Optimal Location of Nerve Block to Minimize Perioperative Opioid Administration in ACL surgery: Comparing True Adductor Canal to Proximal Block

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Study Site: NYU Langone Health: New York, NY

Introduction

Anterior cruciate ligament (ACL) repair is a common outpatient orthopedic surgery. Patients undergoing this procedure experience significant post-operative pain that is poorly controlled by opioid analgesics alone.[1] Multimodal analgesic regimens are used in many centers to help optimize pain control and to reduce reliance on opioids, which are associated with many adverse effects, including nausea, constipation, respiratory depression, tolerance, and hyperalgesia. Multimodal treatments can include medications such as acetaminophen, non-steroidal anti-inflammatory medications, gabapentinoids, periarticular local anesthetic infiltration, ketamine, and peripheral nerve blocks (PNBs). In our institution, we routinely treat ACL surgery patients with opioids, acetaminophen, and adductor canal nerve blocks.

Nerve blocks are commonly used to provide post-operative analgesia for orthopedic procedures. The knee has many nerves and the complete innervation of the knee is complex. There are nerves which are sensory (which control pain) and motor (which control movement).[7,9] The adductor canal block (ACB) is more commonly being used to provide post-operative analgesia since it provides a sensory block with minimal motor block.[1,3] This is very important because this block will decrease post-operative pain and yet allow the patient to participate in post-operative rehabilitation. Adductor canal nerve blocks are performed for knee surgery to help with pain control by anesthetizing nerves of the adductor canal.[1,3,5,7] While the saphenous nerve is one of our targets, our goal is to anesthetize several other small nerves that travel through the adductor canal as well. The adductor canal contains: saphenous nerve, nerve to the vastus medialis, medial femoral cutaneous nerve, and the distal portion of the posterior division of the obturator nerve.[9] More proximal blocks and large volume blocks theoretically produce better pain control due to the larger and more proximal spread of local anesthetic in the adductor canal.[4] Recent studies have revealed that the adductor canal block that many regional anesthesiologists have been performing are anatomically femoral triangle blocks based on the true definitions of the adductor canal and femoral triangle.[12] The apex of the femoral triangle is defined as the intersection between the medial border of the sartorius muscle and the medial border of the adductor longus muscle.[12] The study aims to compare true adductor canal blocks and femoral triangle blocks. We endeavor to confirm our clinical experience, which shows that a more proximal block and a higher concentration of local anesthetic can decrease opioid usage after ACL surgery.

The standard-of care anesthetic plan that we use at NYU Ambulatory Surgery Center includes general anesthesia and an adductor canal nerve block for ACL surgery.

We are planning a study designed as a prospective, randomized, single blinded trial involving human subjects. The goal of this study is to determine an optimal location (proximal or distal) for the nerve block and whether it will make a difference in how much opioid the patient will receive during and after surgery.

For this study, we will use ultrasound to identify the adductor canal and the proximal end of the adductor canal/apex of the femoral triangle to determine the location of the blocks. We will have two randomized groups:

1. ACB within true AC with bupivacaine 0.5% 20cc
2. ACB proximal to true AC with bupivacaine 0.5% 20cc

The data to be collected is total opioid use in first 24 hours (including intraoperative medications). We will send the patient home with a medication log where they can record when and how much pain medication (percocet, etc.) they take. We will call after 24 hours and ask them to give us the information over the phone. We would convert the intraop, PACU, and home narcotics to morphine equivalents and

calculate the total dose in 24 hours and compare each patient use in mg/kg.

Purpose

The purpose of this prospective, randomized blinded study is to determine whether the location of the nerve block plays a role in decreasing pain experienced with ACL surgery and thereby decreasing opioid consumption perioperatively.

Hypothesis

An adductor canal nerve block in a more proximal part of the thigh will provide more effective analgesia and therefore decrease opioid consumption.

