Project Title: A Pilot Study Investigating the Post-Operative Analgesic Effect of NSS-2 BRIDGE device in Subjects Undergoing Major Abdominal Oncologic Surgery: A Randomized, Double-Blind, Placebo Controlled Trial

NCT03555266

Date: August 1, 2018

The purpose of this proposal is to request funds to support a pilot study investigating the use of a Percutaneous Auricular Nerve Field Stimulation device called the NFF-2 BRIDGE, which will be applied to sixty patients undergoing abdominal oncologic surgery with surgeon David Bartlett at Shadyside Hospital. The data collected from this pilot trial will be used to supplement a future grant application to the NIH/NIDA to fund a large-scale randomized, placebo-controlled trial.

Statement of Problem

The current opioid epidemic has led to a renewed interest in exploring non-pharmacological techniques to treat post-operative pain. An increasing number of patients are suffering from the adverse effects of opioid use following surgery, including post-operative nausea and vomiting, respiratory depression, immunosuppression, constipation, and most recently, addiction. 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. To date, there has been virtually no agreement regarding the duration and dosage that qualify for opioid dependence following surgery, nor that a clear estimation of the factors such as biological, psychosocial and socioeconomic that increase the risk of using opioids for extended periods of time after surgery. Therefore, in order to combat this growing health crisis at the ground level, it is incumbent upon the medical community to explore alternative methods of pain control to treat the surgical population in order to reduce the incidence of post-operative opioid addiction.

Project Aims/Goals

Percutaneous Nerve Field Stimulation (PNFS) is one of these recognized methods that ongoing research has shown to be effective as a complementary method of pain management. While PNFS is not a novel concept, clinical indications of auricular field stimulation have been limited in the past due to requirement of bulky, stationary and non-disposable stimulators and electrodes. These technological limitations made it difficult to establish the real clinical potential of auricular stimulation for the perioperative management of pain in surgical patients, despite the demonstration that auriculotherapy has been shown to relieve pain in the postoperative setting.

The NSS-2 BRIDGE (Appendix 1) is a battery operated and disposable percutaneous auricular nerve field stimulator (Innovative Health Solutions, Versailles, IN, USA), that was recently cleared by the FDA and assigned a Class II Risk Designation; a class which includes surgical drapes, pumps and power wheelchairs. The indication for the NSS-2 BRIDGE is for the treatment of clinical symptoms related to opioid consumption and opioid withdrawal. These symptoms include abdominal pain, anxiety and post-operative nausea and vomiting; conditions which are also present following major oncologic abdominal surgery. The use of the NSS-2 BRIDGE device has been demonstrated to provide significant analgesia in patients with abdominal pain syndrome, and clinical trials are ongoing to assess the benefit of this approach for post-operative pain management. As compared to the present use of opioids for perioperative pain management, the use of a complementary, non-pharmacologic approach offers the advantage of analgesia without the associated side effects. **Mechanism of action of the Auricular Percutaneous Electrical Nerve Field**

The NSS-2 BRIDGE devise allows for stimulation to branches of Cranial Nerves V, VII, IX and X, and the occipital nerves, identified by transillumination. Such a stimulation is transmitted to the central nervous and especially the limbic system, which is known to be a key component of the central nervous system response to stress, anxiety and the pain pathway. The nucleus involved by the stimulation

include the amygdala (structure involved in the response to fear and anxiety), the thalamus (structure involved in the management of visceral and somatic pain, addiction), the nucleus of tractus solitarie (structure involved in the control blood pressure) etc…. The stimulation of these nucleus produces a decrease in the transmission of pain impulses from visceral and/or somatic structures to supraspinal areas, a reduction in anxiety and control of blood pressure and associated changes of the sympathetic and parasympathetic nervous system.

The Shadyside Foundation Grant will allow for the purchase of sixty NSS-2 BRIDGE devices (30 active, 30 placebo), and will support a research coordinator in the execution of a pilot study investigating the possible benefit of the device to supplement post-operative pain management. This pilot study will assess the possible benefit of using this non-invasive PNFS device as a way to reduce opioid consumption in patients undergoing abdominal debulking procedures with surgeon Dr. David Bartlett. Preliminary data analysis has demonstrated that in the absence of the NSS-2 BRIDGE device, the average opioid consumption following major abdominal surgery using the current ERAS multimodal protocol is 100 mg IV morphine equivalent. It is expected that the use of the NSS-2 BRIDGE will be associated with a reduction of 50-70% opioid consumption following surgery. The primary endpoint for this pilot study will be overall opioid consumption and will constitute the basis of a National Institute of Drug Abuse (NIDA) proposal on opioid-free surgery. The expected timeline for this trial will be one year, from the start of enrollment to manuscript draft.

