

Title of Study: Auricular Percutaneous Electrical Nerve Field Stimulation for Postoperative Pain Control in Adults

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Auricular Percutaneous Electrical Nerve Field Stimulation for Postoperative Pain Control in Adults

Study Protocol

Inclusion Criteria

- ≥ 18 years of age
- Able to independently consent to participate
- Plans for elective laparoscopic or open colectomy or proctectomy with or without ostomy

Exclusion Criteria

- History of chronic pain disorder (requiring continuous narcotic and/or NSAID use in the week prior to surgery), or active opiate abuse
- Need for emergent procedure, regional anesthesia (does not include escalation of medical management of pain), admission to ICU
- Prolonged postoperative intubation
- Use of intraoperative ketamine or lidocaine drips
- Refusal to receive follow-up phone calls
- Tape allergy/sensitivity
- Latex allergy
- Active pregnancy
- History of seizures
- History of cerebral aneurysm
- Recent organ transplant recipient
- Myocardial infarction within 6 months of study
- Anticoagulation (requiring fully therapeutic anticoagulant, not including anti-platelet agents such as aspirin or clopidogrel)
- Blood clotting disorder
- Other implantable devices/ on-demand electronic device
- MRI planned during study period
- Psoriasis, dermatitis, skin infections around ear

Screening and Informed Consent

Patients will be prescreened by study personnel prior to the clinic visit to determine if they meet inclusion and exclusion criteria. **Inclusion criteria:** ≥18 years of age; able to independently consent to participate; plans to undergo elective laparoscopic or open colectomy and/or proctectomy with or without ostomy. **Exclusion criteria:** history of chronic pain disorder (requiring continuous narcotic and/or NSAID use in the week prior to surgery; active opiate abuse; need for regional anesthesia (regional nerve blocks or epidurals); adhesive allergy/sensitivity; history of anxiety disorder on anxiolytics; planned admission to the Intensive Care Unit or prolonged intubation; need for emergent operation; refusal of follow-up phone calls; active pregnancy; history of seizures; on anticoagulation (fully therapeutic anticoagulant, not including anti-platelet agents such as aspirin or clopidogrel); latex allergy; history of implantable devices or on-demand electronic devices; MRI planned during study; recent organ transplant recipient; history of cerebral aneurysm; psoriasis, dermatitis, or skin infections around ear; blood clotting disorder; myocardial infarction within 6 months of study period; use of intraoperative ketamine or lidocaine drips. If a potential participant meets the screening criteria, a member of the study team will explain the study following the regularly scheduled preoperative clinic visit. Once the patient has had their questions answered and agrees to participate, they will sign the informed consent. Patients may require an additional visit to have a thorough discussion of informed consent; this will not be an official clinic visit and the patient and/or insurance will not be billed for the visit. The patient will receive an information sheet about the study with a copy of their informed consent. Consent will be retained by the study coordinator for future records. The patient will undergo all necessary preoperative workup as determined by the primary surgeon.

Day of Surgery/First Day of Participation

Upon presentation to the preoperative staging area on the day of surgery, subjects will first be asked by a member of the study team to rate their pain (VAS scale), anxiety (STAI scale), and nausea (PONV scale). The Visual Analog Scale (VAS) is a nearly universal score which rates patients' pain on a scale of 0-10. This scale has been well studied and has been employed by both participating institutions as the primary grading system for pain.(1,2) Anxiety will be measured with the State-Trait Anxiety Inventory (STAI), originally published in 1970 as a method to evaluate current anxiety (state anxiety) as well as propensity to become anxious (trait anxiety).(3) The postoperative nausea vomiting (PONV) scale has been shown to be a reliable measure of nausea, and has also been used at both participating institutions.(4) The patients will also submit a blood sample and buccal swab prior to surgery. As standard of care, a urine pregnancy test is a routine preoperative lab for all females of childbearing age. As such, this test will be performed on the morning of surgery.

Auricular Neurostimulation Details and Application:

This protocol has been generously shared by our colleagues at CHW, based on an ongoing, IRB-approved trial (CHW14/208; clinicaltrials.gov # NCT02367729). It has been adapted to fit our patient population. The BRIDGE is an FDA-approved (510(k)140530) and commercially available device manufactured by Key Electronics (Jeffersonville, IN, USA) and distributed by Innovative Health Solutions (Versailles, IN, USA). BRIDGE is an ambulatory, neurological device which consists of a battery powered, externally affixed generator with 4 wire leads attached to 3 electrode/needle arrays and one single point needle. The arrays are designed to produce a field effect similar to surgically implanted peripheral neurostimulators. One BRIDGE device per patient will be used in this study.

