Proposed Research Protocol Form

Title: Does Radiofrequency Ablation of the Articular Nerves of the Knee Prior to Total Knee Replacement Improve Pain Outcomes? A Prospective Randomized Sham-Control Trial with 6 month Follow Up

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1.0 Research Aims/Objective:

1.1 Research Question(s):

Does Cooled Radiofrequency Ablation (C-RFA) of the articular sensory nerve supply to the knee prior to unilateral total knee replacement result in improved post-operative knee pain scores and decreased perioperative analgesic use as compared to standard perioperative medical therapy?

1.2 Null Hypothesis:

Cooled Radiofrequency Ablation (C-RFA) prior to unilateral total knee replacement has no effect on post-operative knee pain scores or pain medication use as compared to standard perioperative medical therapy.

2.0 Research significance:

2.1 Background

More than 300,000 total knee joint replacement surgeries are performed per year in the United States and safe, effective management of post-operative pain in these patients, often elderly, deconditioned, obese, or with co-morbid diseases like sleep apnea, can be challenging and often require a multidisciplinary, multimodal approach[1-4]. Opiates have been a mainstay of

treatment in the post-operative period, although continuous epidurals, peripheral nerve infusions of local anesthetic, intra and periarticular injections have all been used in this patient population with varying degrees of success and complications[5-7]. Inadequately controlled postoperative pain is not uncommon[8,9] and can cause multiple untoward effects, including a hyperdynamic circulatory state, increased oxygen consumption, muscle spasm of the quadriceps muscles, increased risk of DVT and increased risk of pulmonary embolism, whereas overmedication with opiates can cause hypoventilation syndrome, sedation, pruritus, constipation, or delirium, especially in the elderly population. Further, poorly controlled pain inhibits early mobilization and hinders post-operative physical therapy[8], both of which are critical in the early post-operative period to prevent joint adhesions, capsular contraction, muscle atrophy, and delays or limitations in the ultimate functional outcome following TKR.

A new paradigm for treating post-operative pain following TKR may be the use of cooled radiofrequency ablation (C-RFA) of the articular sensory nerve supply of the knee capsule prior to surgery, to desensitize the knee by blocking sensory afferents to the anterior capsule and thereby decrease post-operative pain. The clinical efficacy of radiofrequency neurotomy has been proven in chronic spine pain, cervicogenic headache and trigeminal neuralgia with a strong safety profile in appropriately selected patients. C-RFA is similar in mechanism to conventional RFA: a thermal lesion is created by applying radiofrequency energy through a percutaneous electrode placed at a target neural structure. However, in C-RFA, a constant flow of ambient water is circulated through the electrode via a peristaltic pump, maintaining a lowered tissue temperature by creating a heat sink. By removing heat from tissues immediately adjacent to the electrode tip, a lower but effective lesioning temperature is maintained, resulting in less tissue charring adjacent to the electrode, less tissue impedance[10,11] and more efficient heating and neurolysis of target tissue. The volume of tissue heated and the resultant thermal lesion size is substantially larger with C-RFA[12,13] as compared to conventional RFA, conferring a significant therapeutic advantage[14]. Larger thermal lesions increase the probability of successful neurolysis of pain generators that have significant variability in anatomic location.

To date, few publications have demonstrated the use of RFA for knee pain from OA. Choi et al used conventional RFA of the articular nerves in the knee in elderly patients with chronic knee pain from OA in a double blind randomized controlled trial published in 2011[15]. RFA at three nerve locations was performed with image guidance and each lesion was performed at 70 degrees C for 90 seconds with a 22 gauge cannula. Needle placements were at the region connecting the shaft of the femur to the bilateral epicondyles (superior lateral and superior medial genicular nerves) and the shaft of the tibia meeting the medial epicondyle (inferior genicular nerve)[16-18]. Patients who underwent RFA reported at least a 50% decrease in pain scores at one and three months following the procedure, whereas the sham control group had no demonstrable change in pain at these time points[15]. Oxford knee disability scores and patient satisfaction scores were also significantly improved in the RFA group but unchanged in the control group. No adverse events were reported in the 38 patients enrolled in the study[15]. In a

single case report, conventional RFA of periarticular nerves in a patient with chronic knee pain following TKR was described with favorable clinical results and drastically improved pain control, but the RFA was performed remote to the time of the TKR for the indication of chronic pain, not to treat perioperativ pain in the immediate postoperative and rehabilitative periods[19].

