PROTOCOL TITLE: A Comparison of Analgesic Efficacy of Ultrasound-Guided Genicular Nerve Block versus Saline Injection for Total Knee Replacement: a Prospective, Randomized Controlled Trial

PRINCIPAL INVESTIGATOR:
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OBJECTIVES:

Research Questions:

Do ultrasound-guided genicular nerve blocks with 0.5% bupivacaine provide improved knee analgesia for patients recovering from total knee replacement surgery compared to saline injection?

Hypotheses:

We hypothesize that the combination of ultrasound-guided adductor canal block (ACB) and genicular nerve block will achieve lower opioid consumption and therefore lead to decreased systemic side effects and improved overall satisfaction compared to ultrasound-guided saline injection for patients undergoing minimally invasive elective total knee arthroplasty (TKA).

BACKGROUND:

Total knee arthroplasty is associated with intense early postoperative pain. A sizeable proportion (25–40%) of patients experience severe pain postoperatively despite a comprehensive multimodal analgesic regimen.[1] Enhanced recovery protocols that emphasize early mobilization and hospital discharge remain varied among hospitals. Regional anesthetic techniques have evolved to preserve motor function in an effort to promote early ambulation and hospital discharge, while optimizing sensory blockade for adequate analgesia. The (ACB) of the saphenous nerve has demonstrated reduced opioid consumption and preservation of quadriceps muscle strength when compared to placebo and to femoral nerve blockade [2] however, several studies have shown that despite ACB, many patients may still have at least moderate, movement-related pain. This may be partly because the ACB does not provide analgesia to the posterior aspect of the knee, in which pain is commonly moderate to severe after surgery.

It has been proposed in the literature that complete blockade of the knee joint for adequate analgesia requires blockade of the genicular nerves.[3] The genicular nerves provide sensory innervation to the joint capsule and internal and external ligaments of the knee joint. The superior and inferior medial genicular nerves arise in the posterior popliteal fossa and are sensory branches of the tibial nerve. The superior and inferior lateral genicular nerves are sensory branches of the common peroneal nerve and course anteriorly to the lateral knee. The identification of the genicular nerves using ultrasound has been described in the literature.[4]

At our institution, all patients scheduled to undergo total knee replacement receive periarticular injections as part of their pain management, as this practice demonstrates effectively reduced narcotic consumption and improved patient satisfaction compared to IVPCA.[5]

We hypothesize that the combination of ultrasound-guided ACB and genicular nerve block will further decrease opioid consumption and therefore lead to decreased systemic side effects and improved overall satisfaction compared to ultrasound-guided adductor canal block alone in patients undergoing elective minimally invasive TKA surgery.

INCLUSION AND EXCLUSION CRITERIA:

Patient inclusion criteria:

Participants 40 to 85 years old who are presenting for minimally invasive total knee arthroplasty under spinal anesthesia and are candidates for peripheral nerve blocks. Minimally invasive is defined as custom modified instrumentation, a quadriceps sparing arthrotomy that does not extend beyond 1cm proximal to the patella and surgical techniques that focus on soft tissue protection.

Patient exclusion criteria:

Patient refusal
American Society of Anesthesiologists physical status classification of 4 or higher
Pre-existing neuropathy in the femoral or sciatic distribution
Coagulopathy
Infection at the site
Chronic opioid use (greater than 3 months)
Pregnancy
Medical conditions limiting physical therapy participation
Any other contra-indication to regional anesthesia

- *Adults unable to consent N/A*
- *Individuals who are not yet adults (infants, children, teenagers)N/A*
- *Pregnant women N/A*
- *Prisoners N/A*

STUDY-WIDE NUMBER OF PARTICIPANTS: N/A

(*If this is a multi-center study for which you are the lead investigator, indicate the total number of participants to be accrued across all sites*.)

STUDY-WIDE RECRUITMENT METHODS: N/A

MULTI-SITE RESEARCH: N/A

STUDY TIMELINES:

Subject's participation in the study will last 1 year
Approximately 5 TKA surgeries are performed each week at the Feinberg Pavilion. If we are able to enroll 5 subjects per month it should take about 24 months to complete.

