

Pain after total knee arthroplasty: a comparison of combined continuous adductor canal block with infiltration of local anesthetic between the popliteal artery and capsule of the knee block versus continuous adductor canal block alone on postoperative analgesia

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List of Abbreviations

ACB – adductor canal block
IPACK – infiltration between the popliteal artery and capsule of the knee
FNB – femoral nerve block
TKA – total knee arthroplasty
PACU – post anesthesia recovery unit
DOSC – day of surgery center (preoperative area)
IV – intravenous
PO – per os (oral)
RASS – Richmond agitation sedation score
BPI – brief pain inventory

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Study Summary

| | |
|---------------------------------------|---|
| Title | Pain after total knee arthroplasty: a comparison of combined continuous adductor canal block with infiltration of local anesthetic between the popliteal artery and capsule of the knee block versus continuous adductor canal block alone on postoperative analgesia |
| Short Title | IPACK nerve block for total knee arthroplasty |
| Protocol Number | N/A |
| Phase | IV |
| Methodology | Allocation: Randomized Endpoint Classification: Efficacy Study Intervention Model: Single Group Assignment Masking: Double Blind (Outcomes Assessor, patient) Primary Purpose: Treatment |
| Study Duration | Intervention period immediately prior to surgery with follow-up until hospital discharge |
| Study Center(s) | Ochsner Medical Center Main Campus |
| Objectives | To examine the effect of two approaches to nerve blockade on opioid consumption, patient satisfaction, postoperative pain, mobility, length of hospital stay, and several other secondary outcomes. |
| Number of Subjects | 72 total, approximately 36 in each study arm |
| Diagnosis and Main Inclusion Criteria | <p>Inclusion Criteria:</p> <ul style="list-style-type: none"> • Unilateral, primary tricompartment total knee arthroplasty • Age 18 years or older • ASA I-III • Eligible for spinal or combined spinal epidural anesthetic • Able to speak, read, and understand English • Willing to participate in the trial • Anticipated discharge home from hospital <p>Exclusion Criteria:</p> <ul style="list-style-type: none"> • Contraindication to regional anesthesia or peripheral nerve blocks • Allergy to local anesthetics • Allergy to NSAIDs • Chronic renal insufficiency with Cr > 1.4 or GFR < 60 • Have chronic pain that is not related to their knee joint • Have been using opioids on a chronic basis (daily or almost daily opioid use for 3 months or longer) • Have a pre-existing peripheral neuropathy involving the operative site • Body mass index greater than 40 |

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| Study Regimen | Double-blind, randomized controlled clinical trial to test the efficacy of IPACK on postoperative opioid consumption, patient satisfaction, pain scores, mobility, and several other secondary outcomes in adults undergoing primary unilateral TKA. Enrolled patients will be randomized to either continuous ACB with IPACK or to continuous ACB with sham subcutaneous saline injection. Outcomes assessors and patients will be blinded to the intervention. |
| Duration of administration | Single preoperative IPACK block |
| Reference therapy | No IPACK block/sham subcutaneous saline injection |
| Statistical Methodology | Descriptive statistics per Ochsner statisticians |

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1 Introduction

This document is a protocol for a human research study. This study is to be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization guidelines), applicable government regulations and Institutional research policies and procedures.

1.1 Background

Total knee arthroplasty (TKA) is an effective surgical treatment for end-stage knee osteoarthritis and is commonly performed in the United States. Recovery following TKA is painful and regional anesthesia is often utilized to minimize postoperative pain, improve function, and allow earlier rehabilitation physical therapy. Goals of regional anesthesia are to provide effective analgesia with minimal postoperative muscle weakness to allow for early postoperative rehabilitation while also minimizing fall risk in the immediate postoperative period. While many different regional modalities exist and are effective for improving pain control, there is no consensus for best technique. Popular regional techniques for postoperative analgesia include single injection or continuous femoral nerve block (FNB) and adductor canal block (ACB), sciatic nerve block (SNB), and lumbar epidurals. Each modality requires a technical skill set and has its own limitations, benefits, and risk profile. Interestingly, a study in 2014 showed that approximately 76% of TKA surgeries across the country are still performed under general anesthesia and 87% of these patients do not receive any regional technique, despite overwhelming evidence of improved patient outcomes, decreased length of hospital stay, and improved function with regional techniques.¹ More recently, a 2016 study showed that only 27.3% of patients in a national registry received a peripheral nerve block and this was associated with decreased extended-length recovery room stays and postoperative nausea and/or vomiting.²

