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Project Title: Skeletal muscle and adipose tissue concentrations of cefazolin comparing two different dosing regimens during pediatric posterior spinal fusion surgery

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Protocol

Project Title: Skeletal muscle and adipose tissue concentrations of cefazolin comparing two different dosing regimens during pediatric posterior spinal fusion surgery

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Abstract: The study intendeds to compare the current standard of care for prophylactic cefazolin administered every 3 hours intravenously with continuous infusion of cefazolin during pediatric spinal surgery. Pharmacokinetics, skeletal muscle disposition and subcutaneous adipose tissue penetration of cefazolin under both modes of administration will be determined using a clinical microdialysis technique.

Background: Surgical site infection (SSI) after posterior spinal fusion surgery (PSFS) is a devastating complication that frequently requires medical and surgical management beyond the expected recovery time. SSI's are a common cause of nosocomial infection. The United States Centers for Disease Control and Prevention (CDC) has developed criteria that define surgical site infection (SSI) as infection related to an operative procedure that occurs at or near the surgical incision within 30 days of the procedure or within 90 days if prosthetic material is implanted at surgery. SSIs are often localized to the incision site but can also extend into deeper adjacent structures (1).

Studies have reported the risk of SSI in PSFS ranging from 1.3 to 6.3% (2). The neuromuscular subgroup patients with spastic quadriplegia (cerebral palsy) have the highest incidence of infection (14.3%) compared to adolescent patients with idiopathic scoliosis (1. 5%) (3).

SSI can be prevented with adequate perioperative administration of prophylactic antibiotics. β lactam antibiotics are frequently recommended as a primary choice for perioperative prophylaxis in surgical patients owning to their broad-spectrum activity and generally good safety and tolerability profiles. Cefazolin, a first-generation cephalosporin, has been used as a suitable antibiotic for PSFS because of its spectrum of activity (e.g., against Staphylococcus species and gram-negative bacilli such as E. coli) and adequate tissue concentrations (4).

Achieving and maintaining goal tissue concentrations of prophylactic antibiotics near the surgical site is crucial to maximize their effectiveness. Tissue microdialysis is a technique used in clinical pharmacology to sample directly and continuously the free, unbound drug concentrations, including perioperative antibiotics, in the interstitial fluid of various tissues (5,6). In brief, the probe is continuously perfused at a low flow rate with an aqueous solution (perfusate) that closely resembles the (ionic) composition of the surrounding tissue fluid. Once the probe is implanted into the tissue, substances present in the extracellular fluid at concentration (c_{tissue}) are filtered by diffusion out of the extracellular fluid into the probe, resulting in a concentration ($c_{dialysate}$) in the perfusion medium. The solution moving through the probe (dialysate) is collected at certain time intervals for analysis.

Because of constant perfusion of fresh perfusate, equilibrium between extracellular tissue fluid and the perfusion medium is incomplete, resulting in $c_{tissue} > c_{dialysate}$. The factor by which the concentrations are interrelated is termed recovery. To obtain intestinal concentration from dialysate, microdialysis probes need to be calibrated.

Currently, the only published study by Himebauch et.al prospectively evaluated the skeletal muscle disposition of prophylactic cefazolin using microdialysis sampling in a pediatric cohort with idiopathic scoliosis undergoing PSFS. They found that the skeletal

muscle concentrations of cefazolin achieved with 30mg/kg given every four hours for the duration of surgery was likely to be effective for intraoperative SSI prophylaxis against methicillin-sensitive Staphylo-coccus aureus (MSSA) but might not be effective for intraoperative SSI prophylaxis against Gram-negative pathogens (7). Our study will be performed in a cohort of patients with adolescent idiopathic scoliosis having PSFS. During surgery, unbound cefazolin concentration at interstitial fluid of skeletal muscle and adipose tissue will be measured by clinical microdialysis technique. The comparison of cefazolin disposition in cohorts with two different modes of cefazolin administration will be recorded in skeletal and adipose tissue. End result of the study will be determination of the target attainment for unbound cefazolin of each administration regimen for intraoperative SSI prophylaxis against methicillin-sensitive Staphylo-coccus aureus (MSSA) and Gram-negative bacilli.

