Protocol: The effect of short term patient outcomes with the use of interferential current therapy after total knee arthroplasty

Principal Investigator:

Sun Jin Kim, MD
Assistant Professor, Department of Orthopaedic Surgery
Chief of Adult Reconstruction, Montefiore Medical Center
Montefiore Medical Center
1250 Waters Place
Tower 1
Bronx, NY 10461
Tel: 347-577-4484

Co-Principal Investigator:

Zeynep Seref-Ferlengez, PhD
Research Associate, Department of Orthopaedic Surgery
Montefiore Medical Center
1250 Waters Place
Tower 1
Bronx, NY 10461
Tel: 929-246-6352

Co-Investigators:

Bharat Tiwari, RN Department of Orthopaedic Surgery Montefiore Medical Center 1250 Waters Place, Tower 1 Bronx, NY 10461 Tel: (347)-577-4484	**Jonathan Garcia, PA** Department of Orthopaedic Surgery Montefiore Medical Center 1250 Waters Place, Tower 1 Bronx, NY 10461 Tel: (347)-577-4484

Background/Significance

a. History

The theory of electrical stimulation therapy for pain control has been studied at significant length since it was initially theorized. The theory behind the effectiveness of the use of electrical stimulation for pain was described by Melzack and Wall in 1965 as the gate theory of pain modulation. The gate theory of pain describes how pain simulation can be blocked from reaching the brain by other signals ([1-3]). This theory has provided the bases for pain management with electrical stimulation using different modalities. In the 1950s, the use of intereferential current therapy (IFC), was developed to provide dual current therapy to provide deeper tissue penetration to allow for improved pain relief.

The IFC treatment is a form of electrical therapy that utilizes two simultaneous low frequency electrical stimulations which when they cross interfere with one another resulting in an interference or beat frequency. This beat frequency provides a therapeutic area of relief by blocking painful stimuli at the area of interest. IFC is different from the other electrical treatment modalities used because the cancelation effect allows for establishment of the treatment area to be in the deeper tissues of the body, whereas other electrical modalities can only be used to treat superficial body parts that lie just under the skin. The specific frequency of the signal is patient specific and, therefore, we will plan to have each selected patient establish their correct frequency at the pre-operative visit (see more information regarding the device below). By using these properties of IFC, the hope for results of the treatment for patients in the study will be to reduce swelling and edema and reduce the size and extent of hematoma formation This will improve the quality and speed of recovery from the operation, and secondarily decrease pain and discomfort.

b. Electrical Stimulation for Pain Relief

In the field of orthopaedic surgery, several studies have compared the use of electrical stimulation therapy for patient pain relief with differing results. Two systematic reviews were done comparing use of transcutaneous electrical nerve stimulation (TENS) as a possible adjunct after total knee arthroplasty (TKA). Both studies found significant improvement of pain scales and active knee range of motion ([4, 5]).

More specifically, IFC therapy has also been compared to both TENS and placebo for pain relief. When compared to TENS for back pain, there are conflicting results. Some studies indicate overall pain improvement but no difference between modalities [6, 7]. Another study

found IFC to be more effective in treating chronic low back pain due to deeper tissue penetration [8].

c. Previous use of the device:

One study conducted by Kerlan-Jobe Orthopaedics clinic in 2001 compared IFC therapy to placebo for post-operative pain, edema and range of motion after ACL reconstruction, meniscectomy or knee chondroplasty. In this randomized, double-blind, placebo controlled prospective study, patients were treated post-operatively with IFC therapy providing therapeutic or placebo electrical stimulation. In that study, all IFC subjects reported significantly less pain and greater range of motion all reviewed time points [9].

Objective:

The main objective of this proposed study is to assess the post-operative short term outcomes of the patients who receive IFC treatment during their post- total knee arthroplasty (TKA) surgery hospital stay. The implications of the study would be improved patient outcome which could result in shorter hospital stay, reduced use of opioid medication, decreased need for manipulation under anesthesia and reduced re-admission rate.

Study Design:

It will be a prospective, randomized, single-blinded study. The study device will be used for only 2 days during the post-surgery hospital stay. The patients will be followed until their 6 weeks post-op office visit. We aim to finalize the study in 6 months.

