PROTOCOL TITLE:

Intraosseous vs. Intravenous Vancomycin Administration in Total Shoulder Arthroplasty: Changing the Paradigm

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REVISION HISTORY

Revision #	Version Date	Summary of Changes	Consent Change (Yes/No)
1	3/7/23	The addition of tissue types for sample collection	Yes
2	6/1/23	The removal of Kendra Ihaza from the study team, the addition of Blesson Varghese to the study team, clarification to the exclusion criteria	No
3	8/31/23	Update 1: Correction of Protocol and ICF version history. Version 2 of the Protocol and ICF were approved via Mod00006367 on 6/1/23 with updates to the protocol and ICF. The documents were updated and have been the only documents used to enroll subjects thus far. However, it was noticed that the version numbers were not updated on the documents at that time. Update 2: Clarification of inclusion criteria definition in protocol and screening document	Change 1: Yes, the date Change 2: No

1. Purpose of the Study / Objectives

The purpose of this study is to compare two different antibiotic regimens and techniques during total shoulder arthroplasty.

Primary Objective: Comparable levels of vancomycin will be found in bone, soft tissue, and systemic samples between patient groups.

Secondary Objective: Compare 30 day and 90 day post-operative complication rates (infection) between the control (standard IV administration of vancomycin) vs the interventional group (intraosseous administration of vancomycin). The investigators hypothesize that there will be no difference in complication (infection) rates between groups.

2. Background

Primary total shoulder arthroplasty (TSA) is a common orthopedic procedure whose volume is expected to rapidly increase over the next decade [3]. During TSA, surgeons can choose to utilize anatomic (aTSA) or reverse (RSA) to remove arthritic articular surfaces and insert metal & polyethylene components. Vancomycin is commonly used as a prophylactic antibiotic for total shoulder surgery in an attempt to protect against methicillin resistant staph aureus (MRSA). Recent literature has suggested that intraosseous (IO) infusions are capable of providing equivalent systemic values to those administered via intravenous (IV) access [3,4]. Because of these findings, some began to consider that IO infusions could be a better way to administer prophylactic surgical antibiotics. IO has also recently been shown to significantly reduce periprosthetic joint infection (PJI) in total knee arthroplasty (TKA) [9,10]. This difference is presumably due to the increased concentrations of vancomycin present in bone and soft tissue samples in IO treated patients compared to the standard of care intravenous (IV) vancomycin treated patients [11,12]. Additionally, research has shown significant vancomycin concentration differences present even with limited tourniquet use during TKA [13]. Furthermore, preliminary data on IO injections in total hip arthroplasty have also been shown to provide equal or superior vancomycin concentrations in both bone and soft tissue samples while maintaining significantly lower systemic vancomycin levels in the IO group when compared to the IV group. To date, no protocol exists for the use of IO in total shoulder arthroplasty.

3. Study Design

This study is a prospective, randomized, single-blinded, controlled trial. 20 patients in each treatment arm: 20 patients will be given IV vancomycin, 20 patients will be given IO

vancomycin. This sample size is based on previous studies examining vancomycin concentration in tourniquetless primary total knee arthroplasty between IO vs IV [12,13].

Once the participant has been enrolled, they will be randomized into either the control group or the experimental group by an excel-based software program prior to their procedure.

Control – Standard IV administration of vancomycin

- Patients will receive the Houston Methodist Hospital orthopedic surgeon's standard of care pre-operative antibiotic regimen for primary total shoulder arthroplasty patients. This includes IV abx (typically ancef or cefepime and vancomycin) will be started in the pre-operative period approximately 1 hour prior to incision (vancomycin dose weight-based at approximately 15mg/kg [6,7] generally 1000-1750mg in 500mL NS).

Intervention – Intraosseous (IO) administration of vancomycin

- IV antibiotics (per physician's standard of care): Typically ancef or cefepime is started in pre-op within 1 hour of incision
- IO vancomycin is administered in the OR after sterile prep and draping has occurred (500mg in 100-150mL NS).
- Injection will take place into the proximal humerus

All patients in both groups will be monitored during the surgery and immediately post-operatively for adverse injection reactions (i.e. Red Man Syndrome) as this is the standard of care.

