RESEARCH PROTOCOL TEMPLATE
INVESTIGATOR INITIATED TREATMENT TRIALS

**Title of Project:** A Randomized, Controlled, Double-Blind Trial of 3 Local Anesthetics for Spinal Anesthesia in Primary Total Hip Arthroplasty

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**Abstract**

Hip replacements are commonly performed under spinal anesthesia. Compared to general anesthesia, spinal anesthesia may reduce operative time, cardiopulmonary complications, and the need for blood transfusion.[1] Spinal anesthesia may also allow for earlier ambulation in the postoperative period. Ambulation is encouraged after hip surgery, as delays have been associated with delirium, pneumonia, and increased length of stay.[2] Early ambulation may also lead to better functional recovery.[3] Several spinal local anesthetics exist, each with its own unique pharmacologic properties. In this prospective randomized trial, we will determine if a short-acting spinal medication, mepivacaine, leads to earlier postoperative ambulation following primary hip replacement surgery compared to two other formulations of another long-acting spinal local anesthetic, bupivacaine.

*Note: The Research Plan, A through E, should not exceed 4 pages.*

## A. Specific Aims

State the hypothesis and specific aims. List the long-term objectives and what

the proposed research will accomplish. (Suggested length: a paragraph or two)

The specific aims of this study are to compare isobaric bupivacaine, hyperbaric bupivacaine, and isobaric mepivacaine as spinal anesthetic agents in the following areas:

1. Percentage of patients ambulating at 3 hours (primary outcome)
2. Return of sensory and motor function of lower extremities, incidence of hypotension, urinary retention, transient neurological symptoms (TNS)
3. Postoperative pain levels, opioid consumption, percentage of patients able to meet discharge criteria on same day, length of stay

Hypothesis: we hypothesize that a greater percentage of patients will ambulate early in the mepivacaine group compared to the two bupivacaine groups and that the smallest percentage of patients will ambulate early in the isobaric bupivacaine group.

## B. Background and Significance

Mepivacaine has a shorter duration of action than bupivacaine. Although some early studies suggested that mepivacaine might cause temporary pain in the buttocks and thighs, also known as transient neurological symptoms (TNS), mepivacaine has been utilized safely as a spinal anesthetic[4] and more recent studies have refuted that.[5] Mepivacaine spinal anesthesia has been shown in retrospective studies to facilitate rapid recovery in total knee arthroplasty compared to hyperbaric bupivacaine[5] but this study was limited because the time of evaluation was not controlled and differences in ambulation may have been missed as a result. Both hyperbaric and isobaric bupivacaine provide reliable anesthesia for a variety of surgeries and there appears to be no difference in the failure rate of the two drugs.[6] Even when used in low doses, both provide adequate anesthesia for greater than 60 minutes, which is the expected surgical time for this study. We will be using “low-dose” bupivacaine for both bupivacaine groups in an effort to maximize chance of early ambulation. Early ambulation is known to facilitate better functional recovery and reduce the incidence of some postoperative complications after hip surgery. A shorter-acting spinal anesthetic like mepivacaine may facilitate earlier ambulation in the postoperative period after hip surgery. Shorter time to ambulation could lead to faster discharge, which is desirable by both patients and surgeons and could reduce healthcare costs.

## C. Preliminary Studies/Progress Report

Existing evidence is limited by its retrospective nature[5] and the inherent confounders and lack of controlling that were present. A review comparing isobaric to hyperbaric bupivacaine found that both drugs provide safe anesthesia but that isobaric bupivacaine has a slower onset and longer duration.[6] A prospective, randomized trial comparing two doses of isobaric mepivacaine for ambulatory surgery found that both groups of patients were suitable for same-

day discharge and no patients experienced TNS.[7] Two separate studies in patients having ambulatory surgery found that TNS was rare after spinal anesthesia with mepivacaine.[8,9] However, none of these studies compared all 3 local anesthetics in the same study and they did not study the total hip arthroplasty population.