Before enrollment into the study: During their pre-operative visit, patients will fill out a short questionnaire (The Pain Catastrophizing Scale, PCS short form) to assess their eligibility for the treatment and create a homogenized group of patients. Inclusion criteria is detailed below.
50 patients who are eligible for the study will be enrolled by written consent. Informed written consent will be obtained by PI (Dr. Kim) and the health care professional team (Bharat Tiwari,RN and Jonathan Garcia,PA) during pre-operation office visit.
Once the patient volunteers to enroll to the study, we will establish their patient-specific intensity during their pre-op office visit. We will plan to have patient establish their correct and comfortable intensity before their surgery. The device comes in a carrying case with all the set supplies. At the time of placement, a health care provider will place the pre-packaged sterile electrode roughly 7-10 cm above and below the knee for testing or just above and below the

dressing during on the operated knee. Each set of electrodes will then be connected via a lead wire to the stimulation device.

Establishing the correct and comfortable intensity before operation will be as follows: The stimulation device which has a large power button will be turned on but provide no initial signal intensity. The patient will then be instructed to use the “plus” arrow on the device to slowly increase the signal intensity. The goal is to reach a point of intensity that feels strong but comfortable. The best method is to continue to increase to the point where it becomes slightly uncomfortable and the patient may experience some muscle fasciculations. Once that point is reached, decrease the intensity slightly and then use that intensity for their treatment. This patient specific intensity will be recorded and used for the IFC treatment.

Enrolled patients will be randomly assigned to either **i. IFC treatment or ii. Placebo group** after their surgery. Patients in both groups will continue their regular standard post-operative care in addition to the IFC (or placebo) treatment. In addition to their post-operative standard of care, both groups will receive IFC treatment (or Placebo treatment) two times a day, for two days during their post-op hospital stay.

i. For the IFC treatment group: In addition to their post-operative standard of care, the IFC group will receive IFC treatment two times a day, for two days during their post-op hospital stay. The specific intensity of the IFC signal is patient specific. We will use previously established intensity values for each patient.

Once the intensity is set the program will lock automatically after 1 minute of inactivity or can be manually locked using the “star” button on the device. There is some degree of subjectivity in this portion but that is what provides the user with a patient specific signal. The signal intensity can go up to “100” on the device. The device works for 30 minutes at a time. On the device there is a timer which shows the time and it will automatically turn itself off after 30 minutes. During the time when the device is working, the patient can do any regular activity such as ambulating, physical therapy or sleep without concern.

The electrode has an adhesive pad that can remain on the patient post-operatively if desired or can be removed and replaced for each treatment session. The individual electrodes are re-usable and will be assigned to each patient.

For Placebo group: The standard of care and their physical therapy will not be altered for the placebo group. One set of the devices are programmed to be the placebo devices. The placebo devices can give a sensory stimulus so that the patient will feel the device is being on, but they will not have the therapeutic stimulus.We will monitor and record the same post-surgery outcomes as for the treatment group.

The outcomes will be monitored in the immediate post-operative period by the Orthopaedic Surgery clinical team at Wakefield Hospital as well as at during the first post-op visit by Dr. Kim's office by physician assistant (Jonathan Garcia,PA) and nurse practitioner (Bharat Tiwari,RN). The average hospital stay for TKA patients in the hospital (Wakefield) varies between 48-72 hours post-operatively. Typically, patients have a follow-up visit at 2 weeks and 6 weeks after surgery in the Hutchinson Campus, Tower 1 Orthopaedic Surgery Department clinic.

1. Primary outcome will be the post-operative pain medication usage during the first 24 and 48 hours. Daily opioid use will also be accounted based on electronic medical record reported by the patient's nurse after providing the patient with the specific medication. In addition, patients will be asked to rate their pain based on a set VAS pain scale twice a day before the IFC treatment.

2. Secondary outcomes Fitness for discharge on postoperative day 1and day 2 this will be measured utilizing the AM-PAC "6-Clicks" Basic Mobility Inpatient Short Form. The "6-Clicks" tool measures functional ability by having an assessor rate a patient's ability to perform physical tasks such as turning over in bed, moving from a bed to chair, and climbing steps. Scores are tallied to a total of 24 possible points, giving a quantitative measure of a patient's ability to perform these tasks. We will also use the `time` to reach the discharge as the outcome, pain scores recorded by nursing and physical therapy, complications, and any 30-day post discharge emergency department ED visits. Range of motion will be recorded during the daily physical therapy sessions by PT professionals with a goniometer. Range of motion then be assessed again in clinic at the first post-operative visit. Edema- thigh circumference will be calculated at the superior pole of the patella both prior to the surgery and daily post-operatively.All these outcome scores are done routinely as standard of care and they are recorded in patients charts in EPIC.