Thus, although RFA has been used in patients with chronic knee pain from OA and in one case treating chronic pain many months following knee replacement, C-RFA has not been used in the perioperative management of pain in patients undergoing total knee joint replacement surgery.

The aim of this study is to determine if patients undergoing unilateral total knee replacement obtain any pain relieving benefits from C-RFA of the articular sensory nerve supply prior to surgery, as compared to sham controls who receive only local anesthetic injections of these same nerves without the benefit of ablation treatment.

2.2 Significance

If C-RFA of the articular sensory nerve supply of the knee is found to decrease post-operative opiate consumption, provide meaningful pain relief and enhance post op physical therapy, the procedure can be integrated into the TKR perioperative treatment algorithm. Such treatment, if successful, will ultimately improve short and long term pain outcomes, patient satisfaction, and decreased length of hospital stay in a cost effective manner.

3.0 Investigational Plan/Protocol Specifics

General Design and Procedures.
This study design is a *prospective randomized trial* of C-RFA of 3 articular branches of the knee joint versus sham CRFA to examine the effects on post-operative opiate requirements during the first 48 hours after surgery (primary outcome). We will obtain approval from the Institutional Review Board at Northwestern University and will complete an informed consent process before initiating any study procedure.

Secondary Outcomes include:

a) Visual Analog Scale for pain: (0 (no pain) to 10 (unbearable pain) scale; at rest, mobilization/ weight bearing.
b) Knee Society Scale (clinician); WOMAC (patient)
c) Time to Physical therapy milestones:

   a. Active SLR
   b. Time until patient can get out of bed
   c. Time until patient able to ambulate < 100 feet
   d. Time until patient able to ambulate around room > 100 feet
   e. Time until patient is able to climb stairs (quantify specifics, how many steps are considered appropriate?)

d) Patient Global Perception of Change (GPC)

e) Patient Satisfaction (Likert Scale)
f) Hospital Anxiety and Depression Score (HADS)
e) SF 12 Questionnaire
f) McGill Pain Questionnaire
g) Inpatient length of Stay (LOS; days) and Physical Therapy "clearance for discharge" (days)
h) Complications of the injection procedure
i) Medication related adverse effects

A total of 60 patients will be randomized. Participants will complete assessments at these time points:

1) Baseline: immediately before the CRFA intervention,
2) Immediately prior to surgery (Day of Surgery)
3) 48 hours after the surgery procedure
4) 1, 3 and 6 months following TKR surgery.

A member of the research team will administer and collect the questionnaires. It will take about 5-10 minutes to complete the questionnaires. The research member will visit the patient at 48 hours to administer the questionnaire and collect data points. It will take approximately 5-10 minutes to complete the questionnaire. In addition, a member of the research team will contact the patient by phone or at scheduled surgical visits at 1 month, 3 months and 6 months.

A member of the research team will look in POWERCHART for physical therapy milestones. Other data points such as medication use, length of stay, time for PT clearance, surgical duration will be recorded. Data collection will be placed on a excel sheet and stored in a pass word protected computer in the department of anesthesiology. Paper data sheets will be placed in a binder and stored in a locked filing cabinet in a locked office located in the department of anesthesiology.

Participants

Inclusion criteria include:

1) Adults 30 to 80 years old
2) OA of the knee scheduled to undergo their first unilateral knee joint replacement
3) Willingness to undergo fluoroscopy-guided C-RFA *or* sham treatment.

