Efficacy and Safety of Intraosseous Antibiotic Prophylaxis in Total Hip Replacement: A Prospective Randomized Controlled Trial

NCT: Not yet assigned

Document Date: July 15, 2025

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THE STATE UNIVERSITY OF NEW JERSEY

Title of Project: Efficacy and Safety of Intraosseous Antibiotic Prophylaxis in Total Hip Replacement: A Prospective Randomized Controlled Trial

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Funding Source(s): NJHF Research Grant # PC 110-25

1. Purpose/Specific Aims

With increasing rates of primary total hip and knee arthroplasty, the occurrence of prosthetic joint infection (PJI) is expected to rise in the coming decades.[1] This is not only an issue of morbidity and mortality but places a substantial economic burden on the US healthcare system, with estimates nearing $1.85 billion of spending on PJIs by 2030.[2] Thus, efforts to reduce PJIs improves both clinical and economic outcomes. Most patients receive two grams of cefazolin, a first-generation cephalosporin, intravenously prior to incision for total hip and knee arthroplasty, but there has been increasing interest in alternative, more efficacious modes of administration. While antibiotic administered intravenously is delivered globally throughout the body, concentrations in problematic areas may not reach appropriate thresholds to prevent PJI. The intramedullary canal of long bones, the femur in the setting of total hip arthroplasty, has been shown to be an area of increased biofilm formation in latent PJIs.[3] Recent studies have demonstrated mixed results regarding local application of antibiotics, but most have investigated their utility in the management of pre-existing infection.[4,5] This study aims to investigate local antibiotic administration in a quick, cost-efficient manner, in a prophylactic role in primary joint arthroplasty, with the belief that antibiotic load will be higher locally at all time intervals measured following surgery, and subsequent secondary outcomes such as PJI will be reduced.

1.1 Objectives

Aim 1. Determine whether intraosseous administration of 1 gram of cefazolin increases blood and tissue concentration of cefazolin when compared with the standard surgical prophylaxis doses of intravenous cefazolin. Tissue (intra-articular fat, acetabular and femoral reamings, skin, gluteal muscle) and blood concentration of cefazolin will be compared between patients receiving 1 gram of intraosseous cefazolin and 2 grams of intravenous cefazolin to

patients receiving only 2 grams of intravenous cefazolin (standard of care).

Aim 2. Identify the incidence of periprosthetic joint infections, systemic infections (e.g., urinary tract infection, pneumonia), allergic reactions, antibiotic-related complications, wound healing complications, deep vein thrombosis, pulmonary embolism, and patient-reported outcomes on pain, functionality, and quality of life within 90 days post-surgery.

1.2 Hypotheses

The central hypothesis of this proposal states that patients receiving 1 gram of intraosseous and 2 grams of intravenous cefazolin will have higher concentrations of cefazolin in tissue and blood samples at the time points collected when compared to the standard administration of 2 grams of intravenous cefazolin.

2. Background and Significance

With increasing rates of primary total hip and knee arthroplasty, the occurrence of prosthetic joint infection (PJI) is expected to rise in the coming decades.[1] This is not only an issue of morbidity and mortality but places a substantial economic burden on the US healthcare system, with estimates nearing $1.85 billion of spending on PJIs by 2030.[2] Thus, efforts to reduce PJIs improves both clinical and economic outcomes. Most patients receive two grams of cefazolin, a first-generation cephalosporin, intravenously prior to incision for total hip and knee arthroplasty, but there has been increasing interest in alternative, more efficacious modes of administration. While antibiotic administered intravenously is delivered globally throughout the body, concentrations in problematic areas may not reach appropriate thresholds to prevent PJI. The intramedullary canal of long bones, the femur in the setting of total hip arthroplasty, has been shown to be an area of increased biofilm formation in latent PJIs.[3] Recent studies have demonstrated mixed results regarding local application of antibiotics, but most have investigated their utility in the management of pre-existing infection.[4,5]