Specific Aims

1. This pilot study will prospectively investigate the efficacy of the NSS-2 BRIDGE device in reducing perioperative opioid consumption in opioid-naïve patients undergoing major abdominal surgery using the current SHY ERAS anesthesia protocol

2. To prospectively investigate the incidence of post-operative complications between the standard ERAS anesthesia protocol + active NSS-2 BRIDGE vs. ERAS anesthesia protocol + placebo (in-active) NSS-2 BRIDGE

3. To prospectively investigate role that the NSS-2 BRIDGE device may have in reducing opioid consumption after discharge and facilitating functional recovery

Study Design

The proposed pilot study will be conducted as a single-center prospective randomized double-blind, placebo-controlled 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. Trial will be registered at www.clinicaltrial.gov before beginning recruitment.

Recruitment

Potential subjects will be recruited in the pre-surgical clinic of Dr. David Bartlett once they are scheduled for abdominal debulking surgery. Patients will be asked for their interest in pursuing a research study that involves wearing a percutaneous, auricular field stimulator for five days as a supplementary method of post-operative pain control. Patients who agree to participate in the trial will sign an IRB approved Informed Consent Form.

Randomization Process

Participating patients will be randomized by computer generated random numbers to either the control or intervention group.

Inclusion Criteria:

Over 18 years of age

Open abdominal debulking procedure as per our institution's Enhanced Recovery After Surgery (ERAS) anesthetic protocol.

Exclusion Criteria:

History of active depression, anxiety or catastrophizing

Active alcoholism or drug abuse

Severe chronic pain condition that requires daily preoperative opioid dependence

History of hemophilia

Patients with cardiac pacemakers

Patients with psoriasis vulgaris diagnosis

Treatment Groups

Control Arm: Control group will receive approved ERAS multimodal anesthesia protocol (Appendix 2) plus an inactive placebo NSS-2 BRIDGE device.

Interventional Arm: Intervention group will receive approved ERAS multimodal anesthesia protocol (Appendix 2) plus an active NSS-2 BRIDGE device

Data Collection and Outcome Measures

Once patient has signed the Informed Consent to participate in this pilot study, demographic information and medical history will be collected from each participant on the day of surgery. The NSS-2 BRIDGE device will be applied to the ear by trained researcher in the immediate post-operative setting (PACU), as the research team has completed the necessary training required by the company to apply the device. Rescue analgesia will be permitted as per the approved ERAS multi-modal anesthetic

protocol (Appendix 2), however, the patient 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 NSS- 2 BRIDGE device.

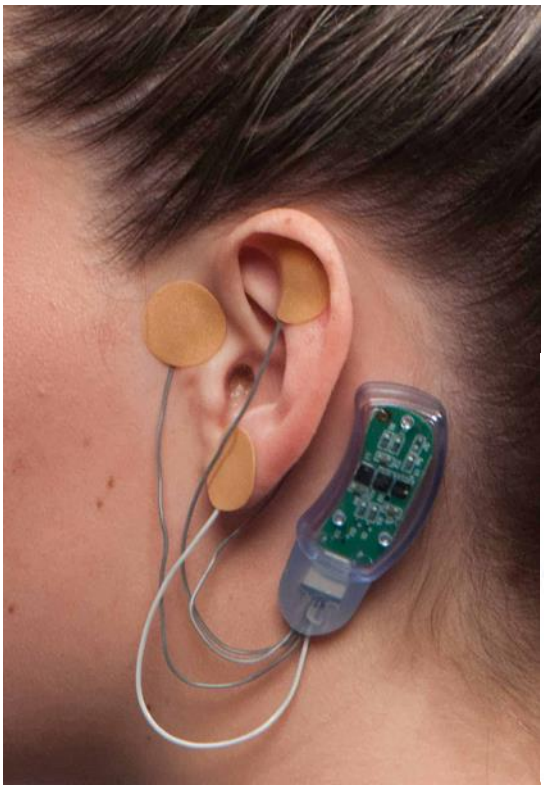
The patient will be assessed 12, 24, 48, 72, 96 and 120 hours post-operatively to collect total opioid consumption, incidence of adverse events, and level of comfort while wearing the NSS-2 BRIDGE device. When the patient is discharged from the hospital, they will be asked to complete a patient satisfaction survey. For patients discharged with the device attached, removal instructions and pre-paid return envelope will be given to patient to remove the device at 120 hours and send back to the hospital. The patient will be contacted 3 months post-operatively to again assess patient satisfaction with the pain management after surgery, and to assess functional recovery.

Pre-and-Post Metric Evaluation

The use of a non-pharmacological NSS-2 BRIDGE has the possibility of providing analgesia to post-surgical patients and reducing the number of opioids required following abdominal 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 sixty 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 NSS-2 BRIDGE device.