Description of study and study procedure

Subjects:
All patients undergoing ACL surgery at NYU will be considered for inclusion with their surgeon's approval. Both males and females will be asked to participate. Their involvement in the study will last approximately 1 year.

Inclusion Criteria:

1. Patients between 18 and 75 years of age.
2. Patients undergoing unilateral ACL surgery.
3. Patients who consent to be randomized.
4. Patients must be English proficient.

Exclusion Criteria:

1. Patients younger than 18 or older than 75 years of age.
2. Patients with a history of chronic pain or who are taking medications intended to treat chronic pain such as strong opioids.
3. Patients with history of neurologic disorder that can interfere with pain sensation.
4. Patients with a history of drug or alcohol abuse.
5. Patients who are unable to understand or follow instructions.
6. Patients with an allergy or a contraindication to any of the medications used in the study or patients with a contraindication to any of the study procedures.
7. Patients with severe liver disease, renal insufficiency, congestive heart failure, and/or significant heart disease.
8. Patients with a BMI over 42.
9. Any patient that the investigators feel cannot comply with all study related procedures.
10. Patients who do not tolerate Percocet.

Number of Subjects:
Our sample size estimate is based on testing the one-sided non-inferiority hypothesis of the total opioid use in first 24 hours (including intraoperative medications), the primary outcome. This study is powered to detect the difference between the two randomized groups. Assume total opioid use in first 24 hours with ACB within true AC with bupivacaine 0.5% 20cc is 32.9±6.0 mg (based on reference paper Abdallah et al., 2016). Considering a non-inferiority margin (Δ) of 15% (i.e., 4.9 mg opioid), and assuming that the true difference in total opioid consumption between two groups is 0, we need 20 patients for each group to achieve 80% power and α=0.05. To account for a 15% dropout rate, we need to obtain data from 23

patients for each group, i.e., a total of 46 patients. We estimate that we'll have to consent about 75 patients to get data, since there may be problems reaching the patients the days after surgery.

Randomization:
Participating subjects will be randomized to one of two groups. The randomization list will be maintained by a member of the study staff. Randomization will be done ahead of time using a computer-generated randomization schedule and using opaque sealed envelopes. These groups include:
1. ACB within true AC with bupivacaine 0.5% 20cc
2. ACB proximal to true AC with bupivacaine 0.5% 20cc

Procedures:
The research portion of this protocol is the randomization of patients. All anesthesia, perineural blocks, hydration, surgical treatment, pain treatment, and post-operative follow up visits are standard of care for this patient population. Brief descriptions of these standards of care procedures are explained below.

Preoperatively, ASA monitors will be applied and an intravenous line will be placed. Patients will receive IV sedation (midazolam and fentanyl) titrated to effect at the discretion of the anesthesiologist. All patients will receive dexamethasone 10mg IV and Zofran 4mg IV intraoperatively for nausea prophylaxis. Intraop narcotics will be limited to fentanyl and dilaudid. No intramuscular or intra-articular opioids will be administered.

Following patient enrollment, the anesthesiologist will receive a sealed opaque envelope from the research coordinator indicating adductor canal block location. Each patient's thigh will be scanned using ultrasound to identify the adductor canal and the apex of the femoral triangle. The distances from the base of the patella will be recorded. The patients will receive an ultrasound-guided single injection adductor canal block or femoral triangle block with 20 mL of 0.5% bupivacaine.

All included patients will receive general anesthesia as the primary anesthetic for the case, as this is our standard of care for patients undergoing ACL surgery.

As per standard practice, all patients will receive standard of care pain control with Percocet postoperatively.

In the PACU, muscle weakness will be assessed and recorded. At this time, patients will be given a medication record to take home, in which they will record their medication use, pain scores, side effects, and any additional medication for 24 hours after they leave the hospital. A member of the study staff will call the patient to collect the information from the medication record. This phone call will take place within 2 business days of the patient's discharge.

Post-operative follow up visits at 3, 6, and 12 months will take place in the surgeon's clinic and are standard of care for all patients regardless of whether they are in the study or not. During these visits, muscle weakness will also be assessed and recorded.