3. Research Design and Methods

The study design is a prospective, randomized control trial designed to compare the efficacy and safety of intraosseous (IO) antibiotic prophylaxis in patients undergoing total hip arthroplasty. Consenting patients will have their blood drawn on arrival the hospital (pre-administration of cefazolin), 30 minutes after receiving 2 grams of intravenous cefazolin preoperatively, 30 minutes after 1 gram intraosseous cefazolin (or placebo), and serially at 30 minutes, 60 minutes, 120 minutes, 180 minutes, and 240 minutes after IO administration. Blood samples will be approximately 10 mL collected in EDTA or sodium citrate evacutainers. Intraoperatively small tissue samples (approximately 1 gram) will be obtained from the proximal femur metaphysis, femoral head, acetabulum reamings, gluteus medius, intraarticular fat, skin (from distal incision), and synovial fat. These samples are not routinely collected as part of the surgical procedure and will be used for the sole purpose of this research study. The study orthopedic surgeon will be responsible for sample collection. An antecubital line will be placed opposite to the arm in which the cefazolin is intravenously injected. Blood samples will be drawn from this line. Tissue samples will be removed intraoperatively and once collected, will be transported by Dr. Brzezinski or his designee (also present during the surgery) to the RWJS pharmaceutical lab (Dr. Brunetti's laboratory) on ice. The samples will be aliquoted and stored at -80° C until analysis. Relevant drug and metabolite (if applicable) concentration will be measured in each of the samples.

3.1. Duration of Study

The duration of study participation includes patient baseline measurements and enrollment, their hospital stays and 90 days post operatively. No special trips are needed to collect samples. All samples/procedures will occur during already scheduled visits/surgical procedures.

3.2 Study Sites

Patient samples will be obtained, measured and analyzed at Robert Wood Johnson Somerset hospital. Standard follow up for total hip replacement will be performed at University Orthopaedic Associates.

3.3 Sample Size Justification

A power analysis was conducted to determine the appropriate sample size for a study comparing intraosseous (IO) 1g cefazolin to placebo administration into the greater trochanter. The primary outcome is the difference in local tissue antibiotic concentrations between the two groups. Based on previous studies evaluating intraosseous vancomycin, the expected mean difference in tissue concentrations between groups was 20 µg/mL, with a standard deviation of 15 µg/mL. The analysis was performed with an alpha level of 0.05 (5% significance) and aimed for 80% power, meaning the study would have an 80% probability of detecting a true difference if one exists. The power analysis indicated that 9 patients per group would be required to detect a statistically significant difference in antibiotic concentrations, resulting in a total of 18 patients for the study. This sample size is sufficient to provide adequate power for detecting the anticipated effect while maintaining a reasonable level of significance.

To account for potential patients lost to follow up or issues with collection, the decision was made to collect 25 samples to ensure appropriate sample sizes are met.

3.4 Subject Selection and Enrollment Considerations

3.5.1 Inclusion Criteria

The subject population will include all patients over the age of 18 scheduled to undergo primary total hip replacement receiving antibiotic prophylaxis for prosthetic joint infection with the institution standards i.v. bolus dose of cefazolin just prior to surgery.

3.5.2 Exclusion Criteria

Patients with reduced renal function (GFR < 30), reduced liver function (AST/ALT >3x upper limit of normal) and weight greater than 120kg will be excluded since these variables may impact cephalosporin pharmacokinetics and pharmacodynamics and confound our results. We will also exclude patients undergoing bilateral total hip arthroplasty. We will also exclude patients with documented cefazolin anaphylaxis, active documented joint infection, history of diabetes, inflammatory arthropathies, patients unable to understand written and/or spoken English and those undergoing revision total hip replacement.

3.5.3 Subject Recruitment

Subjects will be recruited by the study surgeons during patient preoperative visit. As the

patients have already undergone an evaluation to undergo surgery, patients have the capacity to consent to the research study. Patient's will have ample opportunity to consider participation from the time of the visit until the day of the procedure.

3.5.4 Consent Procedures

The study, risks and benefits of participation will be presented to the subjects by the study orthopaedic surgeon. Consent forms will be presented at the time of their routine orthopaedic surgery evaluation visit. All subjects will be encouraged to read over the information and

ask questions before signing the consent form. Patients will be provided a copy of their consent form and present it on the day of surgery to confirm study participation. The patients will be informed that participation is voluntary and they may decide to withdraw at any time point.

3.5.5 Subject Costs and Compensation

There will be no costs to the patient for participation and there is no compensation for patient participation.

3.6 *Chart Review Selection*

Charts will be reviewed to evaluate for demographic information including age, sex, BMI, diabetes, renal function, and liver function.

4. Study Variables

4.1 Independent Variables or Interventions

In this study, the independent variable is the type of treatment administered to participants, which consists of two groups: the intraosseous (IO) cefazolin group and the placebo group (saline). Participants in the IO cefazolin group will receive 1 gram of cefazolin (cefazolin) via an intraosseous injection into the greater trochanter, while participants in the placebo group will receive a saline injection using the same method. Both groups will receive standard intravenous (IV) cefazolin prior to surgical incision, as per usual practice. The primary intervention in this study is the administration of the IO cefazolin or placebo, and the study aims to evaluate the differences in cefazolin concentration in various tissue samples collected during the surgery, including the femoral head, acetabulum, gluteus medius, intra-articular fat, skin, and synovium. These tissue samples will be analyzed to assess the pharmacokinetics of cefazolin and determine if the IO route results in higher local tissue concentrations compared to the systemic effects of the IV administration.

