1. 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.

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2. Purpose of the study

To determine if ultrasound-guided genicular nerve blocks with 0.25% bupivacaine and dexamethasone provide improved knee analgesia for patients recovering from primary total knee replacement surgery compared to saline injection.

3. Background and Significance

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 adductor canal blockade (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 spinal anesthesia as well as infiltration of local anesthetic into the Interspace between the Popliteal Artery and posterior Capsule of the Knee (IPACK) injections as part of their pain management, as this practice provides analgesia while preserving motor function.(5)[1] Postoperatively, all patients receive adductor canal peripheral nerve catheters.

We hypothesize that the combination of ultrasound-guided adductor canal nerve catheter, IPACK block, and singe injection genicular nerve blockade will further decrease opioid consumption and pain scores, therefore leading to decreased systemic side effects and improved overall satisfaction compared to ultrasound-guided adductor canal catheter and IPACK block alone in patients undergoing elective minimally invasive TKA surgery.

4. Design and Procedures

This is a single center, prospective, randomized, controlled, single-blinded study. 40 subjects will be recruited (see #6 Recruitment and Compensation below), 20 in each group.

Primary Outcome:

Cumulative opioid consumption at 24 hours.

Secondary Outcomes:

- Quality of analgesia at rest and with movement, as measured by numerical pain rating scores (NRS-11) up to 48 hours (0h, 6h, 24h, 36h, 48h)
- Cumulative opioid consumption at 48 hours
- Opioid consumption and quality of analgesia based on patient diary after discharge on postoperative day 7 (worst pain score)
- Sleep quality based on number of times awakened on the evening of POD#0
- Subject satisfaction with the block technique at 24h and POD#7
- 20 meter walk test time on POD#1. This will be conducted on 6100, the orthopedic floor. Research staff will conduct the test, which will involve the patient walking at his/her fastest pace to a mark on the floor 10m away, then turning around and returning to the start line.

Preoperative Management

Subjects will be randomized on the morning of surgery to receive either genicular nerve blocks using 15mL 0.25% bupivacaine with 2mg dexamethasone or the same blocks with 15 ml of saline.

Prior to the block in the preoperative holding area, all subjects will receive the standard oral multimodal analgesic regimen, a spinal anesthetic with 12.5 mg of bupivacaine, and posterior capsule infiltration with 20 ml of 0.2% ropivacaine. Subjects will then receive the study intervention.

Single injection genicular nerve block technique

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 nerved 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 was 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 trainee supervised by an anesthesiologist experienced in regional anesthesia.

After skin local anesthetic infiltration, a 10 cm 21G insulated block needle (Sonoplex, Pajunk Medical Systems, Norcross, GA) will be inserted from the lateral aspect of the ultrasound probe and aligned with the ultrasound scanning plane (in-plane approach). In this way, both the needle shaft and tip can be visualized as the needle approaches the genicular nerve. The needle will be redirected as needed. Once satisfactory position of the needle time is confirmed and after frequent negative aspiration, 5mL of a solution containing 15 ml of 0.25% bupivacaine with 2mg dexamethasone, or 5mL saline, will be slowly injected. Spread of local anesthetic will be documented adjacent to the target nerve in real time. This procedure will be performed at the site of the three genicular nerves described above.

Subjects will then undergo the surgical procedure. In the post-anesthesia care unit (PACU), all subjects will receive the standard adductor canal continuous catheter that will be connected to a pump containing 0.2% ropivacaine with infusion rate of 8mL/hr.

Intraoperative Management

Subjects will receive a spinal anesthetic using intravenous propofol infusion for sedation. No muscle relaxation will be permitted. In addition, no long-acting opioids will be administered for analgesia; instead, boluses of fentanyl 25 to 50 mcg will be administered as guided by respiratory parameters and/or hemodynamics. Subjects will maintain spontaneous ventilation throughout surgery. Respiratory rate greater than 18 per minute will be treated by administration of 25 to 50 mcg of fentanyl. At the conclusion of the case, the propofol will be discontinued and the subject awakened. Subjects will be transported to PACU. All subjects will receive intravenous fentanyl and/or oral oxycodone as needed for pain management.

Postoperative Evaluation

Evaluation of both pain intensity (NRS-11 pain scale) and interval opioid consumption will be undertaken at the following time points in a blinded fashion by a member of the research team:

- PACU (30-60 minutes after arrival to PACU)
- 6 hours postoperatively
- 24 hours postoperatively

- 36 hours postoperatively
- 48 hours postoperatively
- POD 7 (morning of POD#7)

All data will be recorded in a REDCap database. Subjects will be provided with a diary to record the relevant data elements. Calls will be made on POD 7 to record the data in the research record by a member of the research team.

Sleep quality will also be assessed by a member of the research team on POD#1 as a function of the number of times the patient was awoken by pain.

Occurrences of adverse events reported by subjects will also be collected during the phone interview on POD#7. Subjects will be queried as to any block related complications (e.g., prolonged motor blockade or numbness) and opioid-related adverse events. Satisfaction with the postoperative pain management experience will also be graded on a 0-10 point scale on POD#7.

