Double Blind Randomized Clinical Trial Comparing Time To Return of Lower Extremity Motor Function Following Spinal Anesthetic With Mepivacaine Versus Low-Dose Bupivacaine For Primary Total Hip and Knee Arthroplasty

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IRB Minimal Risk Protocol Template

Note: If this study establishes a human specimen repository (biobank) for research purposes, do not use this template. Use the Mayo Clinic Human Specimen Repository Protocol Template found on the IRB home page under Forms and Procedures at http://intranet.mayo.edu/charlie/irb/

First-time Use: Use this template to describe your study for a new IRB submission.

1. Complete the questions that apply to your study.
2. Save an electronic copy of this protocol for future revisions.
3. When completing your IRBe application, you will be asked to upload this document to the protocol section.

Modification: To modify this document after your study has been approved:

1. Open your study in IRBe. Click on the study 'Documents' tab and select the most recent version of the protocol. Save it to your files.
2. Open the saved document and activate "Track Changes".
3. Revise the protocol template to reflect the modification points , save the template to your files
4. Create an IRBe Modification for the study and upload the revised protocol template.

General Study Information

Principal Investigator: Matthew P. Abdel, MD
Co-Principal Investigators: Christopher M. Duncan, MD, Hugh M. Smith, MD, PhD
Co-Investigators: Mark W. Pagnano MD, Rafael J. Sierra, MD, Kevin I. Perry, MD, Cody C. Wyles, MD, David J. Harris, MD, Adam W. Amundson MD, Adam D. Niesen, MD, David J. Harris, MD

Study Title: Double Blind Randomized Clinical Trial Comparing Time To Return of Lower Extremity Motor Function Following Spinal Anesthetic With Mepivacaine Versus Low-Dose Bupivacaine For Primary Total Hip and Knee Arthroplasty

Protocol version number and date: Version 1 – 9/3/2018

Research Question and Aims

Hypothesis: Patients treated with mepivacaine spinal anesthetic will have faster return of lower extremity motor function than patients treated with low-dose bupivacaine following primary total hip arthroplasty (THA) and total knee arthroplasty (TKA).

Aims, purpose, or objectives:

#1 Evaluate time to return of lower extremity motor function between mepivacaine and low-dose bupivacaine spinal anesthetic among patients undergoing primary THA and TKA. This will be assessed by measuring time from spinal anesthetic administration to postoperative achievement of Bromage 0 function (return of spontaneous ankle, knee, and hip movement) in the non-operative extremity.

#2 Evaluate postoperative outcomes potentially related to anesthetic administration including pain scores, opioid consumption, urinary retention, transient neurologic symptoms, length of PACU stay, length of hospital stay, time to participation in physical therapy and walking distance with physical therapy. This will be determined by nurse and physical therapy charting and review of the medical record.

Background (*Include relevant experience, gaps in current knowledge, preliminary data, etc*.):

Total knee arthroplasty (TKA) and total hip arthroplasty (THA) are two of the most common orthopedic procedures performed in the United States, with significant growth in procedure volume expected over the coming decades. Coupled with the growing number of surgeries, is a growing cost to perform these procedures. In order to accommodate the increased demand for total joint arthroplasty (TJA) while also reducing complications and costs, optimized recovery pathways are needed to enhance resource utilization. One way to significantly impact recovery and length of stay is for patients to participate in physical therapy earlier in their episode of care. In addition to facilitating patient readiness for discharge from the hospital, early physical therapy and ambulation reduces post-operative complications such as venous thromboembolism and pneumonia. Multiple factors related to anesthesia can affect a patient's ability to participate in physical therapy on the day of surgery; these include post-operative nausea and vomiting, orthostatic hypotension and residual muscle weakness. The use of spinal anesthesia for TJA has been shown to reduce the risk of these complications. Shortening the duration of motor blockade in spinal anesthesia can reduce the time to patient physical therapy readiness, facilitating early ambulation and discharge to home.

Historically, short to intermediate duration local anesthetics such as lidocaine have been used for spinal anesthetics in short duration knee procedures such as knee arthroscopy. However, the use of lidocaine in spinal anesthesia has been dramatically reduced due to a high incidence of transient neurologic symptoms (TNS). TNS was first defined in 1993, and is defined as a painful condition of the buttocks and thighs with possible radiation to the lower extremities, beginning as soon as a few hours after spinal anesthesia and lasting as long as ten days. All local anesthetics can cause TNS but it is most commonly associated with lidocaine and reported to occur in 4% to 40% of patients undergoing spinal anesthesia with lidocaine.