Exclusion criteria include:

1) Conditions that preclude C-RFA or sham intervention (e.g. pregnancy, severe cardiac/pulmonary compromise; acute illness/infection; coagulopathy or bleeding disorder; allergic reactions/contraindications to a local anesthetic).
2) Prior TKR on either knee
3) Inability to write, speak or read in English
4) Patient refusal

Recruitment

Site(s) where study will be performed:
Department of Anesthesiology, 675 N St Clair, Suite 17-200, Chicago, IL 60611
Department of Orthopedic Surgery, 259 E Erie, Suite 13-100, Chicago, IL 60611

Patients who schedule a primary unilateral TKR with their orthopedic surgeon at NM will be asked to participate in the study by authorized research personnel. They will be screened to determine candidacy for the study; if they meet eligibility criteria, they will read and sign an informed consent form to participate. Each participant will be scheduled to see Dr. Walega in the Pain Medicine Center for the intervention procedure. They will be asked to be NPO for this visit and arrange a driver to accompany them home. This procedure will be performed 2-4 weeks prior to their planned knee surgery. The research assistant will calculate Morphine Equivalents (ME) of all analgesic medications including opiates, anti-inflammatories and membrane stabilizers.

Each participant will complete the following written outcome measures prior to the intervention: It will take approximately 10 minutes to complete the questionnaires.*
VAS pain score
WOMAC questionnaire
SF12 questionnaire
Hospital Anxiety and Depression Inventory questionnaire
McGill Questionnaire

Following the intervention procedure the following data points will be recorded:
VAS pain score
PGIC Questionnaire
Patient satisfaction

Randomization and Masking Procedures (Treatment vs Control; T vs C)
A computer-generated 1:1 block randomization scheme will be used to assign participants to receive either a CRFA *or* a sham procedure (wherein no RF energy is delivered after needle placement, and only local anesthetic is delivered). Randomization will be performed by the proceduralist immediately before the injection procedure by opening an opaque envelope to reveal the participant number and group assignment printed on an index card. Participants, surgeons and all other study personnel, including those who will perform follow-up evaluations, will be blinded to group assignment. One board certified, fellowship trained anesthesiologist (DRW) with 16 years of injection experience will perform all injections. Dr. Walega will not be involved in the collection of any primary or secondary data outcome.

Intervention Procedure Description:
At the time of the intervention procedure, a 22 or 20-g angiocatheter will be placed in the participant's hand/arm for peripheral intravenous access for conscious sedation during the procedure. The patient will be positioned supine on a fluoroscopy table with a positioning device under the patient's knee to create 30-40 degrees knee flexion and hemodynamic monitors will be placed including NIBP, pulse oximeter and nasal cannula oxygen at 1-4 L/min. The knee will be prepped with chloroprep for 1 minute and draped in a sterile fashion. A grounding pad will be placed on the patient's contralateral thigh and connected to the RF generator which will be turned on but will not be in the patient's view. Regardless of group assignment, midazolam 0.5-1 mg IV aliquots and/or fentanyl 25-50 mcg IV aliquots will be given as needed to provide

appropriate anxiolysis and analgesia for needle placement and manipulation for the duration of the procedure. NM policies and procedures for conscious sedation will be followed.

For active CRFA, three targets for ablation* will be identified with an AP view of the knee:
1.) Superior lateral genicular nerve
2.) Superior medial genicular nerve
3) Inferior medial genicular nerve
*=locations are based on anatomic studies and Choi et al publication

The skin and deep subcutaneous tissues overlying these target sites will each will be anesthetized using 5-10 mL of 1% lidocaine. An 18 G C-RFA cannulas (Cooled Radiofrequency Kit, Halyard Health), (75 or 100mm) will be placed through the skin to be optimally positioned via an anterior approach at the anatomic location of each of the 3 targets using AP and lateral fluoroscopic imaging. The disposable RF electrode that is supplied with RF kit will be placed into the cannula and attached to the RF generator; sensory and motor testing will be performed to confirm safe and appropriate placement. Following this confirmation, 2 cc of 2% lidocaine will be injected at each of these three sites. After 2 minutes, the targets will be lesioned at 60 degrees Celsius for 2 minutes 30 seconds. Following this, all needles will be removed and Band-Aids placed on the needle placement sites. Participants will be transferred to a recovery area and monitored in a reclining position for at least 30 minutes to allow sedation to wear off.