All patients (IV and IO) will otherwise follow identical post-operative protocols (including post-operative antibiotic administration)

Intra-Op Sample Collection

Samples will be taken from the following locations at the following times:

- Systemic Sample – Start of Case
  - A vancomycin blood level will be drawn by the anesthesiologist staff (CRNA, MD) at the start of skin incision prior to any other samples being taken.
- Soft tissue sample – Deltoid muscle at Start
  - A small sample will be taken from the edge of the deltoid muscle
- Soft tissue sample – Biceps tendon
  - A portion of the excised biceps tendon will be sent. This sample will only be taken if it is readily available for the surgeon to gather.
- Bone Sample – Bone from Humeral Head

        - After the humeral neck is cut with the "cookie cutter" instrument a portion of humeral head/neck will be removed and placed in a separate specimen jar (remainder of head will be sent to pathology as usual).
    - Soft tissue sample – Synovium/Capsule
        - A small soft tissue sample will be taken from the synovium upon entering the shoulder joint.
    - Soft Tissue Sample – Labrum
        - A small soft tissue sample will be taken from the glenoid labrum.
    - Bone Sample- Glenoid reaming
        - Reaming fragments from the glenoid will be collected.
    - Soft tissue sample- Deltoid muscle at the End
        - A small sample of the deltoid muscle will again be taken prior to closure.
    - Systemic Sample
        - A vancomycin blood level will be drawn by the anesthesiologist staff (CRNA, MD) at the time of initiation of closure and should occur simultaneously with the final soft tissue sample collection above

Data Variables to be Recorded

Age (calculated from DOB), date of surgery, discharge date, sex, laterality, study group, pre-op creatinine, post-op creatinine, systemic vancomycin level at incision, soft tissue vancomycin level (synovium start and synovium end), humeral head bone sample vancomycin level, and systemic vancomycin level at initiation of wound closure. Additionally, adverse local/systemic reactions as determined from patient's chart, 30-day complications, 90-day complications, cost, time from antibiotic administration to incision, operative time, and incision time.

Statistical Plan and Power Analysis

Not yet published data from 20 participants from a recent study in our lab utilizing IO vancomycin vs IV vancomycin in a primary total hip arthroplasty (THA). Our research team found that there were significant differences for serum vancomycin levels (ug/mL) at the start of the procedure: IO =0, IV = 28.0 ± 6.1, $p<0.001$; and at closure: IO = 5.8 ± 1.0, IV 21.0 ± 2.5, $p<.001$. A significant difference was also present for acetabular bone: IO = 130.9 ± 14.4, IV = 68.0 ± 7.9, $p=0.001$. IO also resulted in higher, but not statistically significant, tissue levels in all other samples: IM bone 59.4 ± 9.0 vs 33.9 ± 8.5 ($p=.05$), femoral head 41.5 ± 9.5 vs 20.9 ± 6.9 ($p=0.1$), and pulvinar soft tissue 71.8 ± 18.2 vs 61.6 ± 17.6 ($p=0.7$).

Based on previous data from our laboratory using IO vancomycin in total hip arthroplasty along with other previous reports [11-13] using very similar procedures, for a minimum detectable difference between techniques (IO vs IV) of 30 μg/mL for surgical site bone concentrations of vancomycin with a power of 0.8 ($\alpha=0.05$), a minimum total of 14 patients per group (total 28) will be required. Therefore, we will elect to recruit a total of 20 patients per group to account for potential dropouts.

The statistical model for this investigation will be a mixed model analysis of covariance with repeated measures, co-varied on BMI, gender, length of surgical procedure, time of vancomycin administration, and amount of vancomycin administered. If none of the covariates are significant then two sample t-tests will be used to compare the concentration levels between the 2 groups at each sample point including bone, soft tissue, and systemic samples. We will not make any comparisons between different sample types only comparing groups within the same sample type. Potential demographic differences between groups will be measured using two sample t-tests for numerical data and Chi-Square tests (or Fischer's exact tests in cases where sample sizes are <5). Additionally, 30-day and 90-day wound healing and potential infection complications will be analyzed by Chi-Square tests or in cases where sample sizes are <5 Fischer's exact tests will be used.

4. Study Intervention

All research procedures include the intra-operative sample collections (tissue, bone, and systemic blood sample). If the patient is randomized into the interventional group (IO injection of vancomycin) then instead of receiving pre-operative IV vancomycin they will receive it intraoperatively through IO injection. These are the only changes to the patient's care during their hospital stay. All other pre-operative and post-operative care will be standard of care including pre-operative, peri-operative, and post-operative monitoring. There will be no additional study visits and the anticipated time the subject will be in the study is 90 days. The research anticipates it will take 1 year to enroll all study subjects and for investigators to complete primary analyses. The study will not require any additional research clinical visits and will not interfere with the patient's normal postoperative standard of care.