Statement of Compliance

This study will be conducted in accordance with the Code of Federal Regulations on the Protection of Human Subjects (45 CFR Part 46), 21 CFR Parts 50, 56, 312, and 812 as applicable, any other applicable US government research regulations, and institutional research policies and procedures. The International Conference on Harmonisation ("ICH") Guideline for Good Clinical Practice ("GCP") (sometimes referred to as "ICH-GCP" or "E6") will be applied only to the extent that it is compatible with FDA and DHHS

regulations. The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the sponsor and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection Training.

Risks

All medications used in this study are standard of care for surgical patients. The risks of nerve blocks are infection, bleeding, nerve injury, injury to surrounding tissues, and hematoma (collection of blood at the injection site).

Bupivacaine will be administered for the blocks. Bupivacaine carries a risk of severe neurologic and cardiac toxicity if injected intravascularly. However, it should be noted that ultrasound guided bupivacaine adductor canal blocks are standard of care for this surgery and therefore the risk to the patient will not be increased. The use of ultrasound guidance will minimize the possibility of injecting the bupivacaine into a blood vessel.

Randomization will not add risks as both study groups are standard of care.

Protection Against Risks

Experienced anesthesiologists trained in regional anesthesia will perform the blocks as per hospital guidelines. Ultrasound guidance is used to ensure proper anatomic placement of the blocks. Anesthesiologists will be unblinded.

Benefits

It is not known if this study will benefit the patients. All patients undergoing this procedure will have a block whether or not they participate in this study, barring any restrictions. We hope the knowledge gained from this study will benefit future patients.

Patient Recruitment and Consent

All subjects will be required to sign a New York University School of Medicine (NYUSOM) Internal Review Board (IRB) approved informed consent form (ICF) prior to any research procedures. Potential subjects who are scheduled for ACL surgery will be screened ahead of time. Patients will then be given the opportunity to ask questions and will sign the consent form prior to surgery. Subjects will be informed of the study and consented in a private setting. Because the patients would have an adductor canal block regardless of participation in the study, patients are consenting to being randomized to location of the ACB as well as the review of their medical charts. All questions will be answered and patients will not be coerced in any way to participate in the study. Those patients that meet inclusion criteria and are willing to participate in the study will be consented and enrolled. The subject will be given a copy of the consent and one will be placed in the medical chart. The original signed consent will be maintained in the research folder. Because an ACB is standard of care for this surgery regardless of participation in the study, the subject will be responsible for payment for all medical services rendered and will not be reimbursed.
We currently perform 600 ACL reconstruction procedures a year at NYU and therefore estimate that with approximately 10% of patients being enrolled, we can complete the study in 8 months.

Data Safety and Monitoring

The definition of unanticipated problems (UP) involving risk to subjects or others according to the NYU SOM IRB Drug Trial Protocol template is any incident, experience or outcome that meets all of the following criteria: unexpected in nature, severity or frequency, related or possibly related to participation in the research, suggests that the research places subjects or others at greater risk of harm. The definition

of an adverse drug event according to the NYUSOM IRB Drug Trial Protocol is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study.