STUDY ENDPOINTS:

Primary Outcome:

-Post-operative opioid consumption during the hospital stay.

Secondary Outcome:

-Pain scores (Visual Analog Scale pain score; 0 = no pain, 10 = excruciating pain) in the knee at rest and during activity recorded every 6 hours up to discharge.

-Overall global pain score (VAS pain scores; 0 = no pain, 10 = excruciating pain) recorded every 6 hours up to discharge.

-Overall pain burden for the first 36 hours.

-Opioid related side effects

-Time to physical therapy milestones (active straight leg raise, time until patient first gets out of bed, ambulation about the hospital room with or without assistance, ambulating 100 feet and ability to climb stairs)

-Length of hospitalization

-Readmission to the hospital or emergency room visit for evaluation during study period.

PROCEDURES INVOLVED:
All ASA 1-3, 40-85 year old patients who are scheduled for total knee reconstruction surgery and are scheduled to receive a nerve block as part of their postoperative analgesic care will be approached to participate in this study. Patients will be introduced to the study in the Lavin Pavilion12th floor pre- operative clinic by one of the study team members. On the day of surgery in the Feinberg pavilion 5th Floor. The subject will be approached by one of the study team members to answer any questions they have regarding the study. If they had not signed the consent document in the pre-operative clinic they will be asked again if they had reviewed the consent document and whether they would like to participate. Patient participation will last for 12 months.

Sealed opaque envelopes will be pre-randomized into two study medication groups using a computerized random number generator.

The study medication and protocol will consist of Group 1 (Active) – ultrasound-guided adductor canal blockade with 10 ml of 0.25% bupivacaine and ultrasound-guided genicular nerve blocks with 6 ml of 0.5% bupivacaine, and Group 2 (Control) – ultrasound-guided adductor canal block with 10 ml of 0.25% bupivacaine and ultrasound-guided genicular nerve blocks with 6 ml of normal saline. The surgeon will be blinded to the subjects study arm assignment.

An ultrasound-guided ACB will be performed at the level of the mid-thigh of the leg halfway between the superior anterior iliac spine and the patella. The femoral artery, femoral vein, saphenous nerve will be visualized by ultrasonography and the expansion of the adductor canal will be recorded. Sensory assessment of the saphenous distribution will be performed at 30 minutes. The ultrasound-guided genicular nerve block will be performed at the site of the superior lateral, the superior medial, and the inferior medial genicular nerves. The superior lateral genicular nerve is located at the confluence of the lateral femoral shaft and the lateral femoral condyle (in the anteroposterior plane) and at the midpoint of the femur (in the lateral plane). The superior medial genicular nerve site is located at the confluence of the medial femoral

shaft and the medial femoral condyle (in the anteroposterior plane) and at the midpoint of the femur (in the lateral plane). The inferior medial genicular nerve site is located at the confluence of the medial tibial shaft and the tibial flare (in the anteroposterior plane) and the midpoint of the tibia (in the lateral plane). Color Doppler will be used to identify the arterial structures which serve as landmarks for the corresponding nerves. All nerve blocks will be performed by a study team physician.

Postoperative follow-up will be done by study team member blinded to the group allocation. The dosing of oxycodone/hydrocodone-acetaminophen will be as needed with management goal of a Visual Analog Scale (VAS) score of ≤ 4. Patients with pain not managed by oral agents will receive IV medication. Patients will be visited during their hospital stay every six to eight hours until discharge to record pain scores, opioid consumption, and patient satisfaction. In addition, patients will be given a pain diary to record (VAS) pain scores every six hours until hospital discharge.

A study team member will follow up patients by telephone (if discharged prior to) at 48 hours, 72 hours and at 3 weeks and will ask questions pertaining to the patient's pain, narcotic side effects, and satisfaction with pain control. Patients are scheduled to have a follow-up visit with their orthopedic surgeon at approximately 3 weeks and 1 year following surgery. The range of motion, current pain medication use, pain scores and untoward events will be re-recorded during each surgical follow-up visit. Patient's medical record will be reviewed to verify or obtain correct opioid consumption and physical/occupational therapy participation during hospital stay.