Recent studies published, including one study performed at Ochsner Medical Center,⁵ support that ACB provides similar analgesia compared to FNB while preserving straight leg raise and sparing the majority of quadriceps motor function.^{3,4,5} Both ACB and FNB only provide analgesia to the anterior medial part of the knee and most tricompartment TKA patients require supplemental opioid medications to cover joint pain usually attributed to the sciatic and obturator nerves. Historically SNB was used effectively to provide posterior analgesia but now is less used due to concern over increased difficulty with physical therapy due to foot drop. Because peroneal nerve palsy occurs in 0.3-1.3% of TKA,⁶ an additional concern is that foot drop due to SNB may mask surgical injury to the common peroneal nerve.

A novel alternative to SNB is the infiltration of local anesthetic between the popliteal artery and capsule of the knee (IPACK) block that targets the terminal sensory nerve endings to the posterior knee joint. Common practice at our institution incorporates preoperative continuous ACB and single IPACK block. A retrospective review of patients at our institution who received IPACK block with continuous FNB compared to patients who received FNB alone showed similar VAS pain scores with significantly decreased narcotic requirements postoperatively. The same retrospective review showed that patients who received IPACK block with continuous ACB had clinically improved performance with physical therapy and a significantly shorter hospital stay.⁷ The goal of this study is to prospectively examine and hopefully confirm the observations of the retrospective chart review by studying the effect of preoperative IPACK

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block on opioid consumption, patient satisfaction, pain scores, walk distance, hospital length of stay, and several other secondary outcomes.

1.2 Investigational Agent

Infiltration of local anesthetic between the popliteal artery and capsule of the knee (IPACK) block using 20ml of ropivacaine 0.25% with 1:300,000 epinephrine.

1.3 Preclinical Data

N/A

1.4 Clinical Data to Date

No published studies about IPACK exist. An IRB-approved retrospective review of patients at our institution who received IPACK with continuous FNB compared to patients who received FNB alone showed similar VAS pain scores with significantly decreased narcotic requirements postoperatively.⁶ The group of patients who received IPACK block had a 38.8% decrease in the mean opioid consumption in the first 24 hours. The same retrospective review showed that patients who received IPACK with continuous ACB had clinically improved performance with physical therapy and a significantly shorter hospital stay.

1.5 Dose Rationale and Risk/Benefits

We chose 20ml of 0.25% ropivacaine with 1:300,000 epinephrine to use for the IPACK because under ultrasound guidance it appears to provide adequate spread without reaching the sciatic nerve and causing foot drop. Less volume may not reliably provide analgesia. Larger volumes could cause foot drop or even lead to anesthetic toxicity.

2 Study Objectives

The goal of this study is to prospectively examine the effect of preoperative IPACK block on opioid consumption, patient satisfaction, pain scores, walk distance, hospital length of stay, and several other secondary outcomes.

3 Study Design

3.1 General Design

Double blinded, randomized controlled trial. All patients who present for primary, unilateral tricompartment TKA will be screened for inclusion. Consecutive patients who meet preset inclusion and exclusion criteria will be recruited either on day of surgery or in the preoperative anesthesia clinic by one of the study investigators. Written consent will be obtained for study participation. Patients who participate will be randomized into one of two treatment arms: continuous ACB with IPACK block versus continuous ACB with sham subcutaneous saline injection. Randomization will be done using the website random.org's Coin Flipper, selecting the Susan B Anthony coin, and flipping 5 coins. Majority heads will be randomized to receive the IPACK block whereas majority tails will be randomized to receive the sham subcutaneous injection. See Attachment A for an example of this website.