Specific Aims: Determine the skeletal muscle and adipose tissue disposition of prophylactic cefazolin using microdialysis sampling in a cohort of patients diagnosed with idiopathic scoliosis undergoing posterior spinal fusion (PSF) for administration of cefazolin by either continuous infusion or intermittent bolus.

Research Plan: Following Institutional Review Board approval, we plan to recruit up to 20 subjects to participate in this study. The patients will be recruited from the Pediatric Orthopedic Clinic and identified by Dr. Blakemore who will first introduce the study to the potential subjects. If the potential subject and Legally Authorize Representative (LAR) expresses interest in the research, they will be given a letter introducing the study during their visit. If they continue to express interest in learning more about the study, the surgeon and/or surgeons' coordinator will notify the research coordinator who will meet with the patient and family in the pre-surgical clinic to discuss the study in detail. If by chance the subject does not go to the pre-surgical clinic, the subject will be contacted by phone with the IRB approved phone script. Potential study participants will have time to read the consent, have all study related questions answered, and discuss the study with their family, if desired before consent is obtained. Consent will take place either in the pre-surgical clinic or in the preoperative area.

Study Patient Population: Study will be conducted in up to 20 patients, male or female between the ages of 12 to 20-year-old. Recruitment of patients will be from the Pediatric Orthopedic Clinic.

Study Design: We propose a randomized controlled prospective pharmacokinetic study of two regimens of intravenous cefazolin used at our institution.

Inclusion

The general inclusion will be those patients who**:**

- Diagnosis of idiopathic scoliosis
- Planned posterior spinal fusion surgery (PSFS)
- Age: 12-20 years old
- American Society of Anesthesiology status I or II undergoing posterior spinal fusion for at least 6 levels
- No known allergy to cefazolin

Exclusion

The Exclusion criteria will include:

- Known allergy to cefazolin
- Anatomical or other abnormalities that precluded insertion of a microdialysis catheter into the selected paraspinal muscle
- Known renal or hepatic insufficiency or failure

Randomization (see statistical methods and data analysis part)

Group I - Subjects randomized to Group I will receive the first regimen:

The first regimen will consist of a bolus dose of Cefazolin 30mg/kg up to a maximum of 2000mg IV administered prior to surgical incision. The same pre-operative dose of cefazolin will be repeated every 3 hours until the completion of surgery.

Group II - Subjects randomized to Group ll will receive the second regimen:

The second regimen will consist of an initial bolus dose of 30 mg/kg up to maximum of 2000 mg. Following the initial bolus dose a continuous cefazolin drip will start until the end of surgery. Cefazolin drip dose will be 10 mg/(kg*h) up to maximum of 667 mg/h.

Research Related Procedures: Serial skeletal muscle and adipose tissue microdialysis samples will be obtained during the PSFS to measure unbound cefazolin concentrations in the interstitial fluid of both skeletal muscle and adipose tissue.

A set of four microdialysis catheters (CMA63; M Dialysis AB, Solna, Sweden) will be inserted percutaneously after induction of anesthesia. Two dialysis probes will be inserted into a paraspinal muscle, with each catheter tip terminating approximately two vertebral bodies superior to the superior edge of the planned incision. And the other two probes will be inserted subcutaneously. The insertion procedure will be performed following a similar procedure as used in clinical practice for intravenous catheterization: The skin at the site of probe insertions is cleaned and disinfected. The surface of the skin is punctured by a needle. Thereafter, the probe is implanted into the tissue with help of an introducer, which is then removed, leaving the flexible probe under the surface of the skin in the tissue of interest. Each microdialysis system will be connected to a pump (107 Microdialysis Pump) with a flow rate of 1 µl/min for microdialysis sample collection. Prior to probe calibration, microdialysis catheters will be perfused with cefuroxime (calibrator; 10 µg/mL) in normal saline, where cefuroxime acts as a marker antibiotic of similar molecular size and physiochemical properties to the study antibiotics. Cefuroxime will assist in the determination of the rate of movement of molecules across the dialysis membrane according to the retrodialysis method. Microdialysis samples (approximately 30 µL for each dialysate sample) will be taken at 30-min intervals (+ or – 5 minutes) throughout the operative procedure. The recovery of cefazolin in the Microdialysate solution will be interpolated from the loss of calibrator (cefuroxime) across the microdialysis membrane:

Cefazolin Recovery%

$$= 100 \times \frac{C_{cefuroxime,perfusate} - C_{cefuroxime,dialysate}}{C_{cefuroxime,perfusate}} \times Recovery\ Ratio$$

where the recovery ratio of cefazolin recovery and cefuroxime recovery can be predetermined by *in vitro* microdialysis. Therefore, the interstitial concentration of cefazolin can be calculated using the following equation:

$$C_{cefazolin,\ tissue} = 100 \times \frac{C_{cefazolin,dialysate}}{Cefazolin\ Recovery\%}$$

Microdialysis catheters will be removed from the designated tissue using aseptic technique before emergence from anesthesia. All microdialysis samples will be stored at -80ºC until analysis.

Plasma samples (approximately 2 mL each collected in K2EDTA-containing tubes) will be obtained from an arterial catheter timed relative to each cefazolin dose (pre-dose, 5, 15 (+or- 5 minutes), 30(+or- 5 minutes), 60(+or- 5 minutes), 90(+or- 5 minutes), 120(+or- 5 minutes), 180(+or- 5 minutes) and every 60 min afterwards(+or- 5 minutes) until the end of surgery) and at the time of skin closure for standard cefazolin administration. If the patient receives continuous infusion, the plasma samples will be collected at 0 (pre-dose), 5, 15(+or- 5 minutes), 30(+or- 5 minutes), 60(+or- 5 minutes), 90(+or- 5 minutes), 120(+or- 5 minutes), 180(+or- 5 minutes), and every 60 min afterwards (+or- 5 minutes) until the end of surgery. Thus for a 6 hour procedure the blood collected should not exceed 22 ml or less than 5 Tsp. Blood samples will be centrifuged at 3000 rpm for 15 mins and plasma will be transferred and stored at -80ºC until analysis. Both plasma and microdialysis samples will be analyzed utilizing validated high-performance liquid chromatography-tandem mass spectrometry (LC-MS/MS) methodology. The probability of target attainment for unbound cefazolin concentrations at target site for MSSA and Gram-negative pathogens will be calculated in both groups.

In order to put the PK information into perspective the following information will be collected from the patient's chart: patients age, sex, height, BMI, type of surgery, baseline

renal function, intraoperative urine output, blood loss, albumin level, amount of albumin received during surgery, total allogenic and autologous transfusion, total intraoperative dose of cefazolin and other co-medications received during surgery will be recorded. This information will be collected on all patients.

Standard of Care: These patients routinely receive cefazolin as part of their perioperative antibiotic regimen. Patients routinely receive 30mg/kg of cefazolin intravenously to the max up to 2000mg every 3 hours until the end of surgery. Placement of microdialysis catheter will be for the study purposes only. Please note that under the infusion regimen, patients will receive the same amount of antibiotic over time as the current standard of care. Continuous infusion is at this time considered a practice option used by some colleagues locally.

Anesthetic technique will be at the discretion of the staff anesthesiologist and consist of a total intravenous anesthetic utilizing propofol with an opioid infusion. Anesthetic administration will be standardized according to a clinical pathway.

Statistical methods, data analysis and interpretation

Yichao Yu, BS will be the statistician for the study.

(1) **Design.** Single-center, randomized dosing regimen pharmacokinetic study

(2) **Hypothesis.** The null hypothesis is that the probability of target attainment for unbound cefazolin in skeletal muscle and adipose tissue are same for continuous infusion of prophylactic cefazolin and the current standard mode of administration.

Key pharmacokinetic parameters (C_{max}, t_{max}, $t_{1/2}$, CL, AUC) for cefazolin will be determined from time profiles in plasma, subcutaneous adipose tissue and muscle by means of a commercially available software (Phoenix® WinNonlin®, Pharsight Corporation, CA, USA). Plasma and tissue concentrations of cefazolin will also be related to published minimum inhibitory concentration (MIC) values to determine the time above MIC (fT>MIC), which is the major outcome variables

of cefazolin pharmacokinetic and pharmacodynamics (Cef-PD) factor in vivo for the comparison of two different modes of administration of prophylactic cefazolin.