DATA AND SPECIMEN BANKING: N/A

DATA AND SPECIMEN MANAGEMENT:
Study members will have an active Collaborative Institutional Training Initiative (CITI) training certification. Their names and roles will be added to the IRB application.

Each study subject will be assigned a study code number. The code will be used to link study data to patient identification (name) in a separate database that only the investigator has access.

Strict measures will be in place to ensure that no loss of confidentiality occurs. Only study team members will have access to the data. The principal investigator will be responsible for handling and management of the data.

Subject data will be stored on password protected secure computer at Northwestern University 10th floor Arkes (Department of Anesthesiology administrative office). Data access will be password protected and only available to study team members. Access will be controlled by the Principal Investigator. Local data will be stored on Northwestern University, NM servers which are password protected and backed up nightly. Information regarding the perioperative course will be included in the data collection. Data will also be validated by the PI prior to data analysis.

Data will be stored on NM Servers and Department of Anesthesiology computers which are password protected. Paper data will be stored in Arkes Pavilion 10th floor Department of Anesthesiology office research closet which is accessible by key card entry and then key for the closet. Each study subject will be assigned a study code number. The code will be used to link study data to patient identification (name) in a separate database.

The data both electronic and paper will be stored for five (5) years after manuscript preparation. Data both electronic and paper will be destroyed using departmental standards and approved vendors.

PROVISIONS TO MONITOR THE DATA TO ENSURE THE SAFETY OF PARTICIPANTS:

At the start of the study, a Data and Safety Monitoring Board (DSMB) will be appointed and will consist of the PI, a regional anesthesiologist, a statistician (Dr. McCarthy) all with expertise in the area of regional anesthesia complications after blocks for orthopedic surgery. The DSMB members must attest to not having any conflicts of interest with the study. A study team member (TBD) will participate in the DSMB meetings as non-voting member. The DSMB will be charged with oversight of the study's safety and integrity and assessing the risk versus benefits of continuing the study if such questions arise. The DSMB will meet annually in person or by conference call or more often, if necessary, based on the progression of the study. The DSMB will continue to meet until the completion of the study.

The DSMB will review patient recruitment and patient follow-up, compliance with the protocol including protocol violations, timeliness and completeness of data entry, compliance with patient confidentiality and HIPPA regulations, and communications of adverse events to the IRB. The DSMB members should immediately review the data in order to make any requests for additional information or analysis in a time frame that can allow for such requests to be completed before the scheduled DSMB meeting. Members of the DSMB must maintain confidentiality of the study data until otherwise instructed. An interim analysis of the data looking at safety will be conducted by the DSMB when results from the first 50 subjects are available.

WITHDRAWAL OF PARTICIPANTS:

If the subject decides to discontinue their participation in the study, no further exams will be completed. The existent data sheet will be preserved and the removal of a partially completed subject from the data set will be noted in the study manuscript. A research team member will contact the PI by secured-email to inform him about the event that led to early study termination.

RISKS TO PARTICIPANTS:

ACB is a widely practiced technique performed to provide postoperative analgesia for patients undergoing total knee arthroscopy. The major risk of genicular nerve block is infection, which is exceedingly rare given the use of aseptic technique.

Subject's involvement may make them feel emotionally uncomfortable because study team members will ask them questions regarding their pain and satisfaction throughout the study period.

The risks of the study medication include unintentional intravascular injection of the local anesthetic solution. This may cause cardiovascular effects such as hypotension, bradycardia, ventricular arrhythmias or cardiac arrest. Allergic response which can be mild or as severe as anaphylaxis. Rare risks include restlessness, anxiety, dizziness or tremors.

There is the risk of loss of confidentiality even though there are strict measures in place to prevent occurrence.

POTENTIAL BENEFITS TO PARTICIPANTS:
The potential benefit of participating in the study is that patients receiving the both the ACB and genicular nerve block may take less pain medication resulting in fewer side effects and achieve physical therapy milestones sooner than those who do not receive an genicular nerve block.