The estimated amount of time for each subject to participate in this project would be approximately 20 minutes for the informed consent process. All patients in both groups will be monitored during the surgery and post-operatively for adverse injection reactions (i.e. Red Man Syndrome) as this is the standard of care. Additionally, patient medical record (Epic) will be monitored for 90 days after their surgery for differences in rate of infection and/or wound complications. Patients will follow their normal standard of care postoperative clinic visits where the patient will be examined for signs of infection as is the standard of care.

5. Drugs, Biologics, Devices

1) The drug product (Vancomycin) is lawfully marketed in the United States. Vancomycin is a very commonly used antibiotic in orthopedic surgery.

2) This investigation is not intended to be reported to the FDA as a well controlled study for a new indication and there is no intent to use it or support it for significant changes in labeling of the drug.
3) This investigation is not intended to support a significant change in advertising for the drug.
4) There is not a disproportionate increase in risk present for changing the route of administration in the interventional arm (IO injection). The cited studies in Section 2 of the protocol all used 500mg in normal saline as the normal dosage when utilizing IO injection in orthopedic surgery; this is a lower dosage than SOC. All of these studies have shown that there is either higher or equal tissue concentrations in the IO injection groups.
5) This investigation is conducted in compliance with the requirements for review by an IRB with the requirements for informed consent.

6. Collaborative / Multi-site Research

N/A

7. Data Privacy / Confidentiality

Houston Methodist policies for Protected Health Information will be followed, including all requirements for physical and electronic data security, use of encrypted devices and HM password protected servers. All data for this study will be complete, accurate, original, and legible. All physical study data such as data recorded in the intra-operative sample collection sheet will be stored in a locked office cabinet of a qualified member of the research team. All electronic data will be password protected and only accessible by members of the research team. The data for this study will be maintained indefinitely. Any data that is published from this study will be completely de-identified including the removal of any PHI.

The only PHI being used by the research team for this study are dates including discharge dates and birth date (to determine age at time of surgery) as well as MRNs. The use of identifiable data is necessary for the research team to confirm past medical history (example: Diabetes) for the inclusion/exclusion criteria. No PHI will ever be disclosed beyond Houston Methodist. This data will be stored along with other data recorded from Epic on password protected servers accessible only to qualified members of the research team.

Identifier (or parts of)	Recorded	Disclosed	Comment
Names	Yes	No	Recorded prior to any recruitment method. Needed so that qualified members of the research team can

			properly address the patient to inform them about the study.
All elements of dates (except year) for dates directly related to an individual, including birth date, admission date, discharge date, date of death; and all ages over 89 and elements of dates (including year) indicative of such age	Yes	No	Recording birth date to determine age at time of surgery. Recording surgery date of surgery as well.
Phone numbers; Fax numbers	Yes	No	For recruitment purposes. However, the informed consent for this study will only take place in person with a qualified member of the research team.
Medical record numbers	Yes	No	Necessary to confirm past medical history during the screening process.

8. Data and Specimen Banking

N/A

9. Study Population

We will enroll 40 patients.

Inclusion Criteria

- Patient is undergoing anatomic or reverse shoulder arthroplasty
- Patient is able to give informed consent to participate on the study. LAR consents will not be utilized for this study
- Age Range ≥18

Exclusion Criteria

- Previous shoulder surgery if surgeon deems it will affect the study
- BMI above 35
- Contraindication to receiving vancomycin, cefepime, ancef, or other standard of care pre-operative antibiotic (allergy, medical issue, etc).
- Inability to administer the IO infusion
- Refusal to participate
- Diabetes as defined as uncontrolled A1C > 7.5 and eGFR <59

- Immunocompromised or immunosuppressed patients (HIV, Hep C, ESRD, dialysis, transplant, chemo/radiation treatment in last 6 months, medications)

10. Screening and Recruitment [S R]

Potential study patients will be identified by the research team prior to their surgery date by looking at Dr. McCulloch's surgery schedules searching for primary total shoulder arthroplasty surgeries. The potential study patient's medical records will then be viewed in Epic to identify and confirm inclusion and exclusion criteria including age >18, past surgical history on the operative shoulder, BMI level, any contraindication to receiving vancomycin, cefepime, or ancef such as allergy, diabetes, and immunocompromised or immunosuppressed status. If the patient meets the initial criteria to participate in the study then a qualified member of the research team will email or call the patient to inform them about the study and determine if they are interested in possibly participating. Alternatively, the recruitment process may also take place in clinic (6445 Main Street Houston, Texas 77030) after the patient's visit with their physician. In either scenario, meaning phone/email/or in person recruitment, potential study patients will be screened for inclusion and exclusion criteria prior to the informed consent. The informed consent will take place in person with a qualified member of the research team where the patient will be informed about all aspects of the research study to determine if they wish to participate.