Study Population

a. The study population will be adult patients older than 18 with severe knee osteoarthritis that have failed non-operative conservative therapy and now require total knee arthroplasty. All patients will undergo unilateral primary total knee arthroplasty with the Zimmer Persona prosthesis performed by Dr. Kim.
Pre-operative clearance will be done by the Montefiore Geriatrics team prior to day of surgery.
Inclusion criteria: Adult patients with knee osteoarthritis who have failed conservative therapy and undergoing elected TKA.
Exclusion criteria:
i. <18 years old
ii. Any patient with pacemaker or any electrical stimulator device
iii. Significant baseline deformity (flexion contracture)
iv. Patient with clinically diagnosed fibromyalgia?
v. Patients without capacity to consent for the study
vi. Patients not able to have local nerve block or spinal anesthesia
vii. Patients with prior opioid use
viii. Patient who is categorized to have `Severe` fear and anxiety responses to pain, according to the PCS survey.

b. Power/sample size
We will need a sample of 50 subjects in each group to have 80% power to detect a 30% reduction in mean 48 hour opioid use at a two-sided 0.05 significance level, assuming a mean 48 hour opioid use of 84.2mg and a standard deviation of 44.7 in the standard of care group. For this study, we anticipate to start with 25 patients per group.
Drop out/loss to follow up rate: If any patient who is assigned to treatment group decides to leave the study for any reason or any point of the study, they will be dropped out of study. Similarly, if the patient does not show up to post-operative follow up, they will be dropped from the study. The post-op follow up rates are almost at 100%, so we do not anticipate to have more than 10% drop-off. After any potential drop-offs, we aim to have 20 subjects per group at the end of this study.

Participant Recruitment

Patients will be recruited from Dr. Kim's clinic after being selected as candidates for total knee arthroplasty. Dr. Kim and the study team will provide patients with information regarding the study and patients will be allowed to volunteer to participate.

Randomization

Prior to surgery in the clinic visit, patients will be given the The Pain Catastrophizing Scale, PCS short form. Based on the results of surveys, we will only include patients with Mild or Moderate anxiety towards pain. Eligible patients will be asked if they would enroll in the study. The survey will allow the opportunity to find a homogenized patients group for treatment and control groups.

Enrolled patients will be randomly selected into `IFC treatment` or `Control` groups after their surgery. This will enable us to eliminate any possible surgical bias.

We will use block randomization for this study: the surgeon and study group will not interfere in the randomization process to eliminate possible bias. Participants will be randomized in a 1:1 ratio (treatment:placebo). A block randomization scheme with a block size of 6 will be generated and maintained by the study statistician. The statistician will provide the sites with a set of randomization envelopes to be used in the study clinics. The randomization envelopes will be stored by the study coordinators in a locked cabinet. Study staff, not including the investigator who will perform clinical evaluations after surgery, will assign these envelopes in sequential order, by envelope number, to eligible participants. Each randomization envelope will include study treatment arm randomization assignment. Assignment of the randomization envelope is considered the effective act of participant enrollment/randomization.

Risk/Benefit

Risks

i. Skin irritation: four prior studies mention skin irritation or thermal damage with IFC use [10-13]. Two of these studies were using IFC materials from older generation products [10, 11]. In one case report by Ford et al. [13] using IFC after total knee arthroplasty, the issues was theorized to be due to placement near the infrapatellar branch of the saphenous nerve which can be frequently insensate after total knee arthroplasty.

1. In order to limit risk, leads will be placed above and below the dressing to avoid skin irritation due to insensate skin.
2. Patient determined settings will be recorded during pre-operative visit prior to anesthesia local nerve block/spinal injection to prevent patients with slightly diminished sensation post-operatively from using too high a setting.

Loss of concentration, drowsiness, decreased alertness- One case report described a patient having temporary symptoms of loss of concentration, drowsiness, decreased alertness and gait disturbances for 4-5hours after IFC treatment. The reason was theorized to be opioid like reaction due to endogenous opioid release [14]. Although a rare risk, patients will be monitored in the hospital setting by medical staff throughout their admission and use of IFC treatment.

Benefits

Improved post-operative outcomes (pain control, range of motion, edema) can result in: faster return to activities of daily living, decreased time immobilized, reduced risk of DVT, improved quality of life, decreased need for opioid medication post-operatively, decreased risk of opioid dependence, shortened hospital stay.

Data and Safety Monitoring

1. Data and Safety Monitoring Board

This study will be monitored by a Data and Safety Monitoring Board. The Data Safety Monitoring Board (DSMB) will be responsible for oversight of data and safety. The DSMB will be composed of three experts in orthopaedic surgery and clinical trial methodology, Dr. Melvin Adler,MD. , Dr. David Hirsh,MD. and Arminderpal Singh,PA. The DSMB members will be independent of all those participating in the study.