We will use the Tanita MC-780U segmental body composition analyzer or a comparable device to obtain a complete body profile (weight, body fat percentage, body fat mass, BMI, fat free mass, estimated muscle mass, total body water and basal metabolic rate) for each patient. These values will be tested in pharmacokinetic models.

4.1.1 Drug or Device Interventions

In this study, the drug intervention involves the administration of 1 gram of cefazolin (cefazolin) through an intraosseous (IO) injection into the greater trochanter, which is the target site for local antibiotic delivery. The IO injection is administered through a small lateral pokehole at the greater trochanter, where the needle is inserted into the bone to ensure direct delivery of cefazolin into the surrounding tissues. This method is expected to provide higher local tissue concentrations of the antibiotic at the surgical site, potentially improving prophylactic antibiotic efficacy while minimizing systemic exposure. The IO intervention is compared to a placebo group where saline is injected

using the same technique, ensuring blinding of the study. Additionally, all participants in both groups will receive a standard IV dose of cefazolin (2 grams) prior to incision, as per typical preoperative protocols, to maintain standard care.

4.2 Dependent Variables or Outcome Measures

The dependent variables in this study include the concentration of cefazolin in various tissues and plasma samples collected from patients during their total hip replacement surgery. Specifically, tissue samples will be obtained from the proximal femur metaphysis, femoral head, acetabulum reaming, gluteus medius, intra-articular fat, skin, and synovium. These samples will be analyzed for cefazolin levels using high-performance liquid chromatography (HPLC) to determine the pharmacokinetics of the drug after intraosseous versus placebo (saline) administration. The key measurements will focus on the local tissue concentrations of cefazolin at various time points post-intervention, including pre-administration, immediately after the IO injection, and at 30, 60, 120, 180, and 240 minutes following the IO injection. Additionally, plasma cefazolin concentrations will be measured at specified time points to assess systemic drug levels. The study aims to compare these dependent variables between the two groups (IO cefazolin vs. placebo) to evaluate the effectiveness of intraosseous cefazolin in achieving higher local concentrations compared to systemic administration. Secondary dependent variables will include the incidence of 90-day complications, which will be tracked and analyzed to assess any adverse effects associated with the interventions.

4.3 Risk of Harm

The potential risks to subjects are low following collection of blood and tissue. These risks include bruising at the site where blood is drawn, redness and swelling of vein, and minor discomfort or pain. To minimize discomfort, an antecubital venous access line will be placed opposite to the line where cefazolin is to be administered. If the line fails we will draw blood with direct venous sampling. As the patient will be under anesthesia during surgery and the subcutaneous tissue sample will be taken from the surgical incision, additional discomfort is expected to be minimal.

Likewise additional discomfort or complication from IO administration of cefazolin or placebo is expected to be minimal to non-existant. Prior studies investigating intraosseous administration of antibiotic prior to hip or knee procedures have shown no adverse events or added discomfort.[6]

No PHI will be provided with the subject plasma and tissue samples when transported from RWJ to Rutgers University. As such, there will be a considerable reduction in the risk of a privacy breach. While study records will be protected within Dr. Brunetti's locked laboratory and on a password protected two factor authenticated Rutgers drive, there is risk of security compromise. This event is highly unlikely; however, the possibility exists, therefore complete confidentiality cannot be guaranteed.

4.4 Potential for Benefit

Potential for benefit includes lessened risk of periprosthetic joint infection in the treatment group. The proposed research will fill critical knowledge gaps in understanding how intraosseous administration for cefazolin influences the pharmacokinetics of antibiotics. While this proposal focuses upon cefazolin, commonly used pre- operative antibiotics for prevention surgical infections, the knowledge gained will have much larger impact on the

general pharmacokinetics and use of antibiotics for treating/preventing infections in the obese population.

5. Data Handling and Statistical Analysis

Demographic and medical information will be collected into Research Electronic Data Capture (REDCap) (http://www.project-redcap.org). Confidential medical information will be securely stored by Dr. Brunetti in his locked laboratory at Robert Wood Johnson University Hospital – Somerset and a two-factor authentic Rutgers platform for data analyzation. No samples will leave Dr. Brunetti's possession with PHI significantly reducing breaches in patient confidentiality. Subjects will not be identified in any publications or research communications.

