IRB Minimal Risk Protocol Template

Note: If this study establishes a human specimen repository (biobank) for research purposes, do not use this template. Use the Mayo Clinic Human Specimen Repository Protocol Template found on the IRB home page under Forms and Procedures at http://intranet.mayo.edu/charlie/irb/

First-time Use: Use this template to describe your study for a new IRB submission.

1. Complete the questions that apply to your study.
2. Save an electronic copy of this protocol for future revisions.
3. When completing your IRBe application, you will be asked to upload this document to the protocol section.

Modification: To modify this document after your study has been approved:

1. Open your study in IRBe. Click on the study 'Documents' tab and select the most recent version of the protocol. Save it to your files.
2. Open the saved document and activate "Track Changes".
3. Revise the protocol template to reflect the modification points , save the template to your files
4. Create an IRBe Modification for the study and upload the revised protocol template.

General Study Information

Principal Investigator: Kevin Renfree, MD

Study Title: Tissue Concentrations of Vancomycin Achieved With Bier Block Administration versus Intravenous Prophylaxis in Upper Extremity Surgery: A Randomized Controlled Trial

Protocol version number and date: Protocol v.1.0 - 8/23/20

Research Question and Aims

Hypothesis: Vancomycin administered intravenously via a Bier Block achieves superior soft tissue and cancellous bone concentrations compared with systemic IV administration for prophylaxis in upper extremity reconstruction without a higher rate of complications.

Aims, purpose, or objectives: To quantify and compare vancomycin concentration in bone and soft tissue: (1) after Bier Block administration, (2) after systemic intravenous vancomycin administration, (3) determine if there is any difference in complication rate between Bier Block and systemic intravenous administration of vancomycin and (4) determine what complications are associated with Bier Block administration of vancomycin.

Background (*Include relevant experience, gaps in current knowledge, preliminary data, etc*.): Infections in the hand and upper extremity are commonly encountered in clinical practice. Depending on region of practice current literature estimates 25-50 to 123 patient admissions annually due to infections of the hand requiring surgery and IV antibiotics. This challenge has motivated interest in alternative interventions for hand and upper

extremity infections, in particular nonsurgical treatment with high local concentrations of antibiotics. The relatively high vascular supply to the hand and upper extremity may allow for treatment of infection with localized therapy, allowing patients to undergo surgical interventions with potentially lengthy recovery.

Previous studies in primary and revision total knee arthroplasty have shown significantly higher tissue and bone concentrations of a comparatively lower dose of Vancomycin administered by intraosseous regional administration (IORA) when compared to systemic IV administration. These differences remained significant through the following day, despite a period of tourniquet deflation, and have also been shown to be significantly higher in patients with high BMI regardless of dose adjustment. Regional administration of teicoplanin in the lower extremity has also been reported for TKA prophylaxis, resulting in a 10 times higher tissue concentration than systemic IV administration. Importantly, there have not been an increased rates of complications reported with local administration of these antibiotics. Specifically "red man syndrome" or nephrotoxicity, is no more common with IORA of vancomycin than with systemic IV therapy.

Certain types of hardware or implants may limit the feasibility of IORA in the upper extremity, where smaller volumes of cancellous bone are available for injection. However, the cost and availability of supplies for Bier Block administration are favorable compared to IORA making this an appealing option for administration of high doses of vancomycin within a localized tissue area. In addition, the Bier Block method is commonly performed by providers outside of the operating room, is broadly taught, and may have a greater utility for clinical use than IORA. There are several complications of Bier Block reported in the literature, although rare, they include potential for nerve damage, compartment syndrome, skin discoloration or petechiae, and thrombophlebitis. Tissue concentration of antibiotics after administration via Bier Block is currently unknown. To assess tissue concentrations our study will analyze patients undergoing reconstructive procedures of the hand/wrist. These procedures require removal of bone and soft tissue and will have no detrimental effect on the patient.

