Project Title: A Pilot Study Investigating the nCAP Signal Relief Patch in Subjects Undergoing Primary Hip or Knee Replacement Surgery: A Prospective, Randomized, Open Label Trial

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Statement of Problem

The current opioid epidemic has led to a renewed interest in exploring non-pharmacological techniques to treat post-operative pain. Opioids are also not the drug of choice for the treatment of perioperative pain because their administration is associated with adverse effects, including post-operative nausea and vomiting, respiratory depression, immunosuppression, constipation, and opioid use disorder and the risk of opioid overdose and death. In the United States, over $600 billion is spent every year on opioid addiction, including $79 billion related to opioid addiction following surgery. Despite many initiatives to decrease the use of opiates in the preoperative setting, opioids continue to be regularly prescribed before, during, and after surgery. Although the risk of opioid addiction following surgery is recognized, the percentage of patients becoming addicted to opioids following surgery is not well understood. Although guidelines have been published regarding the use of opioids, it is established that opioids are still overused. Therefore, in order to combat this growing health crisis at the ground level, it is incumbent upon the medical community to explore alternative methods to the use of opioids and apply these approaches to surgical population. This is especially important in the context of COVID-19 because it is clear that we have been experiencing an increase in death related to opioid overdose.

Evidence supports the concept that the human body is “electric.” This property is routinely used to monitor organ function such as the heart, the brain, and more. In the case of local trauma and pain, it is established that pain is the result of local inflammation, a local decrease in pH and therefore an accumulation of negative charges. In this respect the nCAP Nano patch is a patch charged negatively. Therefore, when applied at the site of the pain, the

patch redistributes the negative charges at the local level and this redistribution away from the local site has an anti-inflammatory and an analgesic effect.

Specific Aims

1. The primary endpoint will be to prospectively investigate the efficacy of the nCAP Signal Relief Patch in reducing perioperative opioid requirement (up to 72 hours post-op) in opioid-naïve patients undergoing primary unilateral total hip or knee replacement surgery. Opioid requirement will be estimated following the placement of the patch.
2. The secondary endpoint will include the effects of nCAP Signal Relief Patch after the placement on postoperative pain, functional recovery, time to discharge from the hospital, and opioid related complications, such as, PONV, itching, sleep disorders, respiratory depression, and urinary retention.

Study Design

The proposed pilot study will be conducted as a single-center prospective, randomized, open label trial at the University of Pittsburgh Medical Center (UPMC) Shadyside Hospital. Institutional review board approval will be obtained before eligible patients are recruited and consented. The trial will be registered at www.clinicaltrial.gov before beginning recruitment.

The efficacy of this device will be established by comparing postoperative opioid requirement to maintain pain scores ≤ 4 using a Numerical Rating Scale (NRS). Accordingly, pain will be treated according to the following protocol: pain scores ≤ 4, non-opioid analgesics, pain scores between 4 and 6 oxycodone 5 mg q 4 hrs and ≥ 7, oxycodone 10 mg, Hydromorphone IV 0.2-0.5 mg q 3 hr. Data collected following the placement in the treatment group (Standard of Care ERAS protocol + nCAP Signal Relief Patch) will be compared to the data obtained in the control group (Standard of Care ERAS protocol).

Recruitment

Potential subjects may be given a recruitment flyer (attached) in the office of surgeons Drs. O'Malley, Plate, or Klatt. The potential subjects who receive a flyer will then have the option of contacting the study team to discuss the study further, or, if they express interest in participating in the surgeon's office, their name will be given to the study team from the surgeon's office staff.

Potential subjects may also be identified by the study team who has normal access to the Operating Room Schedule and electronic medical records. If a subject is deemed eligible via inclusion/exclusion criteria, a study team member will approach them the morning of their scheduled surgery and discuss the study with them at length and answer any questions they may have. If a potential subject is willing to sign consent, then a physician investigator will be available to review the consent, risks and benefits of participation, and obtain informed consent.

If our research team is contacted prior to the day of surgery, or if we reach out based upon the list of interested potential subjects, study team will discuss the study at length over the phone and answer any questions the potential subjects may have. Subjects interested in participating will be emailed the currently approved informed consent form to review. They will be given the option to sign consent electronically for convenience via REDCap or they can sign consent form on the day of surgery in the pre-operative holding area.

The subject will be approached as soon as they arrive to the hospital (at least 2-3 hours before their surgery) and will be given adequate time to consider the consent and ask questions. The patient will be urged to take as long as necessary to decide whether or not to participate. If the

subject feels they do not have enough time to make a decision, they will not be enrolled in the trial.

All questions will be addressed and it will be made clear that the patient may withdraw from the study at any time. Investigator physician will sign the informed consent with the patient prior to beginning of any study procedures.

Randomization Process

Participating patients will be randomized by computer-generated random numbers to either the control group (standard of care ERAS protocol) or intervention group (nCAP Signal Relief Patch group+ ERAS protocol).