5. Selection of subjects

Criteria for inclusion:

- Subjects scheduled for primary elective total knee arthroplasty
- Age 56-85 years of age
- American Society of Anesthesiologists Physical Status I-III
- BMI 18-40 kg/m2

Criteria for exclusion:

- Inability to cooperate with protocol
- Inability to understand or speak English
- Allergy to ropivacaine, bupivacaine or other local anesthetic
- Contraindication to peripheral nerve block (e.g. local infection, neurologic deficit or disorder, previous trauma or surgery to ipsilateral knee, etc.)
- Revision knee surgery
- Chronic opioid consumption (daily morphine equivalent of >30 mg for at least four weeks prior to surgery)
- History of chronic pain
- History of psychiatric disorder
- History of diabetes mellitus with documented or symptomatic peripheral neuropathy

6. Subject recruitment and compensation

Potential subjects (see inclusion criteria above) will be identified on the surgical schedule several days in advance of the surgical procedure. These individuals will be contacted by telephone and asked for permission to discuss the study. The purpose of the study will be explained, the consent form read out loud, and any questions answered. Potential subjects will be encouraged to take time to discuss the study with family, and will be told

that there will be additional time to answer any questions on the day of surgery. Potential subjects will be told that there is no obligation to take part in the study and their decision will not affect the quality of their care.

On the day of surgery, one of the investigators will approach the potential subject in the preoperative area and answer any remaining questions. Subjects that indicate their interest in participating will then sign an informed consent and complete a HIPAA authorization form. There will be no compensation for subjects for their participation.

7. Consent process

The consent process will be conducted by one of the physician investigators involved in the study. The consent process will take place in the pre-operative area. Throughout the consent process, measures will be taken to maintain privacy, such as conducting face-to-face conversations in private rooms. As much time as necessary will be spent with each potential subject to sufficiently explain and answer all questions, and address all concerns they may have in regard to the study and/or consent process.

8. Subject's Capacity to Give Legally Effective Consent

Subjects who do not have the capacity to give legal consent will not be approached for participation in this study.

9. Study interventions

See #4.

10. Risk/benefit assessment

Risk to the subject

This study involves a single injection genicular nerve block, either with a local anesthetic solution or saline. Risks associated with the nerve block include bleeding, infection, and nerve damage.

Benefits to the subject

There are no direct benefits to the subject. There is potential for improved pain control if the subject is randomized to the treatment arm.

11. Costs

There will be no costs to the subject for participation in the study. Subjects will not be compensated for their participation.

12. Data analysis and statistical considerations

Based on our institutional experience with primary total knee arthroplasty and postoperative opioid consumption, we calculate that 20 patients per group (total of 40) will be required to detect a 30% difference in our primary outcome measure.

Baseline patient demographic and clinical characteristics as well as surgical factors will be compared between treatment groups. The difference in the primary outcome, 24h

opioid consumption, will be assessed via two-sided two-sample t-test. Outcome data distribution will be assessed for normality and log-transformed if necessary. If differences in key patient factors are identified between groups we will pursue a multivariable linear model in order to control for potential confounding of treatment effect estimates. Secondary numeric outcomes of pain score and opioid consumption at 48 hours and post-op day 7 will be compared via t-tests or Mann-Whitney tests as appropriate. Sleep quality during the night of surgery will be assessed via poisson regression of the count of times awakened from sleep. Subject satisfaction with the block technique will be compared using a t-test or Mann-Whitney test as appropriate.

13. Data & Safety Monitoring

In accordance with federal regulations the PI will monitor for, review, and promptly report to the IRB, appropriate institutional officials, sponsor, coordinating center and the appropriate regulatory agency head all unanticipated problems involving risks to subjects or others that occur in the course of a subject's participation in a research study (45 CFR 46.103(b)(5)(i) and 21 CFR 56.108(b)(1)), all AE reports will be reported per the DUHS IRB policies. PI will be monitoring all AEs and submitting reports to the IRB per DUHS IRB policy.

14. Privacy, Data Storage and Confidentiality

Potential subjects and their families will be approached in private rooms. Any guests not involved in the consent process will be asked to leave the room during any communications, unless the subject allows them to be present. Efforts to maintain subject confidentiality will include assignment of following Federal Privacy Regulations which provide safeguards for privacy, security, and authorized access. Except when required by law, subjects will not be identified by name, social security number, address, telephone number, or any other direct personal identifier in study records disclosed outside of Duke University Health System (DUHS). Subjects will be not be revealed in any reports or publications resulting from this study. For records disclosed outside of DUHS, subjects will be assigned a unique code number. The paper/electronic data will be stored as per the RDSP.

References

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3. Egeler C, Jayakumar A, Ford S. Adductor canal block is useful but does not achieve a complete block of the knee. Reg Anesth Pain Med. 2014; 39: 81–82.

4. Meng M, Waldman R, Waldman C, Waldman S. Ultrasound guided genicular nerve block-a motor sparing technique for the treatment of acute and chronic knee pain. Int. J. Anesthesiol. Res. 2015; 3: 37-43.

5. Cullom C, Weed J.T. Anesthetic and Analgesic Management for Outpatient Knee Arthroplasty. Curr Pain Headache Rep. 2017; 21: 23.