methods: This single-blinded randomized control trial was performed from December 2020 to May 2022. Twenty patients were randomized into 1 of 2 groups: IV vancomycin (15 mg/kg) given routinely, or IO vancomycin (500 mg/100cc of NS) injected into the greater trochanter during incision. Serum vancomycin levels were collected at incision and closure. Soft tissue vancomycin levels were taken from the gluteus maximus (at start and end of case), and acetabular pulvinar tissue. Bone vancomycin levels were taken from the femoral head, acetabular reamings, and intramedullary bone. Adverse local/systemic reactions, 30-day complications, and 90-day complications were also tracked.

Results: A statistically significant reduction in serum vancomycin levels was seen when comparing IO to IV vancomycin at both the start and at the end of the procedure. All local tissue samples had higher concentrations of vancomycin in the IO group. Statistically significant increases were present within the acetabular bone reamings, and approached significance in intramedullary femoral bone.

Conclusion: This study demonstrates the utility of IO vancomycin in primary THA with increased local tissue and decreased systemic concentrations. With positive findings in an area without tourniquet use, IO may be considered for antibiotic delivery for alternative procedures.

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Vancomycin is a commonly used prophylactic antibiotic for total joint replacement surgery in an attempt to protect against methicillin resistant staph aureus (MRSA). Recent literature has suggested that using intraosseous (IO) infusions is capable of providing equivalent systemic values to those administered via intravenous (IV) access [1,2]. Because of these findings, some began to consider that IO infusions could be a better way to administer prophylactic surgical antibiotics. A prospective randomized study out of Australia evaluated the local and systemic concentrations of vancomycin after IO versus IV administration and found that low-dose IO vancomycin resulted in tissue concentrations equal or superior to those of systemic administration [3]. The authors reported that IO optimizes timing of vancomycin administration, and the lower dose may reduce the risk of systemic side effects while providing equal or enhanced prophylaxis in total knee arthroplasty (TKA) [3]. Literature has shown this benefit remains, even for those with a higher BMI [4].

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IO infusions have been shown to improve tissue concentrations of antibiotics at the operative site with lower systemic concentrations and reduced infection rates in primary TKA. A study by Park et al found that at 90 days postoperatively, patient(s) who received IO antibiotics had statistically significant lower periprosthetic joint infection (PJI) rates than those who received their antibiotics via IV route [5]. However, no study has evaluated the use of IO vancomycin in total hip arthroplasty (THA). While literature supports the greater trochanter and anterior superior iliac spine as viable intraosseous administration locations [6], the practicality of using such a location outside of the pediatric population has not been assessed. In addition, without the use of a tourniquet, there is concern that serum levels may be elevated when compared to standard intravenous (IV) infusion. The purpose of this randomized prospective single-blinded control study was to 1) test whether or not IO protocols are a feasible option in the administration of vancomycin before THA and 2) to evaluate the safety and efficacy of antibiotic delivery of such a procedure.

Methods

This is a randomized, prospective, single-blinded control study performed at a single tertiary care hospital from December 1, 2020 to May 31, 2022. Institutional review board (IRB) approval was acquired for the study. Twenty (20) patients were randomized into 1 of 2 groups: IV vancomycin (15 mg/kg) given within 1 hour before incision, or IO vancomycin (500 mg in 100cc of normal saline) injected into the greater trochanter at the time of surgical incision. IO dose was determined from previous IO papers showing safe-dose values [3–5]. Patients were blinded as to which group they had been randomized into. Randomization was performed using an excel-based program at a 1:1 ratio. Tissue and serum samples were sent to the lab coded so that lab personnel were blinded. Inclusion criteria were any patient over the age of 18 years who was undergoing a primary THA who consented to the procedure. Exclusion criteria included previous surgery on the hip (including hip scopes), BMI >35, contraindication to receiving vancomycin, cefepime or cefazolin (ie, allergy, etc.), inability to palpate/locate the greater trochanter or successfully administer the IO infusion, diabetics with A1c >7.5%, and immunocompromised or immunosuppressed patients (HIV, Hepatitis C, end stage renal disease (ESRD), post-transplant, chemotherapy or radiation therapy within 6 months of surgery, immunomodulating medications). Patient data collected included age, date of surgery, discharge date, sex, laterality, study group, preop and postop creatinine levels. Intraoperative samples taken for the study are detailed below. Adverse local and systemic reactions as determined from patient's chart, 30-day complications, 90-day complications, time from antibiotic administration to incision, and operative time were recorded.