Bupivacaine has been shown to have the lowest incidence of TNS and is currently the most widely used medication for spinal anesthesia. While advantageous for avoiding TNS, bupivacaine has a slow onset time coupled a long duration of action, which can delay postoperative recovery. Low-dose bupivacaine (10 mg) regimens are increasingly used; however, issues remain with the unpredictable temporal profile. Mepivacaine (70 mg) is a shorter acting local anesthetic compared to bupivacaine with a more predictable duration of action, raising interest as an alternative for procedures such as TKA and THA with consistent performance times.

In this randomized controlled trial, mepivacaine will be compared to low dose bupivacaine spinal anesthetics. The primary outcome will be time from spinal insertion to return of motor function. Secondary outcomes will evaluate pain scores, opioid consumption, urinary retention, transient neurologic symptoms, length of PACU

stay, length of hospital stay, time to participation in physical therapy and walking distance with physical therapy.

Study Design and Methods

Methods: *Describe, in detail, the research activities that will be conducted under this protocol*:

Preoperative Visit and Anesthesiologist Assessment: Patients meeting eligibility criteria will be approached during their surgical preoperative visit by the study coordinator in the clinic of the orthopedic Co-Principal Investigators. Those choosing to participate will be screened for inclusion and exclusion criteria. Patients will be assessed for ability to undergo a spinal anesthetic, but will be counseled that the decision between a spinal and general anesthetic will ultimately be determined by the anesthesiologist on the day of surgery. Thus, patients may be withdrawn on the day of surgery if the staff anesthesiologist does not agree with their candidacy to undergo a spinal anesthetic. Furthermore, patients will be counseled they may be withdrawn from the study if placement of a spinal anesthetic in the operating room proves unsuccessful and a general anesthetic is required.

Randomization and Blinding: Patients will be randomized in a 1:1 fashion. The first arm will be the "Mepivacaine" (70 mg) group and the second arm will be the "Low-Dose Bupivacaine" (10 mg) group. This trial will be conducted in a double-blinded manner. The patient and the postoperative outcomes assessors (PACU and Orthopedic Inpatient Nurses and Physical Therapists) will be the blinded parties. The anesthesia and surgical teams will not be blinded given they won't be responsible for any assessments. After a patient has been consented and enrolled, the study coordinator will randomize the patient to either Mepivacaine or Low-Dose Bupivacaine using a custom electronic randomization system which will be maintained by the study statistician. The surgical team and anesthesia team will be notified after the assignment is complete so the surgical listing can be completed with the appropriate medication.

In Hospital Evaluation: A standardized study card will be used to track patients throughout their various phases of care. At the time of discharge, the cards will be returned to the study coordinator for data entry in a secure spreadsheet available only to study staff. The study will begin with the anesthesiologist recording the time the spinal anesthetic is administered. The anesthesiologist will also record the time of incision, time of surgical closure, and time leaving the OR. The PACU nursing staff will then record the time of PACU entry and exit as well as the status of lower extremity function in the non-operative lower extremity at 15 minute intervals. The choices will be Bromage 3 (no movement), Bromage 2 (ankle movement only), Bromage 1 (ankle and knee movement), Bromage 0 (ankle, knee, and hip movement). Once the patient transitions to the general inpatient floor, the nursing staff will be responsible for recording motor function in a similar fashion at 15 minute intervals until the patient achieves Bromage 0 status. The physical therapy team will be responsible for recording the time of the first physical therapy session and the distance the patient ambulates during this session. Additional data points to be recorded by nursing staff will be total opioid consumption in the first 24 hours after surgery, pain scores, presence of nausea and/or vomiting, presence of orthostatic hypotension, and length of hospital stay. TNS will be evaluated twice, once during hospitalization by either the orthopedic or anesthesia team rounding on the patient on post-operative day one and a follow-up phone call performed on POD 6-9 by a study member not blinded to patient assignment. A standardized questionnaire will be used to determine the presence of symptoms of backache. TNS will be defined as new onset of back pain that radiates

bilaterally to buttock or distally. Back pain that does not meet these criteria will not be considered TNS. (ref. Anesth Analg 2005;101:661-5)

Follow-up Evaluation: Assessment will only take place during the hospitalization for the intended surgery. There will be a single phone call during post-operative day 6-9 for assessment of TNS.

Resources: *Describe the available resources to conduct the research (personnel, time, facilities, mentor commitment, etc.)*:

The Co-Principal Investigator orthopedic surgeons maintain high volume practices specializing in TKA and THA. This group of surgeons works exclusively with the Co-Principal Investigator anesthesiologists who specialize in the care of TKA and THA patients.

Cody Wyles is an orthopedic surgery resident who will assist with study execution and data analysis. A study coordinator in the department of orthopedic surgery will work with the residents and the midlevel providers for the orthopedic consultants to enroll patients at the preoperative visit. Standardized study cards will be created for patients enrolled in the study so that PACU and floor nursing staff as well as physical therapists can track relevant study endpoints. These cards will be returned to the study coordinator for data entry.