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Only the regional anesthesiologist performing the block will know the randomization status. The study participants, outcome assessors/researchers, other anesthesia personnel, surgeons, physician assistants, and nurses will be blinded to the treatment arm. All patients will receive sedation with midazolam and/or fentanyl titrated to comfort during block procedures. Per our standard practice at Ochsner Medical Center, all patients will have either spinal or combined spinal-epidural anesthesia with mepivacaine 1.5% as the primary anesthetic during the surgery and sedation with propofol titrated to comfort. Also per our standard practice at Ochsner Medical Center, multimodal therapy will include ketamine 0.25mg/kg IV (up to 50mg) intraoperatively, dexamethasone 8mg IV intraoperatively, pregablin 150mg PO preoperatively (adjusted to 75mg for age over 70) followed by 75mg nightly (or home gabapentin dose), acetaminophen 1000mg IV followed by 100mg PO every 6 hours postoperatively, and celecoxib 400mg PO on POD #0 followed by 200mg PO daily.

3.2 Primary Study Endpoints

- Cumulative opioid consumption (morphine equivalents) in the first 24 hours

3.3 Secondary Study Endpoints

- Patient satisfaction on day of discharge using the Brief Pain Inventory (BPI) or a similar validated satisfaction survey
- Average pain score at rest and with physical therapy in PACU, POD#1 am, POD#1 pm
- Worst pain score at rest and with physical therapy in PACU, POD#1 am, POD#1 pm
- Walk distance on POD#1 am, POD#1 pm, POD#2
- Time to first intravenous opioid, oral opioid in PACU and after arrival to hospital room
- Time to oral-only opioids
- Pain location
- Hospital length of stay
- Incidence of foot drop
- Incidence of itching, nausea, or vomiting in PACU, POD#1am, POD#1 pm
- Incidence of over-sedation based on Richmond Agitation Sedation (RASS) score

3.4 Primary Safety Endpoints

Not applicable.

4 Subject Selection and Withdrawal

4.1 Inclusion Criteria

- Unilateral, primary tricompartment total knee arthroplasty
- Age 18 years or older
- ASA I-III
- Eligible for spinal or combined spinal epidural anesthetic
- Able to speak, read, and understand English
- Willing to participate in the trial

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4.2 Exclusion Criteria

- Contraindication to regional anesthesia or peripheral nerve blocks
- Allergy to local anesthetics
- Allergy to NSAIDs
- Chronic renal insufficiency with Cr > 1.4 or GFR < 60
- Have chronic pain that is not related to their knee joint
- Have been using opioids on a chronic basis (daily or almost daily opioid use for 3 months or longer)
- Have a pre-existing peripheral neuropathy involving the operative site
- Body mass index greater than or equal to 40

4.3 Subject Recruitment and Screening

All patients scheduled for primary unilateral TKA at Ochsner Medical Center Main Campus will be screened for eligibility. Eligible patients will be provided study information by one of the study investigators on day of surgery or in preoperative anesthesia clinic and given option to participate in the study. Participants will undergo written consent. There is no financial incentive for participation.

4.4 Early Withdrawal of Subjects

4.4.1 When and How to Withdraw Subjects

Patients may voluntarily withdraw at any time of the study. All procedures are performed preoperatively and further patient participation only includes questionnaires while admitted to the hospital. Patients may refuse to answer these questionnaires. Patients may also elect to discontinue their continuous ACB early.

4.4.2 Data Collection and Follow-up for Withdrawn Subjects

All withdrawn subjects will be included in the intention to treat analysis. Already-accrued data for individuals who withdraw from the study will be maintained as part of the study data.

5 Study Drug

5.1 Description

Peripheral nerve blocks will be performed using preservative-free ropivacaine 0.25% with 1:300,000 epinephrine. Dilutions and sham subcutaneous injections will use preservative-free 0.9% saline. Package inserts are included as Attachment C.

5.2 Treatment Regimen

Two treatment regimens exist: 1) continuous ACB and IPACK block both with ropivacaine 0.25% with 1:300,000 epinephrine; and 2) continuous ACB with ropivacaine 0.25% with 1:300,000 epinephrine and sham subcutaneous saline injection.

5.3 Method for Assigning Subjects to Treatment Groups

Subjects will be randomized to one treatment arm at time of trial enrollment. Randomization will be done using the website random.org's Coin Flipper, selecting the Susan B Anthony coin, and flipping 5 coins. Majority heads will be randomized to receive the IPACK block whereas majority tails will be randomized to receive the sham subcutaneous injection.