## D. Research Design and Methods

Describe the research design and procedures to be used (what, when, how) Include the duration of participation and early termination criteria. Provide a flow diagram or timetable. Procedures, situations, or materials that may be hazardous to personnel and the relevant precautions, should be outlined here. (suggested length not more than 2 pages)

This is a prospective, randomized, double-blind study comparing 3 different local anesthetics for spinal anesthesia. All patients between the ages of 18 and 85 years of age, American Society of Anesthesiologists (ASA) Physical Status 1-3, scheduled for elective total hip arthroplasty with one of three board-certified orthopedic surgeons (Hozack, Austin, Brown) and who have no contraindications to spinal anesthesia are eligible. Eligible patients will be called the night before to discuss the purpose and description of the surgery. Those who express interest will be approached the morning of surgery to discuss in more detail and consent will be obtained. A computer-generated randomization sequence will be used to assign patients to one of the three groups. The group assignment will then be shared with the anesthesia team caring for the patient. The surgeon, patient, and study team doing post-op assessments will remain blinded. Spinal anesthesia will be performed with the patient in sitting position unless he or she cannot tolerate that, in which case the patient will be positioned in lateral position with surgical side up (isobaric mepivacaine or isobaric bupivacaine) or surgical side down (hyperbaric bupivacaine). Patients receiving isobaric drugs will sit for 3-5 minutes until T10 dermatome is blocked and patients receiving hyperbaric drug will be placed in Trendelenberg position until T10 level is achieved.

Intraoperatively, blood pressure will be recorded per usual routine ASA standards, which is every 5 minutes at least. Sedation will be given at the discretion of the anesthesia team to maintain moderate sedation or less, defined as purposeful response to verbal or tactile stimulation, no need for airway intervention, and adequate spontaneous ventilation. Hypotension will be treated at the discretion of the intraoperative anesthesia team for blood pressure more than 20% lower than the preoperative reading. As per institutional protocol, all patients without contraindications or allergies receive acetaminophen and gabapentin preoperatively and for 24 hours postoperatively, except patients over 75 years of age do not receive gabapentin. The surgical approach for two of the surgeons is direct anterior approach (Hozack and Brown) and lateral approach for Austin. Any spinal block that is deemed inadequate for surgery based on sensory or motor exam by the anesthesia team will be converted to general anesthesia.

| Time | Event |
|---|---|
| Day before surgery | Phone call to patient to explain study |
| Day of surgery – preoperative period | 1. Enrollment of patients who express interest<br>2. Randomization<br>3. Spinal performed with assigned drug |
| Day of surgery – intraoperative period | 1. All blood pressures recorded<br>2. Surgeon (blinded) rates quality of surgical conditions |
| Day of surgery – postoperative period | 1. Sensory (ice) and motor (thigh flexion, knee extension, and toe dorsiflexion) assessments every 30 minutes in the Postanesthesia Care Unit (PACU)<br>2. First ambulation assessment by physical therapist in PACU or on ward **at 3-3.5 hours after spinal placement. Tests will include Tinnetti and ambulation assessment.**<br>3. Assessment for urinary retention and transient neurological symptoms (TNS) in PACU and on ward<br>4. Pain assessments using 11-point numerical rating scale every hour while in PACU and per routine once on medical floor.<br>5. Second ambulation |

| | |
|---|---|
| | assessment by physical therapist **at 5-5.5 hours if patient unable to walk at first assessment.** |
| Postoperative day 1 | 1. Assessment for TNS<br>2. Assessment of patient satisfaction with anesthesia |
| Postoperative day 2 | Assessment for TNS in person if in hospital or by phone if at home |
| 90 days | Query of Epic to determine if 90-day readmission occurred |

Postoperatively, patient sensory and motor assessments will occur every 30 minutes until strength returns to 5/5 in hip flexion, knee extension, and toe dorsiflexion. The sensory dermatome where numbness is detected at that time will be noted. Patients will be asked on POD 0, 1, and 2 about presence of TNS as defined above: "Do you have any back pain that you didn't have before surgery that goes into your buttocks, thighs, hips, or lower leg?"