Perhaps most importantly, the investigative use of the non-invasive NSS-2 BRIDGE device has the ability to significantly increase patient satisfaction in individuals who are opioid naïve or adverse to taking opioids as a method of pain control. Being able to offer the cancer patients at UPMC Shadyside such an alternative represents a great opportunity to increase patient satisfaction, outcomes and compliance as many patients increasingly fear the use of opioids. The NSS-2 BRIDGE will remain effective on the participant for five days, and will have lasting effects even after discharge from the hospital, which is a time when many patients turn to opioids to control pain. The way the efficacy of this device will be measured will be by comparing total perioperative opioid consumption between the intervention group (Standard of Care ERAS protocol + active NSS-2 BRIDGE) and control group (Standard of Care ERAS protocol + inactive NSS 2 BRIDGE), and total opioid consumption after discharge between the two groups. Other outcome measures include the incidence of respiratory depression, PONV, constipation and length of stay between the intervention and control groups.

Appendix 1: NSS- 2 BRIDGE device



Appendix 2: ERAS ANETHESIA PROTOCOL---SHADYSIDE HOSPITAL

1. Patients will undergo general anesthesia.

   Encourage 1 month or more of abstinence from smoking and alcohol and 30 min walking/exercise every day leading up to surgery

   Protein and carbohydrate rich diet for 1 week prior to surgery

   Regular diet until midnight day before surgery, then clear liquids encouraged until arrival to hospital.

   OSA screening

   Pre-op multimodal analgesia ordered by surgeon to include oral Neurontin, Acetaminophen, and +/-Celebrex depending on case

   PONV risk stratification

   (PONV history, female, non-smoker, opiod/inhalation anesthetic use, emetogenic procedure 1 point each)

- **Day of Surgery**

  DAS Nursing Staff: Heplock IV (KVO), DVT prophylaxis (SQ heparin), Bair Hugger

  Pain Service: Avoid narcotics for block placement

  - Continuous Quadratus Lumborum blocks for post op analgesia . Ropivicaine 0.5% 20 ml (single shot bilat)
  - Decadron 4mg
  - Dexmedetomidine (Precedex) 40 mcg
  - 500 cc IV fluid bolus with block
  - PONV prophylaxis, according to risk score (Attending Anesthesiologist order)
  - Low: no prophylaxis
  - Medium (1-2 risk factors): Scop patch or Perphenazine or Emend
  - High (>2 risk factors): Emend and Scop patch
  - **Anesthesia**
  - Warm IV fluids, underbody warming blanket, and Bair Hugger

- Antibiotics per protocol according to procedure
- Induction – (Guidelines only) Adjust doses as clinically relevant. Propofol (2 mg/kg), Ketamine (0.3 mg/kg), Precedex 0.3 mcg/kg, muscle relaxant, and **NO OPIOIDS**.
- Spinal
- Maintenance - TIVA to include separate infusions of Propofol, Ketamine (0.2 mg/kg/hr), Precedex (0.2-0.8 mcg/kg/hr) titrated to effect. **concentration is NOT in the Alaris library – must be programmed for 100 mg/100cc****
- **NO OPIOIDS**; avoid use of Nitrous Oxide
- Magnesium 2-4 gm IV
- Ketorlac 15 mg IV at end of case if approved by surgeon
- NO IV Acetaminophen (unless not given po pre-op)
- Ondonsatron 4 mg (save Haldol for rescue in PACU). There is NO need to give IV Decadron
- Tidal Volumes recommended at <6-8 cc/kg; PEEP 6-8, FiO2 <80%, recruit lungs
- Fluid Management via Goal Directed Therapy with SVV (Vigileo) if aline in place.
- Avoid NSS (PLtye preferred or LR if not available). Avoid replacement of fluid deficit. 8-10 cc/kg/hr + replacement of EBL as guideline. IVF not to exceed >2L above expected losses.
- Emergence - Discontinue Ketamine/Precedex 45-60 min prior to emergence, then titrate Propofol to closure and emergence.

PACU

- Clear liquid intake to start ASAP in PACU; if aspiration risk, IVF maintenance at 75 cc/hr.
- Ketamine 30 mg PO

The postop orders in the surgeon's care plan include

Oral opiates, IV rescue opiates, acetaminophen, toradol, Celebrex,

The AIPPS orders should be only for

Ketamine infusion

Neurontin at bedtime

PCA if needed (goal is to not use PCA unless necessary such as chronic opiate users, big open cases, etc).

QL block

Age <60 Ropi 0.5% 20 mL, dexmedetomidine 30 mcg, dexamethasone 4 mg per side

Age >60 Ropi 0.5 % 20 mL, dexmedetomidine 20 mcg, dexamethasone 4 mg per side

Plus several hundred mL fluid bolus

Plus glycopyrrolate 0.2 mg IV