After completing the baseline questionnaires explained above, the BRIDGE device will then be placed on the right ear prior to any premedication. The placement of the devices is within standard of care by properly trained medical doctors as already performed as part of separate, ongoing IRB-approved trial at Children's Hospital of Wisconsin (CHW14/208; clinicaltrials.gov # NCT02367729). Training of MDs (Drs. Blank, Otterson, and Peterson) will be performed by representatives of Innovative Health Solutions upon IRB protocol approval.

The BRIDGE Surgical kit consists of: (1) An alcohol swab, (2) prep and stay swab, (3) round fixation plasters, (4) fixation plasters to fasten the generator, (5) Steri-strip adhesive vial, (6) Sterile wire harness pack, (7) Generator, (8) Tweezers, (9) Surgical marker, (10)Transilluminator.

1. The neurostimulator placement will be performed as directed and per training protocol instructions identically to current ongoing IRB approved studies at CHW (CHW14/208; clinicaltrials.gov #NCT02367729).
2. Before neurostimulator placement, the subject should be advised that some discomfort is normal at first but should report if the discomfort persists or gets worse after a few minutes. The patients should be advised that they may feel a slight pulsing sensation and perhaps a warming sensation in the ear to which the electrodes are affixed. The pulsing and warming sensation may disappear after approximately 5 minutes. If the discomfort level increases the offending electrode can be slightly repositioned until the patient's discomfort level decreases to an acceptable level. If there is continued discomfort in one specific electrode, it may be removed by cutting the lead.
3. The electrodes will be placed percutaneously in the external ear with the help of a transilluminator to visualize the neurovascular bundles. Three electrodes will be placed on the ventral and one on the dorsal aspect of the ear. The exact location of the implantation may vary slightly from person to person but is determined by both knowledge of auricular neuro-anatomy and visualization of the neurovascular bundles by transillumination. The electrodes will be taped and secured behind the ear next to the generator itself which is secured to the skin with adhesive. The placement of the devices is within standard of care by properly trained medical doctors as already performed as part of separate, ongoing IRB-approved trial at CHW (CHW14/208; clinicaltrials.gov #NCT02367729).
4. The device will then be activated. Sham devices will appear to be activated, though will not cause neurostimulation, in order to maintain impartiality of the investigators as the status of the device will not be apparent.

5. Device placement will take approximately 5 minutes. The patient will remain at rest for the next 5 minutes in the pre-operative area. Care will be taken not to interfere with standard pre-operative procedures.
6. Patients will be advised not to manipulate the device or immerse the device in water as it is water resistant but not water proof. If showering or washing hair, they should place a dry wash cloth or plastic covering over the area to protect the device.

Randomization Protocol, Material Storage, and Blinding

Subjects will be randomized in a 1:1 ratio to either active or inactive group. Randomization will be determined using a computer program based on random number generation in blocks of 10 subjects at a time. The manufacturer will provide the researchers with one device per package and each package will have a serial number. The inactive devices will be custom-made by the physical manufacturer, Key Electronics, Jeffersonville, IN, and will be identical in every way to the active device except it will lack the battery. The devices will be “made to order” when requested by the PI and will be shipped and packaged as above. Both the subjects and the doctors placing the devices will be blinded, as the active and inactive devices will look identical with identical packaging and placement procedures.

The research coordinator (KH) will have the key for unblinding. In an emergency, the PI will also be able to access the key if needed. All other research coordinators, investigators, statisticians and nurses involved will be blinded as to group assignment. The devices will be stored in the manufacturer's packaging and labeled with a serial number and patient ID number. The devices will be stored in a locked office in the Division of Colorectal Surgery, only accessible by research coordinators. Accompanying folders containing all required study materials (VAS, STAI, and PONV score sheets) for each patient will be stored similarly, adjacent to the devices. The unblinded research coordinator (KH) will prepare the subject packages (device and folder) as per randomization scheme. A blinded study team member will bring each subject's numbered package to the pre-operative area when patient arrives on day of surgery. This team member will ask the subject to complete the pre-operative questionnaires and hand the device (numbered with serial # and patient ID only) to one of the certified MDs for placement.