Dirk Larson is a master level statistician in the Division of Biomedical Statistics and Informatics with significant experience in the department of orthopedics and executing randomized clinical trials. He will serve as the lead statistician.

All funding for the study including statistical and coordinator FTE will be covered by the Department of Orthopedic Surgery and research royalty accounts of the Co-Principal Investigators.

Subject Information

Target accrual is the proposed total number of subjects to be included in this study at Mayo Clinic. A "Subject" may include medical records, images, or specimens generated at Mayo Clinic and/or received from external sources.

Target accrual: 300 patients

Subject population (children, adults, groups): Adult males and females

Inclusion Criteria:

1. Unilateral primary TKA or THA
2. 18+ years of age
3. Able to provide informed consent

Exclusion Criteria:

1. Body mass index (BMI) > 45 kg/m^2
2. Severe drug allergy* to medications used in this study, including non-steroidal anti-inflammatory drugs (i.e. celecoxib and ketorolac), and local anesthetics.
    - **defined as an immune reaction resulting in shortness of breath, hives, anaphylaxis, wheezing, and fever*
    -
3. Contraindication to spinal anesthesia technique (e.g., known spinal stenosis, coagulopathy, sepsis, infection at site of injection, uncooperative, refusal, anticoagulation medications not held within appropriate time frame[*]).
    - *[*]Per ASRA guidelines, Clopidogrel (Plavix) held for at least 7 days, Dabigatran (Pradexa) held for at least 5 days, Rivaroxaban (Xarelto)held for at least 3 days, Warfarin (Coumadin)held for at least 5 days or recent INR of less than 1.4, Enoxaparin (Lovenox) with doses > 1 mg/kg held for close to 24 hours.*
4. Known to be currently pregnant or actively breastfeeding[++]
    - [++] *Patients that have a previous history of menopause, hysterectomy, or tubal ligation will not be required to perform a pregnancy test. Female patients that do not meet this criterion will be asked to submit a urine sample, and will require a negative urine sample in order to proceed with study protocol. Urine sample be collected pre-procedurally.*
5. Impaired cognition
6. Lower extremity motor deficit

Research Activity

Check all that apply and complete the appropriate sections as instructed.

1. ☒ **Drug & Device**: Drugs for which an investigational new drug application is not required. Device for which (i) an investigational device exemption application is not required; or the medical device is cleared/approved for marketing and being used in accordance with its cleared/approved labeling. (Specify in the Methods section)

2. ☐ **Blood**: Collection of blood samples by finger stick, heel stick, ear stick, or venipuncture.

3. ☐ **Biological specimens other than blood**: Prospective collection of human biological specimens by noninvasive means that may include: urine, sweat, saliva, buccal scraping, oral/anal/vaginal swab, sputum, hair and nail clippings, etc.

4. ☐ **Tests & Procedures:** Collection of data through noninvasive tests and procedures routinely employed in clinical practice that may include: MRI, surface EEG, echo, ultrasound, moderate exercise, muscular strength & flexibility testing, biometrics, cognition testing, eye exam, etc. (Specify in the Methods section)

5. ☒ **Data** (medical record, images, or specimens): Research involving use of existing and/or prospectively collected data.

6. ☐ **Digital Record**: Collection of electronic data from voice, video, digital, or image recording. (Specify in the Methods section)

7. ☐ **Survey, Interview, Focus Group:** Research on individual or group characteristics or behavior, survey, interview, oral history, focus group, program evaluation, etc. (Specify in the Methods section)

☐ NIH has issued a *Certificate of Confidentiality* (COC). *When checked, provide the institution and investigator named on the COC and explain why one was requested*. _____

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HIPAA Identifiers and Protected Health Information (PHI)

Protected health information is medical data that can be linked to the subject directly or through a combination of indirect identifiers.

Recording identifiers (including a code) during the conduct of the study allows you to return to the medical record or data source to delete duplicate subjects, check a missing or questionable entry, add new data points, etc. De-identified data is medical information that has been stripped of all HIPAA identifiers so that it cannot be linked back to the subject. De-identified data is **rarely** used in the conduct of a research study involving a chart review.

Review the list of subject identifiers below and, if applicable, check the box next to each HIPAA identifier being recorded at the time of data collection or abstraction. Identifiers apply to any subject enrolled in the study including Mayo Clinic staff, patients and their relatives and household members.

Internal refers to the subject's identifier that will be recorded at Mayo Clinic by the study staff.
External refers to the subject's identifier that will be shared outside of Mayo Clinic.