The DSMB will review data on adverse events, data quality, and subject recruitment every 6 months and/or at the end of study.

The DSMB will prepare meeting minutes and make recommendations about study conduct to the Principal Investigator.

The research team will meet with DSMB and review data on adverse events, data quality, and subject recruitment every three months until the study is completed. If there is any serious adverse event, it will be reported to the Sponsor and to IRB within 5 business days. Similarly, minor adverse events will be reported to the Sponsor within 5 business days and those will be included in the annual progress report or when the study is closed.

2. **Data storage/maintenance of subject confidentiality**

Patient Privacy and Data protection:

The data collected will be kept on an encrypted database accessible only to the PI (Dr. SunJin Kim) caring for the patients enrolled in the study and to the research personnel that is indicated in the IRB. Informed consent forms, patient reported surveys (questionnaires) will be kept in locked storage cabinets in locked room in Orthopaedic Suregry Department (1250 Waters Place, Tower 1, 10th Floor Room E134). When the research data is transferred to digital media, we will de-identify the patients records and will use codes only. The data will not be used for any future study.

3. **Monitoring:**

This is a single site study with low number of enrollment, PI (Dr. Kim) and the research team will be responsible for data monitoring and progress of the study in accordance with GCP guidelines

4. **Data analysis**

We hypothesize that IFC therapy will improve patient's pain management and range of motion as well as decrease soft tissue edema after TKA when compared to control group. Study variables: total opioid consumption per 24h and 48h, VAS pain scale, KOOS pain score, range of motion, thigh circumference, 6-click AMP scores.

The significance level of the test was targeted at 0.05.
All outcomes and PT exam measures will be summarized as mean, standard deviation, and range. Differences between means will be analyzed with a Student's t-test or Mann-Whitney U test.

References

1. Dolhem, R., *[The history of electrostimulation in rehabilitation medicine].* Ann Readapt Med Phys, 2008. **51**(6): p. 427-31.
2. Melzack, R. and P.D. Wall, *Pain mechanisms: a new theory.* Science, 1965. **150**(3699): p. 971-9.

3. Katz, J. and B.N. Rosenbloom, *The golden anniversary of Melzack and Wall's gate control theory of pain: Celebrating 50 years of pain research and management.* Pain Res Manag, 2015. **20**(6): p. 285-6.
4. Zhu, Y., Y. Feng, and L. Peng, *Effect of transcutaneous electrical nerve stimulation for pain control after total knee arthroplasty: A systematic review and meta-analysis.* J Rehabil Med, 2017. **49**(9): p. 700-704.
5. Li, J. and Y. Song, *Transcutaneous electrical nerve stimulation for postoperative pain control after total knee arthroplasty: A meta-analysis of randomized controlled trials.* Medicine (Baltimore), 2017. **96**(37): p. e8036.
6. Hurley, D.A., et al., *A randomized clinical trial of manipulative therapy and interferential therapy for acute low back pain.* Spine (Phila Pa 1976), 2004. **29**(20): p. 2207-16.
7. Facci, L.M., et al., *Effects of transcutaneous electrical nerve stimulation (TENS) and interferential currents (IFC) in patients with nonspecific chronic low back pain: randomized clinical trial.* Sao Paulo Med J, 2011. **129**(4): p. 206-16.
8. Rajfur, J., et al., *Efficacy of Selected Electrical Therapies on Chronic Low Back Pain: A Comparative Clinical Pilot Study.* Med Sci Monit, 2017. **23**: p. 85-100.
9. Jarit, G.J., et al., *The effects of home interferential therapy on post-operative pain, edema, and range of motion of the knee.* Clin J Sport Med, 2003. **13**(1): p. 16-20.
10. Cecily JPartridge , S.S.K., *Adverse Effects of Electrotherapy Used by Physiotherapists.* Physiotherapy, 1999. **85**(6): p. 298-303.
11. Satter, E.K., *Third-degree burns incurred as a result of interferential current therapy.* Am J Dermatopathol, 2008. **30**(3): p. 281-3.
12. Balmaseda, M.T., Jr., et al., *Burns in functional electric stimulation: two case reports.* Arch Phys Med Rehabil, 1987. **68**(7): p. 452-3.
13. Ford, K.S., et al., *Full-thickness burn formation after the use of electrical stimulation for rehabilitation of unicompartmental knee arthroplasty.* J Arthroplasty, 2005. **20**(7): p. 950-3.
14. Keramat, K.U. and A. Gaughran, *An unusual effect of interferential therapy.* BMJ Case Rep, 2012. **2012**.