Statistical Analysis Plan

April 9, 2018

NCT04821245

ID: BRI IRB18-008

Defining Normal Postoperative Magnetic Resonance Imaging after Total Knee Arthroplasty

Human Subjects Protocol

Study Title: Defining Normal Postoperative Magnetic Resonance Imaging after Total Knee Arthroplasty

PRINCIPAL INVESTIGATOR: Joseph M. Neal, MD
Department of Anesthesiology
Virginia Mason Medical Center
1100 Ninth Ave. Seattle WA USA 98101
Joseph.Neal@virginiamason.org
206-223-6980 (day)
206-644-1144 (night and weekend)

SUB-INVESTIGATOR(S): C. Craig Blackmore, MD
Department of Radiology
Virginia Mason Medical Center
Craig.Blackmore@virginiamason.org
206-223-6851 (day)
206-644-1144 (night and weekend)

Peter J. Verdin, MD
Department of Orthopedic Surgery
Virginia Mason Medical Center
Peter.Verdin@virginiamason.org
206-223-7530 (day)
206-644-1144 (night and weekend)

Table of Contents-

A. SPECIFIC AIMS

The purpose of this convenience sample observational study is to define normal magnetic resonance imaging (MRI) appearance of upper leg soft tissues and normal creatine phosphokinase (CPK) and aldolase levels after total knee arthroplasty (TKA). This knowledge is crucial for proper diagnosis and further understanding of the recently described sentinel complication of presumed local

anesthetic-induced myotoxicity after TKA in patients who received a continuous adductor canal block (CACB) for postoperative analgesia.

This study aims primarily to define quadriceps muscle appearance on MRI in 10 asymptomatic volunteers two days after undergoing uneventful TKA. The secondary aim is to investigate baseline and postoperative CPK levels coincident with TKA.

B. BACKGROUND, SIGNIFICANCE, and PRELIMINARY STUDIES

Local anesthetics consistently induce myotoxicity in animal models and in up to 0.5% of humans after ophthalmologic nerve blocks, yet clinically apparent myotoxicity in patients undergoing other peripheral nerve blocks was believed heretofore to be nearly non-existent.[1] This changed after introduction of CACB at Virginia Mason Medical Center when 4 patients developed symptoms, MRI findings, and neurophysiologic testing compatible with local anesthetic-induced myotoxicity.[2] In short order, other cases were reported from the Swedish Orthopedic Institute,[3] and anecdotally from practices throughout the United States. Furthermore, a recent retrospective review of MRIs obtained at VMMC for various indications within a week of TKA failed to identify a consistent pattern of MR findings that might have defined "normal MRI appearance" after TKA (BRI: 16092).[4]

These sentinel complications have resulted in major morbidity for the affected patients. After a normal early postoperative course, the patients rapidly developed flaccid quadriceps muscles and the inability to lift the operative lower extremity against gravity, with consequent halting of their rehabilitative trajectory. While fortunate patients recovered fully or nearly so after weeks to a few months as the unaffected myoblasts regenerated, less fortunate patients have never recovered to baseline.

Because non-ophthalmic myotoxicity has never been described to this degree in humans, little is known about its etiology, diagnosis, and treatment. Definitive diagnosis of myositis requires muscle biopsy, but this invasive and expensive intervention is unlikely to occur. All patients in our series[2] had MRI signals consistent with edema and inflammation, but non-specific for myositis. However, the radiologic literature is silent with regard to what constitutes normal MRI findings immediately after TKA. Consequently, the MRI pathology that we observed, while clearly demonstrating inflammatory changes in the anterior compartment of the upper leg, could conceivably represent normal postoperative findings. We have attempted to study this question by retrospectively reviewing MRIs of patients who underwent leg MRI within a week of TKA.[4] Although we could identify several patients in that cohort with clinical presentations consistent

with undiagnosed myotoxicity, we were unable to confidently discern pathological findings versus 'normal' postoperative changes on imaging.

C. RESEARCH DESIGN AND METHODS (including data analysis)

- Twenty volunteers of various age and sex that are scheduled for unilateral TKA by Dr. Peter Verdin (VM orthopedic surgeon) will be approached by Dr. Verdin to ascertain their willingness to volunteer for this study
- Identified patients will be consented for study participation by the PI (Neal) at least 24 hours prior to their surgery
- All patients will be cared for under the standard VMMC TKA clinical pathway, which includes a 2 day CACB
- If their postoperative course has been normal, the 20 volunteers will undergo unilateral thigh MRI with gadolinium based MRI contrast prior to discharge home on the morning of postoperative day 2. These patients will have pre- and post-op CPK and aldolase levels analyzed.
    - Patients will have their hip and knee motor strength assessed for baseline pre-surgery and again prior to MRI to ensure there is no evidence of atypical muscle weakness.
    - To reduce the likelihood of residual local anesthetic, the CACB infusion will be turned off at 0500 the morning of hospital Day 2
    - The MRI will not occur before 0700 of that day
    - Pre-operative CPK and aldolase will be included with the subject's routine pre-operative blood work
    - Post-operative CPK and aldolase will be drawn the morning of hospital day 2 prior to discharge
- Leg MRIs will be graded using a standardized checklist (developed for our previous retrospective study) by a radiology resident who is unaware of the findings from our retrospective assessment of symptomatic subjects. The resident will be supervised by Dr. Craige Blackmore.
- The radiologist's objective scoring of the MRI, together with the pre- and post-operative CPK and aldolase levels, will be entered into a password-protected spreadsheet. The subjects will be identified initially by their medical record number (MRN). Prior to sharing these results with our colleague Dr. Lauren Steffel (Puget Sound VA Health System), the MRNs will be deleted. Dr. Steffel's role in the study includes design and writing, but she will have no interaction with the subjects.
- This is an observational study in which the convenience sample of 20 volunteers is dictated by the grant monies procured. As an observational study, there will be no statistical analysis.