Bier block administration of regional vancomycin has multiple theoretical advantages. As vancomycin carries a high risk of systemic toxicity, local administration will limit the site of action and minimize systemic complications of the medication. This method should and allow for a lower dose of medication to achieve an equal or greater effect based on previous studies examining IORT. Although the exact pharmacokinetics of vancomycin are not completely described, higher concentrations of vancomycin have been associated with a greater clinical effect. This may provide greater coverage against resistant organisms as well as lower the amount of medication that must be administered to prevent infection. Traditionally vancomycin is administered over one hour with high systemic concentrations and can cause a histamine release known as "red man syndrome" mirroring symptoms of anaphylaxis. Theoretically, administration to a local area will not activate a similar histamine release and will not require the prolonged administration of the medication pre-operatively.

Study Design and Methods

Methods: *Describe in lay terms, completely detailing the research activities that will be conducted by Mayo Clinic staff under this protocol*.

Patients undergoing upper extremity reconstruction by a single surgeon will be included. Patients will be randomized to two arms, with target accrual of 10 cases in the Bier block and systemic intravenous IV groups respectively (20 cases total). Surgical cases will include Trapeziectomy/suspensionplasty (30-60 mins duration), PIPJ/MPJ arthroplasty (60-90 min duration), proximal row carpectomy (60 min), and distal ulnar resection (30-45 mins). The estimated case collection period is approximately 8 months based on averages of case logs from the previous 2 years. Both groups will receive 2 g systemic cefazolin 15 minutes before tourniquet inflation Vancomycin dosing will be identical to previous reports on total knee arthroplasty. In the systemic IV group, 1 g of vancomycin will be delivered over a period of one hour prior to tourniquet inflation. In the Bier Block group, Vancomycin 500 mg will be diluted in 50 cc normal saline, and after exsanguination of the limb and elevation of the tourniquet in the prepped and draped patient, will be injected into a superficial vein in the hand, wrist or forearm. Sample collection times will be recorded from time of skin incision to equalize for any delays in administration of antibiotic via Bier block administration after tourniquet inflation. Time from tourniquet inflation to incision will also be documented for both groups. 5 tissue samples (0.5 cm^3) from each patient in both groups will be obtained: subcutaneous fat (1) and cancellous bone (2) 5-10 minutes after skin incision, subcutaneous fat (3) and cancellous bone (4) 20-25 minutes after skin incision, and subcutaneous fat (5) at skin closure (45-60 minutes after skin incision). In the Bier Block group, after the dressing is applied the tourniquet will be briefly deflated for 30 seconds and then re-inflated. If there are no signs of "red man syndrome" within 5 minutes (skin rash of face/neck/or torso, hypotension, tachycardia), then the tourniquet will again be deflated. Samples will be stored the Mayo Clinic Hospital lab at -90°C, before being transported to Christchurch, New Zealand for analysis using a previously validated technique. Bone samples will be crushed with pliers, finely cut further with a scalpel, then weighed and immersed in phosphate buffered saline pH 7.3 for 15 h at 4C. The fat samples will finely cut with a scalpel, and then treated in a same way as the bone samples. The immersed bone or fat tissue suspension will be vortexed for 30 seconds and centrifuged at 15,000 g for 10 min. The supernatant will be transferred to a clean tube and perchloric acid added to precipitate the proteins. After centrifugation at 15,000 g for 5 min, 50 uL of clear supernatant will be analysed.

Subject Information

Target accrual is the proposed total number of subjects to be included in this study at Mayo Clinic. A "Subject" may include medical records, images, or specimens generated at Mayo Clinic and/or received from external sources.

Target accrual: 20 patients

Subject population (children, adults, groups): Adults undergoing reconstructive procedures of the hand/wrist

Inclusion Criteria: Patients undergoing trapeziectomy/suspensionplasty, proximal interphalangeal joint or metacarpophalangeal joint arthroplasty, proximal row carpectomy, or distal ulnar resection

Exclusion Criteria: Inability to adequately cannulate a superficial vein in the upper extremity within 5 minutes of tourniquet inflation or evidence of subcutaneous extravasation in Bier Block group, history of renal disease, vancomycin allergy, ASA >/= 3, history of lung cancer, known HIV infection, history of organ transplantation, current or treatment with vancomycin in the preceding 7 days, patients under the age of 18, pregnant females (screened with pregnancy test if female under the age of 50).