VULNERABLE POPULATIONS: N/A

COMMUNITY-BASED PARTICIPATORY RESEARCH: N/A

SHARING OF RESULTS WITH PARTICIPANTS: N/A

SETTING:
Study participants will be identified and recruited from the Anesthesiology pre-operative clinic on the 17 Floor of Lavin Pavilion at Northwestern Memorial Hospital. The research will be performed in the pre and post-operative area at Feinberg Pavilion 5th Floor. Post-surgery evaluations will occur on the orthopedics floors on the Feinberg Pavilion. The 3 week and 1 year follow up will occur in the orthopedic surgeon's office within Northwestern Medicine.

RESOURCES AVAILABLE:
The Section of Regional Anesthesiology actively provides care to admitted patients at Feinberg Pavilion. As a Regional Anesthesiologist and member of the Anesthesiology Service I regularly supervise and provide care to patients on this unit. We have a dedicated group of study team members that assist with daily recruitment and follow-up of patients in clinical anesthesiology trials. Study team members all have CITI training.

The primary investigator has expertise using the ultra-sonographic probe for needle guidance for nerve blocks. The study team members will set up the ultrasound machine for each study participant.

-The ability to recruit the number of study participants should be fairly easy given the number of TKA performed yearly.
-The investigator will be present for all scheduled study related nerve blocks.
-The study will be conducted in one of pre and post-operative rooms in the PACU on the 5th floor Feinberg Pavilion.
-Participants will have the immediate availability of the supervising anesthesiologist and attending anesthesiologist of record.
-Participating anesthesiologists and operating room staff and study team members will be briefed on the study prior to the subjects block.

PRIOR APPROVALS:
Department of Anesthesiology Research Committee

RECRUITMENT METHODS:
Subjects will be approached and recruited by a member of the anesthesia research team during the pre-operative clinic visit on the 17th floor Lavin Pavilion of Northwestern Memorial Hospital. Study team members will use Powerchart and Epic from NW to screen potential participants

Describe materials that will be used to recruit subjects. N/A

NUMBER OF LOCAL PARTICIPANTS:
On the basis of the literature [6] we assumed that patients in Group B (Control group) will have an average opioid consumption at 36 hours following surgery of 48 mg IV morphine equivalents (morEq) while patients who receive genicular nerve blocks would experience a decrease of 20% in opioid consumption to an average of 39 mg IV morEq. Standard deviation was estimated to be 15. The effect size is 0.60. Comparison of means of two independent groups (Wilcoxon-Mann-Whitney Test) demonstrated a required total sample size of 94, 47 participants in each group. 80% power, 0.05 alpha level. Six patients will be added to account for lost to follow up or cancelled surgical cases.

Pain burden defined as the area under the numeric rating score for pain for the first 36 hours will be calculated using the trapezoidal method. Time to report first pain and overall patient satisfaction between groups will be compared using the Kruskal-Wallis H test.

CONFIDENTIALITY:
Data is collected on paper by study team members and then entered onto the Department of Anesthesiology password controlled computers located on the 10th floor Arkes Pavilion. Data are stored in a department (NM) server which is also password protected and backed up nightly. Each study subject will be assigned a study code number. The code will be used to link study data to patient identification (name) in a separate database.

The paper folders will be stored in Arkes Pavilion 10th floor Department of Anesthesiology administrative office via key card controlled front door and key controlled closet. Data access will be password protected and only available to study investigators and study team members. Access to the data is controlled by the principal investigator. Data both electronic and paper will be destroyed 5 years after manuscript preparation using current procedures and approved vendors.

PROVISIONS TO PROTECT THE PRIVACY INTERESTS OF PARTICIPANTS:
The subject will have multiple interactions with the study team. The first interaction will be to discuss and obtain written informed consent; then multiple times during the perioperative period. The brief interactions will limit the amount of intrusion into the subject's recovery process.

The research study team is only to be allowed to view the data sheets, Powerchart and EPIC for selected data within the parameters of the study.

COMPENSATION FOR RESEARCH-RELATED INJURY: N/A

ECONOMIC BURDEN TO PARTICIPANTS:
There is no additional cost to participate. The extra block will be paid for by the Department of Anesthesiology.