Sensitive information such as history of HIV will be asked during the screening process. Should a patient admit to that history and consequently be excluded from the study the screening document will immediately be disposed of in a HIPAA bin to later be shredded. Any data from that patient prior to inclusion in the study will be deleted except for their name and "EXCLUDED FROM PARTICIPATION" in the dataset. It is important to note that screening data will not be collected from email and will only be done either in person or over the phone.

11. Withdrawal of Subjects

Subject reserve the right to withdraw from the study at any given time. All risks will be outlined with the subject during the consent process (see Risks section for more details). The research team reserves the right to remove a subject from the study if they deem necessary for reasons such as but not limited to: the subject fails to comply with the study, the participant no longer meets inclusion criteria, the physician feels it unsafe for the participant to continue.

12. Provisions to Protect the Privacy Interests of Subjects

Only members of the research team will screen the patient data, speak with the patient and have access to their information. If requested, the team member providing the consent will cover each research team member and their role in the study with the subject. It will also be explained that all data is de-identified and stored on password protected servers only accessed by said team members.

13. Risks to Subjects

- Local tissue reaction to injection
- Damage to the proximal humerus (i.e. fracture) – minimal
- Hardware damage (i.e. needle breakage, etc).

No patients develop a therapeutic level of vancomycin after a single dose (1g dose) so the risk for overdosing despite infusion times is minimal if not non-existent [14]

Research has also shown that patients receiving rapid infusions of vancomycin in critically ill patients showed that even those who developed RedMan syndrome did not develop vital organ hypoperfusion and maintained hemodynamic pressure. RedMan was resolved with anti-histamine medications [15].

14. Potential Benefits

Periprosthetic joint infection (PJI) is a devastating complication after total shoulder arthroplasty (TSA) with rates estimated between .4 to 2.9% [2-4]. PJI significantly increases the all-cause mortality rate of TSA patients when compared to comparable patient populations [5]. Additionally, PJI is a large economic burden for TSA patients [6]. Therefore, reducing the incidence of PJI in TSA is important. Intraosseous injections (IO) have recently been shown to significantly reduce PJI in total knee arthroplasty (TKA) [7,8]. The dose of vancomycin in IO administration is lower than that of IV administration (500mg in IO vs. 1000-1750mg in IV). This may reduce the risk of systemic side effects such as PJI while providing equal or enhanced prophylaxis in TSA.

15. Financial and Economic Issues

The subject will not incur any costs nor will they receive payment for participation in this study. Patients will not be charged for systemic vancomycin level testing or for vancomycin concentration sampling of bone and soft tissue. These costs will be covered by the research team.

16. Data Safety Plan

All PHI and data will be de-identified and stored on a Houston Methodist password protected server only accessed by the approved study team members.

- Each subject's data will be evaluated at each study visit to examine both harms and benefits to ensure the subject remains safe
- If at any point before or during the study a patient meets 1 or more of the exclusion criteria listed in section 9 of the protocol, they will be immediately suspended from the study
- No adverse events are expected. However, if an unanticipated problem should occur it will be properly documented on either a deviation log or adverse event log with immediate reporting accordingly.

17. Informed Consent Documentation and Process

Once a subject has met all inclusion criteria and expressed interest in participating in the study, a research team member will cover the consent form with the patient in its entirety. This will be done in person at either the initial clinic visit or pre-op visit. All risks and potential side effects and benefits of participating in this study will be thoroughly explained until the subject fully comprehends all aspects of the study. They will then be asked to sign the consent form. It will be made known that the subject still reserves the right to withdraw from the study at any given point. The research team will not recruit from any vulnerable populations.

18. Waiver of Informed Consent and /or Authorization

Not applicable. Preliminary screening will only take place with patients seen within the Orthopedic Surgery department at Houston Methodist Hospital. There will be no waiver of informed consent for this study.

19. References

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