Intraoperative and Postoperative Protocol

Neurostimulation will be delivered below sensation threshold continuously for 5 consecutive days, the duration of the device battery. The anesthesiology team will be informed in the preoperative area of participation in the study prior to BRIDGE application. It will be discussed that any use of regional anesthesia or NSAIDs are not permitted in this study. If the anesthesiologist believes the patient has contraindications to other methods of analgesia or anesthesia, or if it may be in the patient's best interest to incorporate regional anesthetic techniques, the patient will be excluded from the study. Operating room staff will be instructed to avoid manipulating the device while moving patient or during procedure. The device does not interfere with any monitoring routinely used in the operating room.

The patient will undergo general anesthesia per standard of care. There will be no intraoperative or postoperative use of nonsteroidal anti-inflammatory medications (NSAIDs) (i.e. ketorolac, ibuprofen, diclofenac) or regional pain therapies (i.e. epidural anesthesia, transversus abdominis plan blocks); anesthetic plan will otherwise be per treating physician. Once the procedure is over and the patient is extubated and transferred to the postoperative care unit, the patient will continue to receive postoperative pain control per standard of care, as determined by the anesthesia and surgical teams. Auricular neurostimulation has been postulated to decrease the inflammatory response. As NSAIDs (Non-steroidal anti-inflammatory drugs) have a direct inhibitory effect on the inflammatory response, the use of these medications would have a variable effect on the measurement of inflammatory markers and the biological response to surgery. Additionally, NSAIDs are known to have an analgesic effect, which will confound the primary outcome - opioid medication use. Acetaminophen has a benign side effect profile, so the majority will have this included in their regimen. However, NSAIDs have significant risks of kidney injury and bleeding and a large proportion of patients are not eligible. While this would be ideally be randomly distributed between groups; however, in such small study there is risk of imbalanced use that could

further confound our results. Therefore, the postoperative pain regimen will remain standardized for all patients: hydromorphone PCA (no basal rate) while NPO, oxycodone 5-10mg PO q6h PRN once tolerating a diet, and acetaminophen PRN as determined by the primary team.

The nurses caring for the patient during the recovery period after surgery will be alerted to the patient's participation in the study. The immediate postoperative recovery nurse will be alerted by a member of the surgical team upon patient arrival to the post-anesthesia care unit. Once the patient is transferred to the hospital floor, a sign will be placed on the door to the patient's room indicating that they are participating in the study. This sign will include minimal information about the study, along with contact information for study personnel and will not include any identifying health or personal information. Nurses will be encouraged to contact the study team with concerns. While having a sign on the door does compromise some confidentiality, this is routinely performed for research purposes throughout the hospital. Due to the numerous teams caring for surgical patients, as well as the frequent RN shift changes, it is necessary to alert all caregivers about study participation, as protocol violations will jeopardize the integrity of the data. A more detailed sign will be posted in the RN workroom while a patient actively enrolled in the study is on the unit. This will allow a further description of the study in order to maintain confidentiality as well as integrity of data.

The patient will receive standard postoperative care for the duration of their participation. In order to standardize treatment, pain control will be achieved with hydromorphone patient-controlled analgesia (PCA). Total PCA narcotic dosage will be calculated at the end of every shift per usual nursing practice. Use of NSAIDs will not be permitted, but oral and intravenous acetaminophen will be allowed. Demand doses, lockout interval, and maximum hourly dosage of the PCA will be determined by the primary team; there will be no basal rate. VAS scores will also be obtained and recorded once daily or more by the nurse per usual practice. STAI and PONV scores will be recorded once daily by a member of the study team. The full STAI survey will be administered on device days 1, the follow up visit, and device day 30; the remainder of the study days will only consist of the first page of the STAI survey (the trait anxiety, a transient metric). The study team will also obtain twice daily blood samples and buccal swabs for four days after placement and in the morning day five. Respiratory depression will be determined by need for opioid reversal agents (i.e. naloxone) while hospitalized. These events are routinely documented as part of good clinical practice along with alerting the primary team caring for the patient. Time to first flatus and first bowel movement will be recorded in the medical record by the nurse as part of routine postoperative care. Postoperative ileus will be measured by need for nasogastric tube insertion and nasogastric decompression; again, these events are routinely documented in the medical record as part of routine medical care. Diet will be advanced as determined by the primary care team. Once the patient is able to tolerate oral intake, the PCA will be discontinued and oral opioid medications started (oxycodone 5-10mg q6H as needed). Escalation of this oral pain regimen will be noted but will not warrant exclusion from the study. Patients needing additional pain control with regional anesthesia techniques will be excluded from the study at that time. Patients will be discharged from the hospital once discharge criteria are met as determined by the treating physician. All patients will receive a standard narcotic pain medication prescription at discharge (oxycodone 5mg q6H PRN #60). The patients will receive an information sheet upon discharge with study and device information as well as contact information for study team members.