Intraosseous Technique and Intraoperative Samples

Once a patient was randomized into 1 of the 2 subject groups, the remainder of the protocol proceeded identically. Both groups also received weight-based preoperative IV cephazolin during the study period to ensure acceptable preoperative antibiotic compliance should the intervention group be unsuccessful. Eighteen (18) patients underwent a postero-lateral approach (9 IV, 9 IO), while 2 patients underwent a direct anterior approach (1 IV, 1 IO). Before incision, the intervention group received an IO injection of vancomycin into the greater trochanter, following which the surgery would proceed routinely per the operating surgeon. During the procedure the same samples were taken in all patients. Serum vancomycin levels were collected at the time of incision and at the initiation of closure. Soft tissue vancomycin levels were taken from the following locations during the case: gluteus maximus (at the start and end of case) and pulvinar tissue within the acetabulum after hip dislocation. Bone vancomycin levels were taken from the following locations: femoral head (taken after femoral head was removed), acetabular reamings (taken from first reamer used within the acetabulum), and intramedullary bone (taken after canal was established for broaching but prior to broaching, from the medial calcar).

Sample Preparation

Once samples were collected, they were minced and then weighted. Collagenase I at a concentration of 20 mg/mL in PBS, was used for samples' digestion (overnight 36 °C). Stock solution (10 mg/mL) of Vancomycin (VANC) and working solution (1 mg/mL) were prepared in Phosphate buffered saline (PBS). Calibration standard solutions were prepared by serial dilution with PBS. The final concentrations for calibration standard solutions were 500, 250, 125, 62.5, 31.25, 15.63 and 7.81 mg/L. Finally; the samples were homogenized with a sonicator. Caffeine was added as internal control in the vial containing the digested sample, at a final concentration of 2 mg/mL. The different samples (femur, acetabulum, intramedullary bone, pulvinar, gluteus maximum) were centrifuged at 15,000 rpm for 5 minute and supernatant was collected and filtered before injection into the HPLC machine. Chromatography was performed on a Waters e2695 Alliance HT HPLC system. The pH was adjusted using phosphoric acid. Separation was carried out isocratically with a flow rate of 0.36 mL/minute at room temperature with UV detection at 205 nm. The run time for each sample was 25 minute. The characteristic elution peak of vancomycin was at 11 minute, while caffeine (internal standard) was at 20 minute.

Statistical Analysis

Vancomycin tissue concentrations were compared using a mixed model ANOVA with BMI, incision time, and vancomycin dose entered into the model as covariates to determine potential influence on concentration measurements. Following initial analysis, review of Type III tests of fixed effects revealed that none of the covariates were significant. Therefore, an independent samples *t*-test was used for final comparison between groups. Type I error was set at alpha = 0.05 for all analyses. A Priori power analysis was conducted based on estimated mean differences of 20 ug/mL with standard deviation estimates of 15 ug/mL for mean tissue sample concentrations. Using these estimates, a priori power analysis at 80% power calculated 10 patients in each arm. Data from previous IO versus IV trials in the TKA literature reported similar sample sizes [3–5].

Results

Patient demographics between the 2 cohorts had no statistical differences (Table 1). IV vancomycin was ordered by weight-based

Table 1
Patient Demographics.

Independent Variable	IV (n = 10)	IO (n = 10)	*P*-Value
Males (n)	80.00%	70.00%	.606
Females (n)	20.00%	30.00%	
Age (y)	68.73 ± 1.78	67.88 ± 1.29	.705
BMI (kg/m^2)	27.37 ± 1.48	27.85 ± 1.54	.824
Δ Creatinine (mg/dL)	−0.001 ± 0.05	−0.012 ± 0.02	.932

Values are presented as means ± Standard Error for age (y), body mass index (BMI, kg/m^2), and Δ Creatinine (mg/dL) and proportions of males and females in each group. No significant interactions were observed between groups at $\alpha = 0.05$.

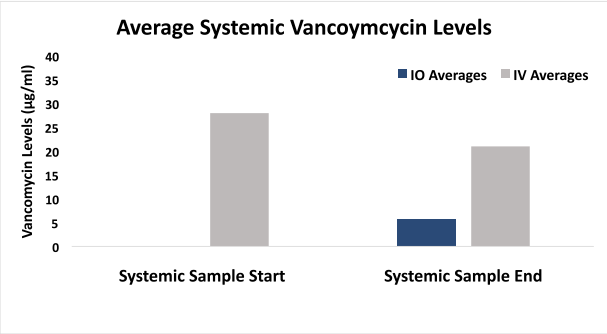

Fig. 1. Graph showing the serum vancomycin levels (ug/mL) for patients in both the IV and IO antibiotic administration group at the start of the case and at the end of the case. These samples were drawn from a unique draw location within the upper extremity.