5.4 Preparation and Administration of Study Drug

Preservative-free ropivacaine 0.25% with 1:300,000 epinephrine will be prepared on day of surgery by diluting ropivacaine 0.5% with sterile saline and adding the appropriate amount of epinephrine. A total of 20ml will be used during adductor canal catheter placement and 20ml will be used in the IPACK block. All drug preparations will be performed by a member of the regional anesthesia team.

5.5 Subject Compliance Monitoring

Study investigators will ensure that correct multimodal therapy is ordered and review the medication record to ensure appropriate administration by nursing.

5.6 Prior and Concomitant Therapy

Patients taking opioid medications daily or almost daily for 3 months or greater preoperatively will not be included in this study.

5.7 Packaging

Not applicable.

5.8 Blinding of Study Drug

Physicians performing the study intervention will not be blinded to the drug or technique. Outcome assessors and patients will be blinded to the study intervention performed.

5.9 Receiving, Storage, Dispensing and Return

5.9.1 Receipt of Drug Supplies

Upon receipt of the of the study treatment supplies, an inventory must be performed and a drug receipt log filled out and signed by the person accepting the shipment. It is important that the designated study staff counts and verifies that the shipment contains all the items noted in the shipment inventory. Any damaged or unusable study drug in a given shipment (active drug or comparator) will be documented in the study files. The investigator must notify study sponsor of any damaged or unusable study treatments that were supplied to the investigator's site.

5.9.2 Storage

Study drugs are securely stored in the pyxis and regional anesthesia block cart.

5.9.3 Dispensing of Study Drug

Study drugs will be dispensed from the pyxis and regional anesthesia block cart by a member of the regional anesthesia team on day of surgery.

5.9.4 Return or Destruction of Study Drug

At the completion of the study, there will be a final reconciliation of drug shipped, drug consumed, and drug remaining. This reconciliation will be logged on the drug reconciliation form, signed and dated. Any discrepancies noted will be investigated, resolved, and documented prior to return or destruction of unused study drug. Drug destroyed on site will be documented in the study files.

6 Study Procedures

6.1 Day of Surgery (POD #0)

Prior to regional interventions, patients will be placed on standard ASA monitors with EtCO₂ monitoring and supplemental oxygen by nasal cannula. A time out will be performed with the regional team, pre-op nurse, and patient prior to any sedating medications. Sedation will be accomplished with midazolam and fentanyl titrated to patient comfort at the discretion of the regional team.

Continuous adductor canal block placement

A high-frequency linear ultrasound transducer will be used to identify the adductor canal. The transducer will be placed at the mid-thigh, approximately half the distance between the inguinal crease and the patella, and at least 12 cm above the patella. The superficial femoral artery will be identified when it courses dorsal/lateral to the sartorius muscle in the short-axis. The hyperechoic structure located lateral/anterior to the artery will be the target catheter site at the adductor canal. A 17-gauge Tuohy needle will be placed lateral to the superficial femoral artery and within the adductor canal, using an in-plane ultrasound technique by a member of the regional anesthesia team. A total of 20ml of local anesthesia will be injected into the adductor canal. A flexible spring-wound 19-gauge epidural catheter will be advanced 1-2 cm into the adductor canal. The needle will be removed and a test dose of 5ml lidocaine 1.5% with 1:200,000 epinephrine will be injected into the catheter under ultrasound observation. The continuous catheter will be secured with surgical glue and liquid adhesive, and covered with a clear occlusive dressing. The catheter will be attached to a portable electronic infusion pump when the patient reaches PACU. In PACU, an initial 5ml bolus and then 8ml/h continuous infusion of ropivacaine 0.2% will be initiated through the continuous adductor canal catheter.

IPACK block placement

A high-frequency curvilinear ultrasound transducer will be used to identify the popliteal artery just proximal to the femoral condyles along the shaft of the femur in the short-axis. A 21g peripheral nerve block needle will be advanced using an in-plane ultrasound technique until the needle tip is located between the popliteal artery and femoral shaft. A total of 15ml of local anesthesia will be injected at this location with an additional 5ml of local anesthesia injected as the needle is withdrawn.