Urinary retention will be defined by inability to urinate within 8 hours OR a report of distended or painful bladder occurring on POD 0, either by patient report or on palpation by nursing.

90-day readmissions will be queried in Epic.

## E. Statistical Methods

If not a pilot study, provide biostatistical design, power calculations determining the number of participants, and the proposed analysis. (suggested length: ½ page)

The study was powered using estimates of the study's primary endpoint which is the percent of patients successfully ambulating within a 3-hour window post-surgery. The time window is based on realistic expectations of when Physical Therapy assessments will be performed with a near 0 percent chance of missing first ambulation. The assumptions are also supported by available data in the literature on duration of spinal blocks as well as our clinical experience and time to postoperative ambulation for these surgical procedures. We believe that it is reasonable to expect ambulation within 3 hrs in 70% of patients for mepivacaine, 35% of patients for hyperbaric bupivacaine, and 25% of patients for isobaric bupivacaine. With a one-way ANOVA for 3 groups and alpha set at 0.05, the study will require 44 patients per group (N=132) to achieve 80% power to detect a statistically significant difference between the 3 groups in the percent of patients ambulating within 3 hours. Allowing for a 10% dropout and screen failure rate the study will require a total of 144 patients.

## F. Gender/Minority/Pediatric Inclusion for Research

All protocols must include documentation of the inclusion of women and minorities in the research protocol. If women and minorities are not to be included, provide rationale for exclusion.

Women and minorities will be included in this research protocol.

## G. Human Subjects

1. Provide number, age range, and health status of the subject population. List criteria for inclusion or exclusion.

   This study will include 144 subjects. Patients between the ages of 18 and 85 will be included. ASA physical status 1, 2, and 3 will be included. Patients who have a contraindication to spinal anesthesia will be excluded as will patients with body mass index (BMI) greater or equal to 40 $kg/m^2$. Patients with pre-existing neuropathy in the lower extremities will also be excluded and any patient deemed a poor study candidate by the attending anesthesiologist will be excluded at his or her discretion. Patients in wheelchairs and those who cannot ambulate 25 feet with or without an assist device will be excluded. Those who take greater than the equivalent of 25 mg IV morphine (oxycodone 30 mg) daily will be excluded.
2. Identify sources of research material in the form of specimens, records or data.

   All data will be from interviewing patients before and after surgery and from review of Epic record (TJUH) or Meditech record and paper records (ROSH) from their admission. Rothman databases may be accessed if data are missing from Epic.
3. Describe plans for recruitment and consent procedures to be followed.

   As described above, patients will be called the night before surgery to discuss purpose of study and determine if further steps and official consent should take place on the day of surgery. Patients expressing interest by phone and those who are not able to be contacted by phone but are eligible will be approached on the day of surgery to discuss the purpose, risks and benefits, and any questions. If available, family members will be involved in consent process as well.
4. Describe risks and assess likelihood and seriousness.

   One risk of the study is premature resolution of spinal block necessitating general anesthesia conversion (unlikely and moderate severity). The other main risk is that early ambulation could put patients at risk for falls, although this risk is minimized by having the physical therapist walk with the patient during this session and patients without adequate resolution of spinal level would not attempt ambulation at that time.
5. Describe procedures for protecting against or minimizing potential risks.

   Only patients who are undergoing primary unilateral hip arthroplasty with one of 3 surgeons with typical operating times of 60 minutes or less will be candidates. This minimizes risk of patients being enrolled whose surgeries

would outlast the spinal duration. The risk of falls is minimized by physical therapists walking with the patients.