CONSENT PROCESS:
The consent process will take place on the 17th Floor Lavin Pavilion, at Northwestern Memorial Hospital. Subjects who have reviewed the document but have not signed prior to the surgical date will be approached again on the day of surgery on the 5th Floor Feinberg Pavilion. The research study team will spent greater than 10 minutes discussing the study. Ample time will be allowed for patient to answer questions regarding the study and the consent document. The subject will also be informed that there is no conflict of interest between the PI and the protocol. The PI will not receive financial remuneration nor will the study participation affect the subject's financial charges for their care.

Waiver or Alteration of Consent Process: **N/A**

Participants who are not yet adults (infants, children, teenagers):**N/A**

PROCESS TO DOCUMENT CONSENT IN WRITING:
We will be following HRP-091. Consent attached to EIRB+ application

DRUGS OR DEVICES:
The FDA approved Sonosite M-Turbo Ultrasound Machine will be stored on the 5th floor Feinberg Pavilion at Northwestern Memorial Hospital in the anesthesiology store room behind a locked door. The ultrasound machine is owned by the Department of the hospital and is stickered by biomedical engineering.

Appendix A

DATA COLLECTION FORM
Ultrasound-guided genicular nerve block
Investigator: Antoun Nader, M.D.

Subject: ____ ▪ Date of procedure:___/___/__ TKA description:_____
Surgical Procedure: □ L □ R **Baseline (24hr) pain score**:_____ Sex: □M □F Weight: ___lbs/kg ▪ Height: ___in Age: ____
Subject Demographics: Caucasian: ___ African American: __ Asian:___Hispanic: __
Middle Eastern: __Other: _____

Time to complete block (needle in–needle out):____
Time of block placement:___ Sensory Assessment at 30 minutes: □Yes □No
Pain Score (VAS 0-10) after the performance of the block: _____
Immediate Complications: □ None □Yes If yes, explain:
Delayed Complications: □ None □Yes If yes, explain:

Follow-up: Time to 1st pain:_____ Location:

	6hr	12hr	18hr	24hr	30hr	36hr	42hr	48hr
Time:								
NRS (0-10) At rest During Activity								
Pain medication: Norco ____mg								
Oxycodone								
Dilaudid								
Side effects (0-3) 1=mild, 2=mod, 3=severe Nausea Vomit Dizzy								
Patient Satisfaction (0-10) Pain Control								

Anterior_____Posterior____Other_____

Physical Therapy Milestones	Time
Active straight leg raise	
Time until patient first gets out of bed	
Ambulation about the hospital room with or without assistance	
Ambulating 100 feet	
Ability to climb stairs	

Time of Discharge:_____ Date:___/___/_____ Length of hospitalization: _____

	72hr	3wks
Time:		
NRS (0-10) At rest During Activity		
Pain medication: Norco ____mg Oxycodone Dilaudid Tramodol		
Side effects (0-3) 1=mild, 2=mod, 3=severe Nausea Vomit Dizzy		
Patient Satisfaction (0-10) Pain Control		

Follow up:

Pain Scores (0-10)
At Rest: @ 3wk _____ and @ 1year_____
During Activity: @ 3wk _____ and @ 1year_____

Block Satisfaction @ 3wk (0-10):
□VS □S □Not Sat nor US □US □VUS

Range of motion: @ 3wk _____and @ 1year _____.

Readmission to the hospital or emergency room visit:
□Yes □No

Appendix B: Code Identifier List

A comparison of analgesic efficacy of ultrasound-guided genicular nerve block versus saline injection for total knee replacement: a prospective, randomized controlled trial.

Subject ID #	Subject Name	MRN	Telephone Number	Age/Gender	DOS
1					
2					
3					
4					
5					
6					
7					
8					
9					
10					
11					
12					
13					
14					
15					
16					
17					
18					
19					
20					
….100.					

Appendix C: Pain Journal

Subject # _____

Post Operative	Pain Score 0 (Low) 10 (High)
6 Hours Post Operative	
12 Hours Post Operative	
18 Hours Post Operative	
24 Hours Post Operative	
30 Hours Post Operative	
36 Hours Post Operative	
42 Hours Post Operative	
48 Hours Post Operative	