dosing and the start time was established to complete before incision. Completion of dose before incision was confirmed during surgical time out and confirmed through review of the records to be completed within 1 hour of incision. There was a statistically significant reduction in serum vancomycin levels (ug/mL) when comparing IO to IV vancomycin administration at both the start of the procedure (IO = 0, IV = 28.0 ± 6.1, $P < .001$) and at the time of closure (IO = 5.8 ± 1.0, IV 21.0 ± 2.5, $P < .001$) (Fig. 1). Despite this, vancomycin concentration levels were higher in all tissue samples tested. A statistically significant increase in IO tissue concentration compared to IV was present within the acetabular bone reamings (IO = 130.9 ± 14.4, IV = 68.0 ± 7.9; $P = .001$), and approached significance in the intramedullary femoral bone (IO = 59.4 ± 9.0, IV = 33.9 ± 8.5; $P = .053$). The remainder of tissue samples had higher concentrations of vancomycin, but these were not statistically significant. The tissue vancomycin levels in all other samples are as follows: gluteus maximus (GM) initial (IO = 69.08 ± 15.30, IV = 63.77 ± 13.76; $P = .80$), GM at closing (IO = 78.22 ± 10.72, IV = 57.14 ± 12.04; $P = .22$), pulvinar soft tissue (IO = 71.8 ± 18.2, IV = 61.6 ± 17.6; $P = .7$), and femoral head bone sample (IO = 41.5 ± 9.5, IV = 20.9 ± 6.9; $P = .1$) (Fig. 2).

Serum creatinine levels were equivalent between the 2 groups (IO = −0.012 ± 0.019, IV = −0.007 ± 0.045; $P = .93$), with no evidence of acute kidney injury (AKI) in either cohort group. There were no immediate complications identified within the IO group related to the injection during the case or in the immediate aftermath with the injection site. Reported 30-day complications were 1 in the IV group (surgical related) and 2 in the IO (both unrelated to the intervention). The IV patient had serosanguinous wound drainage 8 days postop, which resolved without further surgical intervention. One patient in the IO group presented to the ED for rectal bleeding (which was found to not be related to the study) and the other IO patient had a fall off steps at home on postop day 17 resulting in a Vancouver B2 periprosthetic fracture requiring revision. There was no infection at the surgical site at time of revision, or at 90 days postop from the revision. There were no reported 90-day complications in either group.

Discussion

This unique, first-time study presents a novel application of a trending technique of IO administration of antibiotics during total joint replacements. Previous studies performed exclusively within TKA patients have shown promising results in both increased tissue concentrations and decreased systemic concentrations of antibiotics [1–4], and their ability to decrease infection rates and systemic complications due to these concentrations [5,7]. Initially, we agreed with authors that tourniquet use was vital to the success of the procedure [1,2]. However, further studies demonstrated increased concentrations within the tissues, even after the tourniquet had been deflated in TKA [3]. With this discovery in mind, our institution sought to investigate whether these benefits seen within the TKA literature could be extended to other locations. We have shown that concentrations of antibiotics are statistically higher in bone samples and higher throughout all tissue samples when using IO compared to IV, even without the capability of restricting blood flow to the area. In addition, systemic/serum vancomycin levels were significantly lower in all IO samples.

Infection rates for THA range anywhere from 0.4% to 1.4%, cause severe morbidity to the patient and are costly to the healthcare industry [8], however some suggest that these numbers may be drastically under reported [9]. Literature has shown that staphylococcus aureus and coagulase-negative staphylococci are the most common bacteria to cause THA infections, with enterococci, enterobacteriaceae and streptocci also being common [10]. Some risk factors for PJI in hips include increased BMI, diabetes, smoking, renal failure and preoperative MRSA colonization [11]. In addition, the direct anterior approach has been shown to have higher PJI

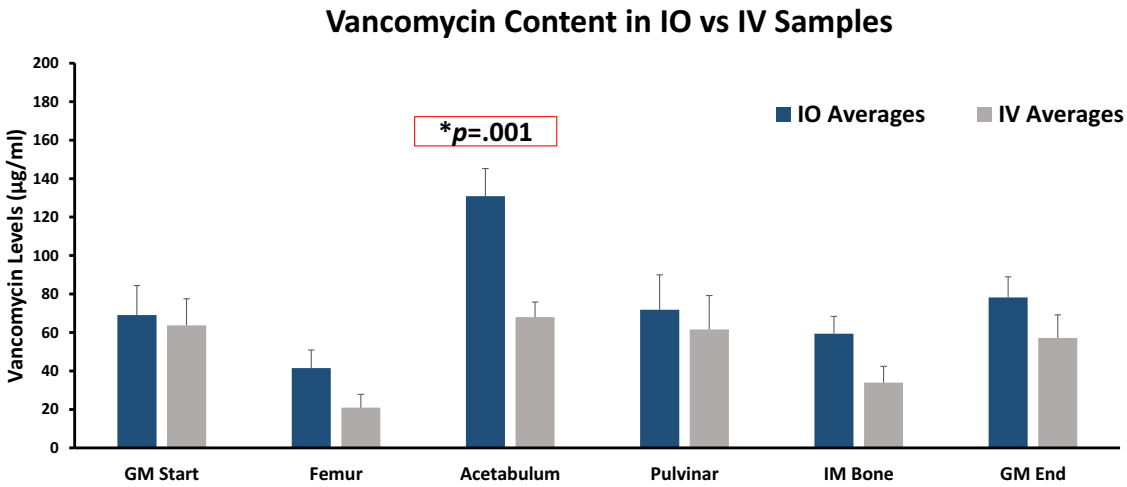

Fig. 2. Graph showing the local tissue and bone vancomycin concentrations (ug/mL) for patients in both the IV and IO antibiotic administration group at each of the 6 locations, highlighting statistically significant findings.