For sham control, the three targets for ablation will be identified in a similar manner. The skin overlying the target sites identified with image guidance will each be anesthetized using 5-10 mL of 1% lidocaine. A 3.5 or 5 inch 22 gauge Whitacre needle will be placed through the skin to be optimally positioned at the anatomic location of each of the 3 targets using AP and lateral fluoroscopic imaging. Following this placement confirmation, 2 cc of 2% lidocaine will be injected at each of these sites. Non-disposable radiofrequency electrodes will be placed through these needles and attached to a RF generator. The same auditory and visual experience of RF lesioning will be mimicked in the sham group as presented in the treatment group (see above). After 2 minutes and 30 seconds, the electrodes and needles will be removed and Band-Aids placed on the needle placement sites. Participants will be transferred to a recovery area and monitored in a reclining position for at least 30 minutes to allow sedation to wear off.

Economic Burden to Subjects: None

Subject Reimbursement: Participants will receive $100 after completing the 3 month follow up and another $50 after completing the 6 month follow up. Participants will be required to provide their name, telephone number, and mailing address. The telephone number will be used to contact the participants at study intervals and to verify correct mailing address prior to sending payment. Participants will be told there is a 4 to 6 week processing time. They will be asked to sign an accountability log to document payment.

Statistical Analyses:
Baseline characteristics (e.g., sociodemographic variables, primary and secondary outcomes) will be compared between treatment groups using t-tests or chi-square tests for categorical variables. We will conduct intent-to-treat (ITT) analyses for all primary and secondary outcomes

using a series of generalized mixed-effects regressions. All statistical tests will be two-sided with significance set at $p \leq .05$. SAS statistical software version 9.2 (SAS Institute Inc., Cary, NC, USA) will be used for statistical analyses.

In preliminary analysis, the distributional aspects of the variables under consideration will be examined through descriptive statistics. These statistics will include measures of location (mean, median, quartiles) and measures of dispersion (range, standard deviation, variance) for continuous variables and frequencies of the levels of categorical variables. These measures will also assist with a data cleaning/screening procedure to eliminate any possible copying, handling, recording or measurement errors. In addition to the features described above, the dependence of outcome measures will need to be properly accounted for in the data analysis as measures will be made at multiple times for the same participant. Consequently, these observations tend to be correlated and require statistical techniques that can properly account for the correlation in order to draw valid inference. Our general approach for analyzing these multiple types of data in this trial will be the Generalized Linear Mixed-Effect Models (GLMM).

Statistical Power

The power analysis for this study was performed using data from Choi et al and assumptions regarding perioperative opiate requirements in patients undergoing TKR without an indwelling epidural catheter or peripheral nerve block. A sample size of 28 per group is needed to detect a difference in analgesic use of 15 morphine equivalents (ME) per 24 hour cycle, assuming the controls use 47 ME per 24 hours cycle with a standard deviation of 19 ME with a power of .81 at alpha = 0.05. The sample size calculation was computed using a two-sided Mann-Whitney Test (PASS). To correct for lost to follow up and dropout rates, we will recruit 30 patients into each treatment group.

Duration of follow-up This trial is designed with 6-month duration of follow up after surgery.

Use of only one exposure to the intervention

We will not allow repeat injections for either treatment group. No patients will receive intra-articular or peri-articular steroids in this study.