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Sham subcutaneous saline injection

A high-frequency curvilinear ultrasound transducer will be used to identify the popliteal artery just proximal to the femoral condyles along the shaft of the femur in the short-axis as done with the IPACK block. A total of 1-2 ml of saline will be injected subcutaneously through a peripheral nerve block needle.

6.2 Postoperative Course

No further procedures are required.

At 24 hours, the cumulative opioid consumption will be summated. An outcomes assessor will survey the patient at pre-specified times for secondary outcomes. Additional secondary outcomes will be pulled from the electronic medical record.

Per standard of care at Ochsner Medical Center, patients that meet clinical milestones will be discharged home on the afternoon of POD#1 with an on-Q pain ball that will be removed by the patient after approximately 48 hours.

7 Statistical Plan

7.1 Sample Size Determination

Prior published literature demonstrates analgesic equivalence between adductor canal block and femoral nerve block.^{3,4} An institutional retrospective study here showed a 38.8% effect difference between femoral nerve block with and without IPACK. Using this information, for an effect size of 0.4, power of 0.8, and significance level of 0.05 we determined a sample size of 64 patients. Assuming a dropout rate of 10%, we will include 72 patients in this study with approximately 36 patients per study arm.

7.2 Statistical Methods

A t-test will be used to compare the two arms of the study. We will apply other statistical methods as per Ochsner's statistics team & researchers.

7.3 Subject Population(s) for Analysis

- Unilateral, primary tricompartment total knee arthroplasty
- Age 18 years or older
- ASA I-III
- Eligible for spinal or combined spinal epidural anesthetic
- Able to speak, read, and understand English
- Willing to participate in the trial
- Do not meet any exclusion criteria previously defined in this protocol

8 Safety and Adverse Events

8.1 Definitions

Adverse Event

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An **adverse event** (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries should be regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

Serious Adverse Event

Adverse events are classified as serious or non-serious. A **serious adverse event** is any AE that is:

- fatal
- life-threatening
- requires or prolongs hospital stay
- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect
- an important medical event

Important medical events are those that may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardize the subject, and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in in-patient hospitalization, or intensive treatment of bronchospasm in an emergency department would typically be considered serious.

All adverse events that do not meet any of the criteria for serious should be regarded as **non-serious adverse events**.

Adverse Event Reporting Period

The study period during which adverse events must be reported is normally defined as the period from the initiation of any study procedures to the end of the study treatment follow-up. For this study, the study treatment follow-up is defined as 30 days following the last administration of study treatment.

Preexisting Condition

A preexisting condition is one that is present at the start of the study. A preexisting condition should be recorded as an adverse event if the frequency, intensity, or the character of the condition worsens during the study period.

General Physical Examination Findings

At screening, any clinically significant abnormality should be recorded as a preexisting condition. At the end of the study, any new clinically significant findings/abnormalities that meet the definition of an adverse event must also be recorded and documented as an adverse event.

Post-study Adverse Event

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All unresolved adverse events should be followed by the investigator until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the investigator should instruct each subject to report any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study. The investigator should notify the study sponsor of any death or adverse event occurring at any time after a subject has discontinued or terminated study participation that may reasonably be related to this study. The sponsor should also be notified if the investigator should become aware of the development of cancer or of a congenital anomaly in a subsequently conceived offspring of a subject that has participated in this study.

Abnormal Laboratory Values

A clinical laboratory abnormality should be documented as an adverse event if any one of the following conditions is met:

- The laboratory abnormality is not otherwise refuted by a repeat test to confirm the abnormality
- The abnormality suggests a disease and/or organ toxicity
- The abnormality is of a degree that requires active management; e.g. change of dose, discontinuation of the drug, more frequent follow-up assessments, further diagnostic investigation, etc.

Hospitalization, Prolonged Hospitalization or Surgery

Any adverse event that results in hospitalization or prolonged hospitalization should be documented and reported as a serious adverse event unless specifically instructed otherwise in this protocol. Any condition responsible for surgery should be documented as an adverse event if the condition meets the criteria for an adverse event.