Check all that apply:	INTERNAL	EXTERNAL
Name	X	
Mayo Clinic medical record or patient registration number, lab accession, specimen or radiologic image number	X	
Subject ID, subject code or any other person-specific unique identifying number, characteristic or code that can link the subject to their medical data		
Dates: All elements of dates [month, day, and year] directly related to an individual, their birth date, date of death, date of diagnosis, etc. **Note:** Recording a year only is not a unique identifier.	X	
Social Security number		
Medical device identifiers and serial numbers		
Biometric identifiers, including finger and voice prints, full face photographic images and any comparable images		
Web Universal Resource Locators (URLs), Internet Protocol (IP) address numbers, email address	X	
Street address, city, county, precinct, zip code, and their equivalent geocodes		
Phone or fax numbers		
Account, member, certificate or professional license numbers, health beneficiary numbers		
Vehicle identifiers and serial numbers, including license plate numbers		
Check 'None' when none of the identifiers listed above will be recorded, maintained, or shared during the conduct of this study. (exempt category 4)	☐ None	☒ None

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Data Analysis

Power analyses and study endpoints are not required for minimal risk research, pilot or feasibility studies.

☐ No statistical information. *If checked, please explain*:

Statistical Considerations

Randomization

Subjects will be randomized into one of two study groups: mepivacaine or low-dose bupivacaine. In order to ensure balance on the subject demographics between the two study groups, the subjects will be stratified on procedure (TKA vs THA), gender, age group (≥70 vs. <70) and BMI (≥32 vs. <32). Within each stratum, subjects will be assigned to either of the two study groups using a computerized dynamic allocation program housed in an online application developed by personnel in the Division of Biomedical Statistics and Informatics. Using dynamic allocation will ensure that the subject allocation will remain balanced on the stratification factors and the study group assignment throughout the entire subject accrual phase.

Sample Size

An a priori power analysis was conducted using internal data from Mayo patients undergoing primary TJA with mepivacaine (N=6) and low-dose bupivacaine (N=5). In these two cohorts, standard deviations of the time to return of full lower extremity motor function were 37 minutes and 89 minutes, respectively, yielding a pooled estimate of the common standard deviation equal to 65.6 minutes. Assuming that similar variability will be observed in the proposed study, a sample of 150 subjects per group (300 total) will be required to have 80% power to detect a difference of at least 30 minutes in mean time to return to full lower extremity motor function between the 2 study groups. With the typical volume of the participating surgical group, we anticipate enrollment will be complete within 3 months.

Endpoints

Primary: Evaluate time to return of lower extremity motor function between mepivacaine and low-dose bupivacaine spinal anesthetic among patients undergoing primary THA and TKA. This will be assessed by measuring time from spinal anesthetic administration to postoperative achievement of Bromage 0 function (return of spontaneous ankle, knee, and hip movement) in the non-operative extremity.

Secondary: Evaluate postoperative outcomes potentially related to anesthetic administration including pain scores, opioid consumption, urinary retention, transient neurologic symptoms, length of PACU stay, length of hospital stay, time to participation in physical therapy and walking distance with physical therapy. This will be determined by nurse and physical therapy charting and review of the medical record.

Analysis

Dirk Larson will lead the data analysis effort. All pre- and post-operative data will be entered by the study coordinator into standardized Excel Spreadsheets and RedCap forms as appropriate. The data will primarily be collected by the lead Study Coordinator and checked for accuracy and completeness by Cody Wyles. All outcomes will be reported descriptively using appropriate summary statistics, including 95% confidence intervals, where appropriate. Because this is a prospective, randomized trial, no formal between-group comparisons of baseline covariates will be performed. The primary study outcome will be time to return of full lower extremity motor function. Secondarily, we will assess a variety of both continuous and categorical outcomes between groups including pain scores, opioid consumption, urinary retention, transient neurologic symptoms, length of PACU stay, length of hospital stay, time to participation in physical therapy and walking distance with physical therapy. Outcomes measured on a continuous scale, including time to full lower extremity motor function, length of PACU stay and hospital stay, time to participation in physical therapy, and walking distance will be compared between the 2 study groups using two-sample t-tests if the data are sufficiently normally distributed; otherwise non-parametric Wilcoxon rank sum tests will be used. Ordinal variables such as pain scores will be analyzed using non- parametric Wilcoxon rank sum tests. Binary and nominal categorical outcomes will be compared between the study groups using chi-square tests or Fisher's exact tests, if low expected cell counts are observed. All statistical tests will be two-sided and the threshold of statistical significance will be set at $\alpha = 0.05$.

While it is expected that the study enrollment will be complete in approximately 4 to 6 months, one interim analysis will be performed at 2 months, or once half the subjects have been enrolled, whichever comes first. The Lan-DeMets alpha spending function with O'Brien-Fleming type boundaries will be utilized to maintain the overall type 1 error rate at alpha=0.05, regardless of the timing of the analysis.