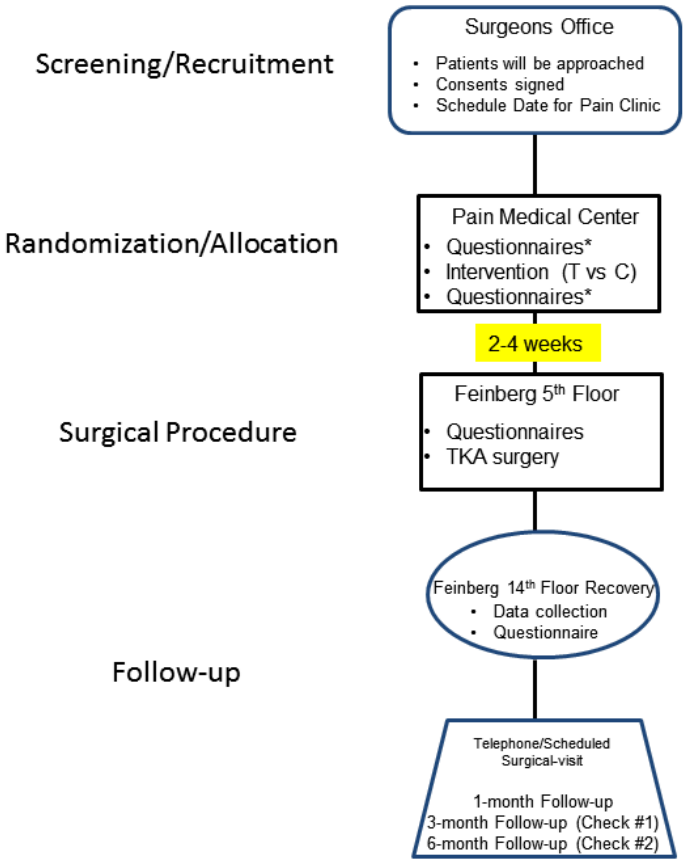
Blinding In the current proposal, Dr. Walega is responsible for performing all of the active C-RFA and sham control procedures. To accommodate proper blinding, identical auditory, visual and tactile experiences for both treatment groups will be maintained. We will use deception to protect blind. The proceduralist will be blinded to all follow-up data until the study is completed. Similarly, the research assistants who perform all follow-up data will be blinded to group assignments until the conclusion of the study. We will also query patients at the 3-month follow-up to assess their beliefs on what treatment they believe they had and whether they would recommend the treatment to a friend.

Maintaining Confidentiality The data will be collected and stored in a password-protected computer located in the Department of Anesthesiology. Participants will each be assigned an ID number, which will be used as the sole identifier on any documents. Subject data will be compiled onto a single password protected file, where they will only be identified by their ID number.

An enrollment log will be the only file where subject names are correlated with ID numbers. This will be kept in a separate, secure, password-protected file in compliance with HIPPA and hospital policy within the Department of Anesthesiology.
The randomization assignment will be kept in a binder in a locked cabinet in the pain clinic. A copy of the randomization table will kept in a separate, secure, password protected file on a computer located in the department of anesthesiology.

Risks/Benefits:
The risks of C-RFA of the articular sensory branches of the knee are minimal. Sensory and motor testing of the target structure prior to lesioning reduces the risk of any neurologic injury and the motor nerves are not located at the planned lesion sites. Bleeding or infection can occur with any needle intervention.

Summary of Recruitment:



4.0 Data Analysis:

Primary outcome:

- Between-group difference in analgesic use (MQS III score) at 48 hours.

Secondary outcomes: Between groups at 48 hours, 1, 3, 6 months in:

1. Visual Analog Scale for pain (at rest, with mobilization or weight bearing)
2. Knee Society Scale (clinician); WOMAC (patient)
4. Physical therapy milestones
    a. Time to active SLR
    b. Time until patient can get out of bed
    c. Time until patient able to ambulate < 100 feet
    d. Time until patient able to ambulate around room > 100 feet
    e. Time until patient is able to climb stairs (quantify specifics, how many steps are considered appropriate?)
5. Patient Global Perception of Change (GPC)
6. Patient Satisfaction (Likert scale)
6. Hospital Anxiety and Depression Score (HADI)
7. SF12
8. McGill Pain Questionnaire
9. Inpatient length of Stay (LOS; days) and Physical Therapy "clearance for discharge" (days)
10. Complications of the injection procedure
11. Medication related adverse events (i.e. sedation, nausea, pruritus, delirium)

4.2 Interpretation of Anticipated Results:

Statistical analysis

Means and standard deviations of participant demographic data, as well as mEQ, VAS, and other outcome scores will be calculated. Two tailed paired t tests will be used for parametric data; Wilcoxon rank sum tests will be used for non-parametric data in order to compare differences in outcome measures between the two treatment groups.