(3) **Statistical Methods.** Statistical analysis and plots will be performed using Microsoft Excel (Microsoft Corp, Redmond, Washington, USA) and R studio (R Studio Inc, Boston, Massachusetts, USA). The probability of target attainment for unbound cefazolin can be determined as $fT>MIC/T_{total}$; ratios will be expressed as mean ± SD. The major analysis will be a comparison of median $fT>MIC/T_{total}$ between two dosing regimen by the Wilcoxon rank-sum test. A p-value < 0.05, two-sided is considered statistically significant.

(4) **Randomization.** Up to 20 scoliosis patients will be recruited in this study. Simple randomization will be used with each patient has probability 0.5 to be assigned in Group I or Group II. Computer program will generate a uniform random variable between 0 to 1, with subject be assigned to Group I if the value is less than 0.5 and assigned to Group II if the value is greater than 0.5.

(5) **Sample size.** This exploratory pilot study will utilize a sample size of n=20. Background information needed to perform detailed power analysis are lacking.

(6) **Technical support.** The statistical design has been worked out by the Department of Pharmaceutics team. Statistical analysis will also be carried out by them.

Administrative responsibilities

Study Resources: The principal investigator will oversee the data collection, data analysis and will maintain the records in confidence. Should any evidence suggest that the study protocol require modification, the PI will notify the IRB in a timely manner for review and approval. Each subject will be identified by number, not by name, on all data forms. To protect confidentiality, all data will be numerically coded and information linking the numeric codes to individual participant's names will be kept in a locked file in the PI's office.

Possible Discomforts and Risks: Microdialysis catheter placement is a safe process as it has been done successfully in multiple studies over the years. Any adverse events with microdialysis catheter will be monitored up to the resolution of the adverse event and reported. Plastic cannula insertion might cause moderate pain. The procedure of MD probe insertion may cause pain comparable to a standard Intramuscular (i.m.) or Subcutaneous (s.c.) injection. This pain should vanish after a few minutes. A minor hematoma at the site of the probe insertion cannot completely be excluded. The risks of drawing blood from a vein include discomfort at the site of puncture; possible bruising and swelling around the puncture site; rarely an infection; and, uncommonly, faintness from the procedure.

Study participant's identities will be kept strictly confidential. Confidentiality will be maintained by assigning each participant a number, which will be used in all data tabulation. All findings from the study will be reported in a manner that precludes identification of any individual participant. These records, like all other study-associated records will be kept in the strictest confidence, and stored as encrypted files.

There is no financial risk associated with participating in this study. There will be no additional charges incurred from participating in this study than what would be normally charged if not enrolled within the study

Possible Benefits: Benefit of this study will be to determine if the addition of continuous intravenous infusion of antibiotic is superior to scheduled 3 hourly intravenous bolus of antibiotic. This will be achieved by evaluating the skeletal muscle and adipose tissue disposition of prophylactic antibiotic cefazolin using micro-dialysis sampling for both techniques. If the disposition of prophylactic antibiotic regimen using continuous drip in addition to schedule doses is superior then this might lead to further decrease in the incidence of nosocomial infection during PSFS.

Conflict of Interest: No conflict of interest exists for the PI or any of the Co-Investigators.

Safety Monitoring and Assessment

The purpose of this study is to compare two different dosing regimens of prophylactic

cefazolin during PSFS by using microdialysis technique, thus there is low risk associated with the study.

Safety review plan and Monitoring

The principal investigator (PI) will be responsible for ensuring participants' safety includes review of adverse events as well as study progress, data integrity and study outcomes. The monitoring procedures are delineated in the protocol. Only subjects who meet all inclusion criteria in the protocol will be enrolled in the study.

Adverse event reporting plan

All risks have been described in the consent form. All adverse events experienced by the participant during the time frame specified in the protocol need to be reported. Every adverse event that is reported to either the principal investigator or the designated research associates by medical staff caring for the subject will be documented.

As a subset of the reported adverse events, all serious adverse events, whether should they occur, whether study-related or expected, will be documented in serious and unexpected AE reporting form and reported by the principal investigator to the IRB within five days of discovery.

In addition, the principal investigator will follow the procedure in the UF IRB Adverse Event Evaluation and Reporting Guide. Any unanticipated problems involving risks to subjects or others will also be reported to UF IRB per the IRB-01 Definitions and Reporting Guide. Aggregate reports of adverse events will be prepared at the end of the study for IRB review.

References:

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