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Biospecimens

Collection of blood samples. When multiple groups are involved copy and paste the appropriate section below for example repeat section b when drawing blood from children and adults with cancer.

a. **From healthy, non-pregnant, adult subjects who weigh at least 110 pounds**. For a minimal risk application, the amount of blood drawn from these subjects may not exceed 550ml in an 8 week period and collection may not occur more frequently than 2 times per week.
   Volume per blood draw: _____ml
   Frequency of blood draw (e.g. single draw, time(s) per week, per year, etc.) _____

b. **From other adults and children considering age, weight, and health of subject.** For a minimal risk application, the amount of blood drawn from these subjects may not exceed the lesser of 50 ml or 3 ml per kg in an 8 week period, and collection may not occur more frequently than 2 times per week.
   Volume per blood draw: _____ml
   Frequency of blood draw (e.g. single draw, time(s) per week, per year, etc.) _____

Prospective collection of biological specimens other than blood: Collection of bone and soft tissue samples - 2.5 cm^3 in total from each patient in 0.5 cm^3 samples.

Review of medical records, images, specimens

Check all that apply (data includes medical records, images, specimens).

☐ Only data that exists before the IRB submission date will be collected.

Date Range for Specimens and/or Review of Medical Records:
Examples: *01/01/1999 through 12/31/2015*, or all records through *mm/dd/yyyy*.

Note: The Date Range must include the period for collection of baseline data, as well as follow-up data, if applicable.

☒ The study involves data that exist at the time of IRB submission **and** data that will be generated after IRB submission. Include this activity in the Methods section.
Examples

- The study plans to conduct a retrospective chart review and ask subjects to complete a questionnaire.
- The study plans to include subjects previously diagnosed with a specific disease and add newly diagnosed subjects in the future.

☐ The study will use data that have been collected under another IRB protocol. Include in the Methods section and enter the IRB number from which the research material will be obtained. *When appropriate, note when subjects have provided consent for future use of their data and/or specimens as described in this protocol*.

Enter one IRB number per line, add more lines as needed

☐ Data ☐ Specimens ☐ Data & Specimens _____

☐ Data ☐ Specimens ☐ Data & Specimens _____

☐ Data ☐ Specimens ☐ Data & Specimens _____

Data Analysis

Power analyses may not be appropriate if this is a feasibility or pilot study, but end-point analysis plans are always appropriate even if only exploratory. Provide all information requested below, or provide justification if not including all of the information.

Power Statement: Previous studies examining IORA of vancomycin show approximately a 4.5 fold increase in tissue concentration compared to systemic administration. A priori analysis shows that 10 patients per study arm will be required to achieve 80% statistical power with a type I error rate of 0.05.

Data Analysis Plan: Means, standard deviations, and the 95% confidence limits will be calculated for the concentrations in the different samples. Different tissue samples will be pooled according to collection time. Coefficient of variations (CV) of concentration level will be summarized at each time interval for the comparison between two arms. Repeat measure analysis of variance will be used to compare the average level of concentration across time between groups adjusted by BMI, age, and length of surgical procedure; Shapiro-Wilk test will be used to assess the normality of the residuals. Adverse event will be recorded by contingency table.

Endpoints
Primary: Tissue concentrations of vancomycin in the hand and wrist following Bier Block administration versus systemic IV administration
Secondary: Complications rate of Bier Block administered vancomycin, modes of adverse events, safety of Bier Block administered vancomycin,. which rarely can cause a reaction that includes low blood pressure and skin redness or flushing. This is temporary and can usually be treated effectively with an antihistamine. In previous studies using a similar technique of intraosseous administration followed by tourniquet release, this has not been seen. Antihistamine will be on hand so that it can be administered should this reaction occur. Additionally,

patients will be observed post-operatively for signs of phelibitis, but this is not felt to be a greater risk resulting from Bier block administration (intravenous) compared to standard intravenous administration used clinically.