Pharmacokinetic parameters of total and free cefazolin after a single dose (samples from AIM 1) will be evaluated by noncompartmental analysis methods (using PKanalix 2024). The following pharmacokinetic parameters will be determined: 1) Area under the plasma concentration-time curve (AUC); 2) Systemic clearance (CL); 3) Maximum plasma concentration of cefazolin (C_{max}); 4) Volume of distribution (V_d); 5) Time period with concentrations above the MIC level. Individual patient plasma and tissue data will be analyzed using a mixed-effect modeling approach where the mean population pharmacokinetic parameters and the variability of these parameters between patients will be quantified. A semi-physiological compartmental model of cefazolin disposition will be developed based on the total and lean body mass, bone mass, and percent of the fat tissue (based on the structural model developed for the data from Toma et al. study).[13] The effect of multiple factors on pharmacokinetic parameters will be evaluated using the covariate analysis approach. Various measures of body size (such as, total body weight, lean body weight, BMI, and body composition (using the BIA technique),[14] patients' clinical characteristics (different measures of renal function, hepatic function, plasma albumin, etc.), and demographic information will be evaluated. All continuous covariates will be centered to their median values and evaluated as linear, exponential, and power function. Several covariates will be incorporated in a multiplicative fashion. The statistical significance of the difference in the objective function value between the model with or without a certain covariate will be tested (forward inclusion $p < 0.005$, backward elimination $p < 0.001$). Additive and exponential error models will be tested for interindividual and residual variability. The first order conditional estimation with interaction (FOCE-I) will be utilized. Model evaluation will be performed based on the likelihood ratio test (or Akaike information criterion for non-nested models), goodness-of-fit plots, and precision of parameter estimates. Data analysis will be performed using Matlab (version, 2013b, MathWorks, Natick, MA) and MONOLIX (version 2024, Lixoft, Simulations Plus). Dr. Brunetti & Andrew Wassef will be responsible for pharmacokinetic modeling. Monte-Carlo simulations will be performed based on the established model structure and parameters to identify optimized dosing strategies for cefazolin in patients.

Target attainment will be compared between IV and IO administration groups. Chi- square will be used to compare the proportion of target attainment between each group and a multivariable logistic regression model will be created to identify variables that influence target attainment.

***Alternative data analysis approach*:** Logistic regression will be used for analysis with BMI as a covariate and dose as the predictor of interest. As a secondary analysis, linear regression will be used with cefazolin concentration as the outcome, BMI as a covariate, and dose the predictor of interest. The following patient data will be collected: age, gender, race, weight, height, serum creatinine (and Cockcroft-Gault CrCl), plasma cystatin-C (and calculated CKD-EPI CrCl), BMI, concomitant medications, fat-free weight, and comorbidities. A multivariate regression model will be constructed to identify predictors of failure to reach adequate tissue cefazolin concentrations. All analyses will be performed using R (R Foundation for Statistical Computing, Vienna, Austria) and SAS 9.2 (SAS Institute, Cary, NC).

6. Data and Safety Monitoring

Adverse event data will be reported as percentages and stratified according to drug-related and non-drug related.

7. Reporting Results

7.1 Individual Results

Individual results will not be reported since these data are not intended to alter current therapy. Rather, we will provide aggregate results to study subjects upon request.

7.2 Aggregate Results

Study subjects may ask for this information by contacting the Principal Investigator. This information will be included in patient consent form.

7.3 Professional Reporting

The investigators of this proposal recognize the importance of sharing any data obtained with the research community. Data will be shared in accordance with the NIH Data Sharing Policy and Implementation Guidance, including but not limited to the following principles. The researchers will cooperate fully with each other to develop and follow strategies for data management, analysis and public release. It is the intent of the investigators to encourage sharing of data and other information related to this project through publication, presentation or other scientific communications consistent with academic standards. We also will utilize the supplementary data resources available for many of the journals to disseminate raw or more detailed data, such as computer code generated in the project We will also make every reasonable effort to provide raw data to individual researchers upon request. The research resources of the academic units involved are available to all investigators in the application as well as the scientific community within the guidelines of the Institutions involved in this project. In addition, sharing of data and resources among the key personnel involved in this project will be achieved by integrating the latest mean of communications with secured access to “Sakai” within Rutgers as well as monthly meeting.

NIH issued a Certificate of Confidentiality for this study.

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