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PROTOCOL TITLE:

Intraosseous Vancomycin in Primary Total Hip Arthroplasty – Designing a Protocol

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INSTRUCTIONS:

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VERSION NUMBER/DATE

REVISION HISTORY

Revision #	Version Date	Summary of Changes	Consent Change (Yes/No)
1	12/3/2021	Adding doctors Timothy Brown, Kwan Park, and Stephen Incavo as sub-investigators. Edited intra-operative sample collection procedures to include glut max at start and end of the case, pulvinar tissue sample, and an additional systemic sample taken at incision. These samples gathering changes were made in order to ensure more consistent sample gathering across all participating physicians on the study. The additional systemic	Yes

		sample taken at incision was added to include a baseline systemic vancomycin level present at the initiation of the surgical case.	
2	4/25/2022	Changed 15 patients per group to 20 to ensure the research team is able to recruit 30 patients under the current intraoperative sample protocol. Edited section 19 of protocol to include additional justification for HIPAA waiver.	

1. Study Summary

N/A

2. Purpose of the Study / Objectives

Purpose of this study is to compare two different antibiotic regimens and techniques during total hip 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 research team hypothesizes that there will be no difference in complication (infection) rates between groups.

3. Background

Vancomycin is commonly used as a prophylactic antibiotic for total joint replacement surgery in an attempt to protect against methicillin resistant staph aureus (MRSA). Recent literature has suggested that using intraosseus (IO) infusions are 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 in Australia evaluated the local and systemic concentrations of vancomycin after IO vs. IV administration and found that low-dose IO vancomycin resulted in tissue concentrations equal or superior to those of systemic administration [3]. The researchers concluded 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 TKA [3]. Literature has shown that this benefit remains intact,

even for those with a higher BMI [4]. No protocol exists for the use of IO in total hip arthroplasty (THA). While literature supports the greater trochanter and anterior superior iliac spine as viable intraosseus administration locations [5], the practicality of using such a location outside of the pediatric population has not been assessed. We intend to test whether or not IO protocols are a feasible option in the administration of vancomycin prior to THA.

4. 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.

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 hip 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 antibioitcs (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 150mL NS).
- Injection will take place into the greater trochanter (within a pre-specified region)

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 incision and should occur simultaneously with the final soft tissue sample collection above
- Soft tissue sample – Glut Max Start
  - A small soft tissue sample will be taken from the glut max upon entering the hip joint. This sample will only be taken if it is readily available for the surgeon to gather.

- Bone Sample – Bone from Femoral Head
  - After the femoral neck is cut with the "cookie cutter" instrument a portion of femoral 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 - Pulvinar
  - A sample will be taken from Pulvinar tissue located between the acetabulum and femoral head.
- Bone Sample – Acetabulum Reamings
  - The reamings from the first acetabulum reamer will be placed in a specimen jar for testing.
- Bone Sample – Intramedullary Bone
  - Just prior to insertion of final femoral implant (after removal of trial implants) a small portion of intramedullary bone will be taken for sample and placed in a specimen cup
- Soft Tissue Sample – Glut Max End
  - A small soft tissue sample will be taken from the glut max prior to initiation of wound closure. This sample will only be taken if it is readily available for the surgeon to gather.
- 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

Inclusion Criteria

- Patient is undergoing a primary total hip arthroplasty.
- Patient gives informed consent to participate in the study.
- Age Range >18

Exclusion Criteria

- Previous surgery on the hip (including hip scopes)
- BMI above 35
- Contraindication to receiving vancomycin, cefepime, ancef, or other standard of care pre-operative antibiotic (allergy, medical issue, etc).
- Inability to locate the greater trochanter or administer the IO infusion
- Refusal to participate
- Diabetes
- Immunocompromised or immunosuppressed patients (HIV, Hep C, ESRD, dialysis, transplant, chemo/radiation treatment in last 6 months, medications)

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 (glut max start, pulvinar tissue, glut max end), femoral head bone sample vanc level, acetabulum reamings vanc level, intramedullary bone vanc 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.

5. 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 years to enroll all study subjects and for investigators to complete primary analyses.

6. Drugs, Biologics, Devices

N/A

7. Collaborative / Multi-site Research

N/A

8. 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 as a result of 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.

9. Data and Specimen Banking

N/A

10. Study Population

Described in Section 4 “Study Design”

11. Screening and Recruitment S R

Potential study patients will be identified by the research team prior to their surgery date by looking at Dr. Incavo’s, Dr. Clyburn’s, Dr. Park’s, and Dr. Brown’s surgery schedules searching for primary total hip 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 hip, 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 at 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.

12. Withdrawal of Subjects

Patients may be withdrawn from the study if it is discovered that they have any of the exclusion criteria that was not previously identified during the recruitment and screening process. If this is the case the patient will be informed of their removal from the study and the reason why they were removed from the study

13. Provisions to Protect the Privacy Interests of Subjects

If a patient has indicated on their electronic medical record in Epic that they do not want to participate in research or share any of their personal information that request will be honored and they will not be included in this research study.

14. Risks to Subjects

Local tissue reaction to injection
Damage to the greater trochanter (i.e. fracture) – minimal as the IO injection will occur in the same location as medical standard of care for IO injections in pediatric patients.
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 [12]

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 [13].

15. Potential Benefits

Red Man Syndrome is generally quoted to occur in 5–13% of patients, especially when the infusion is given over less than 1 hour [8]. However, there are varied incidence reports, ranging between 3.7 and 47% in infected patients [9] to between 30 and 90% of healthy volunteers receiving vancomycin [10]. Additionally, the rate of nephrotoxicity with use of modern preparations of vancomycin varies in the literature, with the incidence ranging from as low as 0% in the absence of concurrent nephrotoxins to over 40% [11]. 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 Red Man Syndrome while providing equal or enhanced prophylaxis in THA.

16. Financial and Economic Issues

N/A

17. Data Safety Plan

The study will be monitored by clinicians involved in the study. Interim analysis will be performed yearly.

18. Informed Consent Documentation and Process

The initial identification and screening process are described in section 11 of this protocol. Following screening, patients will meet with a qualified member of the research team to explain all aspects of the study and answer any questions that the patient may have. Then, should the patient agree to participate in the study, both the patient and the member of the research team will sign the informed consent. The patient will be encouraged to take a copy of the informed consent for their records should they have any additional questions at a later time.

19. Waiver of Informed Consent and /or Authorization

There will be no waiver of informed consent for this study.

The research team requests a waiver of authorization for preparatory for research. The use of PHI involves no more than a minimal risk to the privacy of individuals. Only qualified members of the research team will have access to this information and it will be stored on password protected Houston Methodist servers. Identifiers will be destroyed at the earliest opportunity consistent with conduct of the research study. This will include removing PHI at the end of every month. It would not be practical to conduct this research study without preliminary screening of potential study patients. Without the waiver the research team would have to request fan authorization to view PHI from every patient of Dr. Clyburn, Dr. Kwan Park, Dr. Stephen Incavo, and Dr.

Timothy S. Brown. The research could not be practicably conducted without access to and use of PHI.

20. References

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