1. Types of data or events:
   a. Intravascular injection
   b. Local anesthetic toxicity
   c. Hematoma formation
   d. Infection at injection site
   e. Neurologic injury
   f. Allergic reaction
2. Responsibilities and roles for gathering, evaluating, and monitoring the data:
   a. All data from the first 24 hours (including details about adverse/unexpected events) will be collected by the study team.
3. Information about the monitoring entity:
   a. Principal Investigator Dr. Prianka Desai as well as Dr. Kathy Chuy, Dr. Shruthima Thangada, and Dr. Jovan Popovic comprise the Data Safety Monitoring Board (DSMB).
4. Reporting adverse events and unanticipated problems to the monitoring entity:
   a. The time frame for reporting SAE and UP to the DSMB is by telephone within 24 hours of awareness of the event.
   b. The time frame for reporting SAE and UP to the IRB is to submit reports promptly, but no later than 5 working days, from the time the investigator becomes aware of the event. The Principal Investigator will submit a Reportable Events Form for all reportable information to the IRB as per NYUSOM IRB policy.
5. Assessments:
   a. Specific study stopping points are a serious adverse event. The monitoring entity will review data after the enrollment of 20 patients and assess the data for unanticipated problems involving risks to patients.
6. Criteria for action:
   a. Events will be reported to the anesthesia department QA. The types of events and data that will be captured and analyzed are adverse events, serious adverse events and unanticipated problems.
   b. Although rare, systemic local anesthesia toxicity is a serious adverse event (SAE). If this SAE happens, it will happen at the time that the block is placed when the patient is monitored in the operating room and is under the care of the attending anesthesiologist. The attending anesthesiologist will take appropriate measures.
   c. Nerve injury related to the block is very rare, although possible, since the block is done under ultrasound guidance. Nerve injury would be evaluated by the anesthesiologist and surgeon.
   d. If the pain management or physical therapy teams report any untoward findings, the DSMB will convene to discuss feasibility of continuing this study. The Principal Investigator is responsible for monitoring and any/all DSMB unexpected findings will be reported to the IRB as per IRB policy.
7. Procedure for communicating:
   a. The Principal Investigator will submit a Reportable Events Form for all reportable information to the IRB within 5 working days from when the Principal Investigator learns of the event or new information.

Adverse Event Reporting:
All adverse events will be recorded in the study file and reviewed during the interim and final analysis. All serious adverse events will be reported to the IRB as per policy.

Data Collection
All patient related data pertinent to the study will be stored on password-protected computers under MCIT firewall located in the Anesthesiology Department. Data will be stored using electronic data capture with

REDCap, and accessible only to research staff. Any identifiers will be removed when data is sent out for statistical analysis. We will also be sending patients home with a medication record to assess the amount of Percocet taken, the time it was taken, the pain score at the time of administration, side effects, and any additional medication or therapy used for their pain. A member of the study team will call patients 1-2 business days after surgery to collect this information. The randomized adductor canal block is the study procedure. No additional study procedures will be done after the surgery. Below is a list of specific data that will be collected from the subject's medical charts.

The following data will be collected:

-Patient demographics (age, sex, ASA status, height, weight, BMI, comorbidities).

-Dose of IV fentanyl and dilaudid administered in the operating room.

-All opioid pain medications (oral and IV) administered from the time of arrival to the OR until 24 hours after leaving the hospital.

-Any adverse reactions to the pain medication

-Motor block (muscle weakness): in PACU and measured in surgeons' clinic at 3, 6 and 12 months.

We will present at Anesthesiology science meetings and submit the manuscript for publication to Anesthesia journals. No PHI will be used in this dissemination.

Outcomes

The following outcomes will be assessed:

Primary outcome Total opioid consumption intraop and postop from arrival to the OR until 24 hours after leaving the hospital, expressed as morphine equivalents. Pain scores up to 24 hours after leaving the hospital. Side effects such as nausea, itching, constipation.
Secondary outcomes Motor block reported by the patient and objectively measured at 3, 6 and 12 months.

Statistics:

Patient characteristics at baseline will be summarized using descriptive statistics. The Fisher's Exact Test will be used to compare categorical variables and the Wilcoxon's Rank Sum Test will be used to compare continuous or ordinal variables between groups. The primary outcome, total opioid consumption, between two groups will be assessed by a one-sided non-inferiority test with assuming a true value zero. The secondary outcome will be compared by the Wilcoxon's Rank Sum Test. All statistical analyses will be done by SAS 9.4 (SAS Institute, Cary, NC), and the statistical significance level is considered as 0.05.

Registration:

The study will be registered with clinicaltrials.gov once it is approved.

Works Cited

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