6. Describe potential benefits and importance to the subjects and others.
   Patients who receive mepivacaine spinal anesthesia may be able to ambulate sooner after surgery. Early ambulation could theoretically lead to decreased hospital length of stay. A shorter duration of spinal anesthesia may also lead to less urinary retention and systemic hypotension.
7. Discuss why risks are reasonable in relation to benefits.
   There is always a risk of conversion to general anesthesia when spinal anesthesia is used. That risk may be greater in this study because low doses of bupivacaine are used or mepivacaine is used. However, data from existing studies as well as our clinical experience suggest that with the three surgeons in this study this risk should be low. This is weighed against the moderate to good probability that patients may ambulate sooner and therefore have a chance at earlier discharge, which would be a benefit.

## H. Data and Safety Monitoring Plan

All protocols that pose greater than minimal risk must have a Data and Safety Monitoring Plan (see DHSP policy G 616 "Independent Monitoring of Investigator-Initiated Clinical Trials."

Dr. Jordan Goldhammer will be the independent study monitor. Quarterly meetings in person or via telephone with the PI will take place and adverse events will be discussed. Any event determined to be severe will be addressed immediately.

1. Describe the Data and Safety Monitoring Plan (DSMP)
   a. reporting mechanisms for adverse events to the IRB, FDA, and NIH.
   b. adverse event (AE) grading
   c. plan for unanticipated AE reporting
   d. plan for annual reporting of AEs
   e. interim efficacy analysis where appropriate

2. If applicable, describe the Data and Safety Monitoring Board (DSMB) that will be responsible for monitoring the study. Indicate Chair, members, areas of expertise, frequency of meetings, distribution of reports.

   N/A

## I. Literature Cited

List only literature cited within the text. (suggested length: no more than 12 references)

1. Basques BA, et al. General Compared with Spinal Anesthesia for Total Hip Arthroplasty. J Bone Joint Surg Am 2015; 97(6): 455-61.

2. Kamel HK, et al. Time to Ambulation After Hip Fracture Surgery: Relation to Hospitalization Outcomes. J Gerontol A Biol Sci Med Sci 2003; 58(11): 1042-5.
3. Oldmeadow LB, et al. No Rest for the Wounded: Early Ambulation after Hip Surgery Accelerates Recovery. Anz J Surg 2006; 76(7): 607-11.
4. Pawlowski J, et al. Anesthetic and Recovery Profiles of Lidocaine versus Mepivacaine for Spinal Anesthesia in Patients Undergoing Outpatient Orthopedic Arthroscopic Procedures. J Clin Anesth 2012; 24(2): 109-15.
5. Mahan MC, et al. Mepivacaine Spinal Anesthesia Facilitates Rapid Recovery in Total Knee Arthroplasty Compared to Bupivacaine. J Arthroplasty 2018; 33(6): 1699-1704.
6. Uppal V, Retter S, Shanthanna H, Prabhakar C, McKeen DM. Hyperbaric Versus Isobaric Bupivacaine for Spinal Anesthesia: Systematic Review and Meta-analysis for Adult Patients Undergoing Noncesarean Delivery Surgery. Anesth Analg 2017;125:1627-1637.
7. Pawlowski J, Sukhani R, Pappas Al, et al. The Anesthetic and Recovery Profile of Two Doses (60 and 80 mg) of Plain Mepivacaine for Ambulatory Spinal Anesthesia. Anesth Analg 2000;91:580-584.
8. Liguori GA, Zayas VM, Chisholm MF. Transient Neurologic Symptoms after Spinal Anesthesia with Mepivacaine and Lidocaine. Anesthesiology 1998;88:619-623.
9. YaDeau JT, Liguori GA, Zayas VM. The Incidence of Transient Neurologic Symptoms After Spinal Anesthesia with Mepivacaine. Anesth Analg 2005;101:661-665.

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Principal Investigator/ Date

Date 3/21/2019

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