Inclusion Criteria:

- Over 18 years of age
- Scheduled for elective primary unilateral hip or knee replacement surgery

Exclusion Criteria:

- Active clinical depression, anxiety, or catastrophizing
- Raw score equal to or greater than 19 on the PROMIS Anxiety 8a - Adult v1.0
- Active alcoholism or drug abuse
- Severe chronic pain condition that requires daily preoperative opioid dependence
- Total surgery revision, bilateral hip replacement, multiple surgeries

Treatment Groups

Each subject will undergo surgery and anesthesia using the approved ERAS protocol.

Control Arm (n=30): Control group will receive approved ERAS multimodal anesthesia protocol (standard of care).

Interventional Arm (n=30): Intervention group will receive approved ERAS multimodal anesthesia protocol plus an nCAP Signal Relief Patch.

Data Collection and Outcome Measures

After signing an informed consent, subjects will complete the PROMIS Emotional Distress – Anxiety – Short Form 8a before completing any other questionnaires. Subjects who have a raw score <19 will be enrolled in the study. Any subject who scores ≥ 19 will be considered a screen failure and excluded from the study.

Once the subject is enrolled, they will be asked to complete the Pain Catastrophizing Scale (PCS), the PROMIS® Emotional Distress-Depression - Short Form 8a, and the PROMIS® Item Bank v1.0 – Sleep- Disturbance – Short Form 8a prior to surgery. The subject will also conduct a baseline functionality test to assess mobility and strength in their leg. The functional recovery will be assessed by determining the patient ability to walk 100 feet, go up 5 steps and raise their leg on the day of surgery. Scores can be 0 (no ability to raise the leg), 1 (some ability to raise the leg), and 2 (complete ability to raise the leg).

Once these assessments are completed, subjects will be equally randomized to the intervention group (nCAP signal relief Patch + standard of care) or control group (standard of care). Both the control group and intervention group will receive approved ERAS multimodal standard of care. Only the interventional group will receive an nCAP Signal Relief Patch. Randomization will occur by assigning the participant a subject ID number, and this ID number will correspond to a treatment allocation based on a pre-designed randomization schema.

Subjects will undergo surgery using the approved ERAS anesthetic and post-operative pain management protocols.

After surgery, the subjects randomized to the intervention group will have the nCAP Signal Relief patch applied to their surgical dressing by a trained researcher in the immediate Post Anesthesia Care Unit (PACU). Subjects will be made aware at the time of consent and throughout the trial that they can drop out of the study at any time if they do not like wearing the nCAP Signal Relief Patch. The control group will not receive a patch but will receive the standard of care ERAS protocol. Subjects in the intervention group will be instructed to keep the nCAP Signal Relief Patch on their surgical dressing to avoid the risk for skin irritation.

Pain using a Numerical Rating Scale (NRS) at rest and with movement as well as opioid requirement will be assessed in the PACU and daily until discharge.

Subjects assigned to the intervention group should keep the nCAP Signal Relief Patch in place for 72 hours on their surgical dressing and they will be instructed to remove it at home.

Once the subject is discharged, they will be asked to complete a pain and opioid diary to record pain-related outcomes. They will be contacted via email (REDCAP survey) on post-operative day 1,2,3, 7, 14, and 30 to record postoperative opioid consumption, non-opioid consumption, NRS pain at rest and with movement, pain catastrophizing (via Pain Catastrophizing Scale) sleep quality (via PROMIS Sleep Disturbance Short Form 8a) and to assess functional recovery. Functional recovery will be assessed by determining the patient ability to walk 100 feet, go up 5 steps and raise their leg on postoperative days 1, 2, 3, 7, 14, and 30 as well as the pain associated with it. Patient satisfaction with pain management after surgery will be assessed at the 30 day follow up (0- least satisfied to 10-most satisfied). Subjects who are contacted via REDCap to complete follow-up questionnaires and do not complete them on the day they are assigned will be contacted via telephone for a reminder. They will be considered lost to follow up after 3 phone attempts.

Information will be collected from the medical record, including: patient demographics, medical history, medication summary while in the hospital, as well as progress notes from the entire encounter to determine the existence of adverse events.

Pre-and-Post Metric Evaluation

The use of a non-pharmacological nCAP Signal Relief Patch has the possibility of providing analgesia to post-surgical patients and reducing the number of opioids required following surgery. This will significantly impact patient outcomes, as patients will experience fewer opioid-related side effects (such as respiratory depression, post-operative nausea and vomiting, constipation, and delirium). This will also impact clinicians caring for post-operative patients, as there is the real potential they will have fewer conditions to monitor and treat as the patient recovers from surgery. The projected number of patients served by this project will initially be 70 enrolled participants at Shadyside Hospital, however, the data collected from this trial will serve countless patients and the community at large as physicians strive to move away from opioid use following surgery. Data collected from this pilot study will support a future proposal to the National Institute of Drug Abuse (NIDA) to fund a full-scale, randomized, placebo-controlled trial using the nCAP Signal Relief Patch.

Perhaps most importantly, the investigative use of the non-invasive nCAP Signal Relief patch has the ability to significantly decrease opioid requirement, postoperative pain, the hospital length of stay, the needs for opioid prescription following discharge from the hospital, improve early functional recovery, and increase patient satisfaction.

Being able to offer the orthopedic patients at UPMC Shadyside Hospital such an alternative might represent a non-pharmacological approach to pain management and an alternative to opioid, increase patient satisfaction, and improve early functional recovery.