Neither the condition, hospitalization, prolonged hospitalization, nor surgery are reported as an adverse event in the following circumstances:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for a preexisting condition. Surgery should **not** be reported as an outcome of an adverse event if the purpose of the surgery was elective or diagnostic and the outcome was uneventful.
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study.
- Hospitalization or prolonged hospitalization for therapy of the target disease of the study, unless it is a worsening or increase in frequency of hospital admissions as judged by the clinical investigator.

8.2 Recording of Adverse Events

At each contact with the subject, the investigator must seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events should be recorded immediately in the source document, and also in the appropriate adverse event module of the case report form (CRF). All clearly related signs, symptoms, and abnormal diagnostic procedures results should be recorded in the source document, though should be grouped under one diagnosis.

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All adverse events occurring during the study period must be recorded. The clinical course of each event should be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause. Serious adverse events that are still ongoing at the end of the study period must be followed up to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be possibly related to the study treatment or study participation should be recorded and reported immediately.

8.3 Reporting of Serious Adverse Events

8.3.1 Study Sponsor Notification by Investigator

A serious adverse event must be reported to the study sponsor by telephone within 24 hours of the event. A Serious Adverse Event (SAE) form must be completed by the investigator and faxed to the study sponsor within 24 hours. The investigator will keep a copy of this SAE form on file at the study site. Report serious adverse events by phone and facsimile to:

Matthew Patterson, phone 504-842-3755, fax 504-842-2036

At the time of the initial report, the following information should be provided:

- Study identifier
- Study Center
- Subject number
- A description of the event
- Date of onset
- Current status
- Whether study treatment was discontinued
- The reason why the event is classified as serious
- Investigator assessment of the association between the event and study treatment

Within the following 48 hours, the investigator must provide further information on the serious adverse event in the form of a written narrative. This should include a copy of the completed Serious Adverse Event form, and any other diagnostic information that will assist the understanding of the event. Significant new information on ongoing serious adverse events should be provided promptly to the study sponsor

8.3.2 EC/IRB Notification by Investigator

Reports of all serious adverse events (including follow-up information) must be submitted to the EC/IRB within 10 working days. Copies of each report and documentation of EC/IRB notification and receipt will be kept in the Clinical Investigator's binder.

8.3.3 FDA Notification by Sponsor

The study sponsor shall notify the FDA by telephone or by facsimile transmission of any unexpected fatal or life-threatening experience associated with the use of the drug as soon as possible but no later than 7 calendar days from the sponsor's original receipt of the information.

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If a previous adverse event that was not initially deemed reportable is later found to fit the criteria for reporting, the study sponsor will submit the adverse event in a written report to the FDA as soon as possible, but no later than 15 calendar days from the time the determination is made.

8.4 Unblinding Procedures

Physicians performing the study intervention will not be blinded to the drug or technique. The study participants, outcome assessors/researchers, other anesthesia personnel, surgeons, physician assistants, and nurses will be blinded to the treatment arm. Unblinding will occur at the conclusion of the study in order to facilitate group analysis.

8.5 Stopping Rules

Not applicable.

8.6 Medical Monitoring

It is the responsibility of the Principal Investigator to oversee the safety of the study at his/her site. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above, as well as the construction and implementation of a site data and safety-monitoring plan (see section 9 Auditing, Monitoring and Inspecting). Medical monitoring will include a regular assessment of the number and type of serious adverse events.

8.6.1 Internal Data and Safety Monitoring Board

8.6.2 Independent Data and Safety Monitoring Board

9 Data Handling and Record Keeping

9.1 Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

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9.2 Source Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial.

9.3 Case Report Forms

The study case report form (CRF) is the primary data collection instrument for the study. All data requested on the CRF must be recorded. All missing data must be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, write "N/D". If the item is not applicable to the individual case, write "N/A". All entries should be printed legibly in black ink. If any entry error has been made, to correct such an error, draw a single straight line through the incorrect entry and enter the correct data above it. All such changes must be initialed and dated. DO NOT ERASE OR WHITE OUT ERRORS. For clarification of illegible or uncertain entries, print the clarification above the item, then initial and date it.