At the first outpatient follow-up visit, the VAS, STAI, and PONV scores will be repeated by study personnel. Patients will also fill out the device-specific survey at this time. Patients will also receive a phone call on device day 30 by the study coordinator, PI, or co-PI. At this time, the patient will again be asked to complete the VAS score, STAI, and PONV scores via telephone, and will be asked if he or she is still requiring narcotic pain medication, or if a refill of the narcotic pain medications was needed.

Device Removal

If the patient is discharged prior to the 5 day life of the BRIDGE device, he or she will be contacted via telephone by study personnel to obtain all remaining VAS, STAI, and PONV data on a daily basis until the evening of the fourth postoperative day (fifth device day). If the patient is hospitalized longer than the 5 day life of the BRIDGE device, the study coordinator, PI, or co-PI will remove the device according to standard

protocol. Prior to discharge, the patient will be instructed by a member of the study team on removal of the device after 5 days as well as what to do if the device is dislodged (see below). The subject will be given a handout with information on device handling and a place to record the date and time of device removal and date and time of device return. The handout will also contain contact information for study personnel. If a device falls off completely, it should not be reapplied. If individual electrodes are dislodged, they can be reapplied with household adhesive tape. If a patient requests withdrawal from the study or removal of the device before the 5-day life has expired, time of removal, VAS, STAI, and PONV scores will be recorded.

Follow-up phone call with study results

The device key will be opened 30 days after the final surgery per protocol. The patients will be contacted by phone to disclose the results of their device (active vs. inactive). Prior to disclosure of the device, the patients will be asked if they felt their device was active or inactive. This data will be recorded in order to determine if patient perception influenced results. Patients will also receive a letter disclosing the activity of their individual devices. Lastly, if results are significant and able to be published, patients will receive the publication by mail.

Data Collection

The following data will be extracted from the medical record:

- Surgical data:
 - Type of colon resection (right, left, sigmoid, total, etc.)
 - Operative technique (laparoscopic, hand-assisted, robotic, open)
 - Presence and type of ostomy, if applicable
- Demographics: age, sex, comorbidities, previous symptoms, diagnosis, indication for operation
- Total daily dosage of narcotics during hospitalization (milligrams of hydromorphone, converted to morphine equivalents), including intraoperative narcotics
- VAS scores (daily maximum and AUC)
- Number of emeses
- Laboratory values (if ordered by primary team)
- Respiratory depression, determined by need for opioid reversal agent (naloxone)
- Rescue methods for pain control (need for pain team consult, need for regional anesthesia)
- Complications (per Clavien-Dindo Classification)
- Return of bowel function (time to first flatus, time to first bowel movement)
 - Postoperative ileus, determined by need for NG tube insertion
- Length of stay (in days, including day of surgery)
- Rate of readmission
- Patient satisfaction scores
- Discharge destination (i.e. home, skilled nursing facility)
- Incidence of withdrawal (i.e. patients requesting to terminate study/remove device) and reason
- Need for additional narcotic prescription refills after discharge

The following data are study-specific and will be collected by the study personnel:

- STAI, and PONV scores during 5 day life of BRIDGE device, at a minimum once daily
- Need for device modification or removal, if applicable

- Biospecimens. Samples will be immediately de-identified after collection and coded with the study ID number. They will be stored in the Divisions research facilities de-identified for analysis.
- VAS, STAI, and PONV scores at first follow-up appointment as well as device day 30
- Device-specific survey

1. Bijur, P.E., W. Silver, and E.J. Gallagher, Reliability of the visual analog scale for measurement of acute pain. *Acad Emerg Med*, 2001. 8(12): p. 1153-7.
2. Scott, J. and E.C. Huskisson, Graphic representation of pain. *Pain*, 1976. 2(2): p. 175-84.
3. Julian, L.J., Measures of anxiety: State-Trait Anxiety Inventory (STAI), Beck Anxiety Inventory (BAI), and Hospital Anxiety and Depression Scale-Anxiety (HADS-A). *Arthritis Care Res (Hoboken)*, 2011. 63 Suppl 11: p. S467-72.
4. Wengritzky, R., et al., Development and validation of a postoperative nausea and vomiting intensity scale. *Br J Anaesth*, 2010. 104(2): p. 158-66