rates than those performed through a nonanterior approach [12]. If an infection occurs, overall complications with in situ antibiotic spacer treatments can approach 26% [13], with the most common complications being mechanical failure of the spacer or persistent infection [14]. This significant complication rate in treatment of periprosthetic joint infection (PJI) of the hip is responsible for 1-year mortality rates reported at ~4.2% and 5-year mortality reported to be as high as 21% [15]. Thus, it behooves surgeons to seek any way to improve outcomes and lower the risk of PJI. Our data showed antibiotic concentrations are higher in those treated with IO vancomycin versus IV, supporting the efficacy of this antibiotic delivery method. Literature has already shown that these higher concentrations decrease the infection rates in TKA [5], and further studies will be necessary show the same for THA.

A component of surgery that has been shown to decrease surgical site infections is administration of antibiotics within 1 hour of incision [16]. Vancomycin is commonly used as antibiotic prophylaxis in THA cases for patients with penicillin allergies, those colonized with MRSA and those considered high risk for infection [16,17]. However, literature has shown that a large majority of patients who receive vancomycin as a preoperative antibiotic are underdosed based on their weight or receive incomplete doses [17,18]. A study by Feder et al showed that patients whose vancomycin administration was begun <30 minutes from incision were more likely to be admitted for infection concern and more likely to have a diagnosed PJI [17]. This was largely due to incomplete administration of the appropriate dose. In addition, a study by Kheir et al found that patients who were underdosed due to receiving a standard 1g of vancomcyin (rather than a weight-based dose) were shown to increase their risk of subsequently developing MRSA PJI [18]. This becomes even more important when noting that those at higher risk for underdosing, such as obese patients, also carry with them higher baseline infection risk [19]. Using IO infiltration for the delivery of vancomycin has shown to increase tissue concentrations above IV in all locations, and within the bone, statistically significantly so, which would decrease the risk of underdosing patients. It's important to note that in our study, IV-based vancomycin was weight-based, while IO-based vancomycin was given as a standard dose (500mg). Even with this difference, the IO values in tissue were greater. More recent studies have indicated that dual-agent prophylaxis reduces rates of PJI, however concern regarding systemic complications remain when using dual agents [16,20].

While decreasing your PJI risk is desirable, the biggest concern with using dual agents for antibiotic prophylaxis is causing an acute kidney injury (AKI). A study by Courtney et al showed that patients who received cefazolin and vancomycin together as prophylaxis for total joint replacement were more likely to have an acute kidney injury and the severity of injury was higher, with more Grade II and Grade III injuries in those receiving dual agents [20]. Incidence of AKI in primary THA has been linked to perioperative antibiotic choice [20,21], and those who sustain an AKI have been shown to have poorer overall outcomes, increase length of stay and increased cost of hospitalization compared to those who did not sustain an AKI [21]. However, a study by Harper et al showed that using IO vancomycin in TKA did not increase the incidence of AKI when compared to IV administration of vancomycin [7]. IO administration ensures adequate vancomycin dosing locally and avoids underdosing, allows for dual agent coverage and simultaneously minimizes systemic complications normally associated with using vancomycin.

Limitations of the study include small sample size, patient characteristics and outcome measures. While larger study samples allow for broader application of the findings, the power analysis determined the sample size was adequate, and we were able to acquire statistically significant results. This lends to increased confidence that the findings were reliable. While our BMI cutoff was <35, our mean BMI was <28, which could be the result of selection bias. We attempted to counteract this by performing screening and enrollment without taking into account body habitus, to avoid excluding undesirable fat distributions. Finally, the results are unable to conclude if surgical outcomes or infections are decreased with this antibiotic delivery method.

Conclusion

This first-of-its-kind study demonstrates the efficacy and utility of IO delivery of vancomycin in primary THA, with increased local tissue concentrations and decreased systemic concentrations. By showing IO administration of antibiotics works in locations with large volumes of soft tissue without blood flow restriction, it is a promising step in improving THA outcomes. Future studies will aim to determine if adiposity amount and/or BMI affects the deliverable concentration to the tissues and whether this translates to clinical reductions in infection, as has been shown previously in TKA.

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