9.4 Records Retention

For FDA-regulated studies the following sample language is appropriate:

It is the investigator's responsibility to retain study essential documents for at least 2 years after the last approval of a marketing application in their country and until there are no pending or contemplated marketing applications in their country or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period if required by an agreement with the sponsor. In such an instance, it is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

10 Study Monitoring, Auditing, and Inspecting

10.1 Study Monitoring Plan

Not applicable.

10.2 Auditing and Inspecting

The investigator will permit study-related monitoring, audits, and inspections by the EC/IRB, the sponsor, government regulatory bodies, and University compliance and quality assurance groups of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable University compliance and quality assurance offices.

11 Ethical Considerations

This study is to be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization guidelines), applicable government regulations and Institutional research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted independent Ethics Committee (EC) or Institutional Review Board (IRB), in agreement with local legal prescriptions, for formal approval of the study conduct. The decision of the EC/IRB concerning the conduct of the study will be made in writing to the investigator and a copy of this decision will be provided to the sponsor before commencement of this study. The investigator should provide a list of EC/IRB members and their affiliate to the sponsor.

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. See Attachment D for a copy of the Subject Informed Consent Form. This consent form will be submitted with the protocol for review and approval by the EC/IRB for the study. The formal consent of a subject, using the EC/IRB-approved consent form, must be obtained before that subject is submitted to any study procedure. This consent form must be signed by the subject or legally acceptable surrogate, and the investigator-designated research professional obtaining the consent.

12 Study Finances

12.1 Funding Source

Internally funded

12.2 Conflict of Interest

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by a properly constituted Conflict of Interest Committee with a Committee-sanctioned conflict management plan that has been reviewed and approved by the study sponsor prior to participation in this study. All University of Pennsylvania investigators will follow the University conflict of interest policy.

12.3 Subject Stipends or Payments

Not applicable.

13 Publication Plan

Neither the complete nor any part of the results of the study carried out under this protocol, nor any of the information provided by the sponsor for the purposes of performing the study, will be

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published or passed on to any third party without the consent of the study sponsor. Any investigator involved with this study is obligated to provide the sponsor with complete test results and all data derived from the study.

14 References

1. Memtsoudis SG et al. "Inpatient falls after total knee arthroplasty: the role of anesthesia type and peripheral nerve blocks." *Anesthesiology*. 2014 Mar; 120(3):551-63.
2. Gabriel RA et al. "Utilization of femoral nerve blocks for total knee arthroplasty." *J Arthroplasty*. 2016 Aug; 31(8):1680-5.
3. Gao F et al. "Adductor canal block versus femoral nerve block for analgesia after total knee arthroplasty: a systematic review and meta-analysis." *Clin J Pain*. 2016 Jun 17; epub.
4. Jiang et al. "Analgesic efficacy of adductor canal block in total knee arthroplasty: a meta-analysis and systematic review." *Orthop Surg*. 2016 Aug; 8(3):294-300.
5. Patterson ME et al. "The adductor canal block provides effective analgesia similar to a femoral nerve block in patients undergoing total knee arthroplasty – a retrospective study." *J Clin Anesth*. 2015 Feb; 27(1):39-44.
6. Nercessian OA et al. "Peroneal nerve palsy after total knee arthroplasty." *J Arthroplasty*. 2005; 20(8):1068-73.
7. Thobhani A et al. "Novel regional techniques in total knee arthroplasty promote reduced length of stay: an analysis of 106 patients." *Submitted and under review for publication*.

15 Attachments

- A: random.org simulation
- B: Brief Pain Inventory
- C: Study Drug Package Inserts
- D: Subject Informed Consent Form

ATTACHMENT A

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This form allows you to flip virtual coins. The randomness comes from atmospheric noise, which for many purposes is better than the pseudo-random number algorithms typically used in computer programs.

Flip virtual coin(s) of type

Flip Coin(s)

Reset Form

It is not always easy to decide what is heads and tails on a given coin. [Numismatics](#) (the scientific study of money) defines the [obverse](#) and [reverse](#) of a coin rather than heads and tails. The obverse (principal side) of a coin typically features a symbol intended to be evocative of stately power, such as the head of a monarch or well-known state representative. In the case of coins that do not have royalty or state representatives on them, the side that features the name of the country is usually considered the obverse.

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Coin Flipper

You flipped 5 coins of type US \$1 - Susan B. Anthony:



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