D. PROTECTION OF HUMAN SUBJECTS

1. RISKS TO THE SUBJECTS:
   a. Human Subject involvement and characteristics
   - The TKA patients who volunteer for this study will have pre- and post-operative CPK and aldolase analysis and unilateral leg MRI with radiologic contrast the morning of hospital day 2
   - The 20 volunteers will be between age 50 and 75. They will meet inclusion and exclusion criteria. Subjects will include both sexes
   -Volunteers can withdraw from the study at any time

ENROLLMENT
-Collaborating sites
None

INCLUSION/EXCLUSION CRITERIA
Inclusion criteria

- Anticipated unilateral TKA performed under the standard VMMC TKA pathway
- Subjects will be operated by a single surgeon (Dr. Verdin) to eliminate possible confounders related to surgical technique
- Planned 2 night stay at VMMC
- Subjects must be willing to volunteer for MRI study and CPK blood draws
- Age 50 to 75 years; either sex

Exclusion criteria

- Any contraindication to the use of spinal anesthesia or ACB-based analgesia
- Operative tourniquet time in excess 120 min and/or inflation pressure in excess of 300 mmHg
- History of muscle wasting or related disease
- History of pre-existing neurologic condition affecting the lower extremities
- Allergy to gadolinium based MRI contrast.
- Renal insufficiency
- Standard contraindications to MRI examination
- Children are excluded. They generally do not receive TKA

TOTAL PLANNED ENROLLMENT

Targeted/Planned enrollment: number of subjects (n= 20)

Ethnic Category	**Sex/Gender**		
	Females	Males	Total

Volunteers will be recruited without regard to sex or ethnic category. Although we will strive to have some mix of male and female volunteers, there is no set number that we wish to attain. Reported cases of myotoxicity have occurred in both sexes, but more males, as is consistent with the TKA population dynamic.

A. Sources of Materials:

-CPK and aldolase blood analysis and unilateral leg MRI with their results

-Virginia Mason radiology personnel and laboratory personnel will handle the CPK and aldolase specimens and MRI images in the usual fashion, which includes the patient's name, MRN.

-Results of the above exams will be entered into a password-protected spreadsheet that will be accessible only to the PI. When the final data are sent to the Sub-Is for analysis, the patient's MRN will be removed such that the only remaining identification will be "Subject 1, Subject 2, etc."

B. Potential Risks:

-The potential risk associated with the MRI exam is the rare occurrence of allergic reaction to gadolinium based MRI contrast.

-The potential risk of CPK and aldolase analysis is that inherent to phlebotomy, i.e., rare chance of infection, bruising, mild discomfort

-Potential social risks include breach of confidentiality or privacy

-There are no alternative treatments available

C. Adequacy of Protection Against Risks:

1. Recruitment and Informed Consent

-Potential volunteers will be identified by Dr. Verdin during his pre-surgical examination process. The volunteers will then be consented by Dr. Neal in person, when possible, or by phone. The consent process will take place at least one day prior to the surgical procedure. As noted, children and special classes will not be included in the study. Consent will be

documented using approved BRI consent forms – written and signed, with copies for subject and research study archives.

2. Protection against Risk:
   - Standard assessment of allergy or MRI-associated risk prior to MRI study
   - Standard care during phlebotomy
   - Referral to psychological counseling if indicated
   - All data will be de-identified completely except for the linkage of the subject's MRN to their data set. As noted, the MRN will be removed from the spreadsheet when it is sent to co-investigators for analysis
   - The data spreadsheet will reside on Dr. Neal's password-protected computer and will itself be password protected.

D. Potential Benefits of the Proposed Research to The Subjects And Others.
   - There is no benefit to the subject for participation in this study

E. Importance of the Knowledge to Be Gained
   - The results of this study should define the effectiveness of MRI and/or CPK and aldolase as diagnostic tools in future patients with suspected local anesthetic-induced myotoxicity
   - For this previously unknown complication, new knowledge is critical for both understanding the proper diagnosis and for complication management. We have tried other routes to understand the diagnostic paradigm, to no avail. The low risk and inconvenience of postoperative MRI and CPK studies will facilitate further knowledge related to this complication.

F. Subject Safety and Minimizing Risks
   - Dr. Neal will contact patients on postoperative day 2 to ensure their desire to continue with the study
   - Dr. Neal will monitor adverse events and their reporting. Other than the rare allergic reaction to radiologic contrast, no adverse events are anticipated
   - Dr. Neal will have post-MRI contact with the subjects to ensure the absence of concerns on their part. Subjects will have Dr. Neal's contact information.

E. Reference/Literature Citations

1. Zink W, Graf BM. Local anesthetic myotoxicity. *Reg Anesth Pain Med* 2004;29:333-340.

2. Neal JM, Salinas FV, Choi DS. Local anesthetic-induced myotoxicity after continuous adductor canal block. *Reg Anesth Pain Med* 2016;41:723-727.
3. Neal JM, Salinas FV, Choi DS. Reply to Drs. Kelly, Fritsch, Lansdown and Kim. *Reg Anesth Pain Med* 2017;42:414.
4. Neal JM, Blackmore CC. Magnetic Resonance Imaging of the Quadriceps Muscle After Total Knee Arthroplasty. Benaroya Research Center Institutional Review Board #16092.