Auricular Percutaneous Electrical Nerve Field Stimulation (PENFS) using the BRIDGE device for Post-Operative Pain Control in Patients Undergoing Liver Transplantation

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Purpose of the Study

Pain after liver transplantation is unavoidable but it often has significant consequences for patients during their recovery. Opioid medications are the cornerstone of all pain control plans post-liver transplantation; nonetheless, they come at a cost with multiple side effects and potential serious adverse effects. Opioids have a profound impact on postoperative gastrointestinal (GI) motility via activation of the μ-opioid receptors of the small and large intestines. Slowed gastrointestinal motility causes discomfort, pain, and nausea. In fact, opioid medications have been shown to increase the incidence of postoperative ileus which can result in delayed time to return of bowel function, longer hospital stays, increased incidence of complications, and decreased patient satisfaction. With the use of a novel Auricular Percutaneous Electrical Nerve Field Stimulation (PENFS): the BRIDGE device (manufactured by Key Electronics [Jeffersonville, IN, USA] and distributed by Innovative Health Solutions [Versailles, IN, USA]), pain perception in post-operative patients may be modulated. There is ample data on the efficacy of auricular acupuncture and various transcutaneous auricular neurostimulation devices for acute pain relief, including post-operative pain. However, the novelty of this device is in using alternating currents of stimulation over a large field and with higher voltage in order to influence central pain areas.This has the potential to reduce the use of opioid medications, which in turn will reduce the incidence of postoperative ileus and reduce patient need for and dependence on narcotic pain medications. This can have an enormous economic impact due to decreased length of hospital stays for patients who undergo liver transplantation. The aim of the current project is to investigate the effectiveness this new, FDA cleared device in reducing or preventing post liver transplantation opioid use with improved pain control.If effective, this alternative approach may revolutionize post-operative pain management and have a substantial impact on health care costs and morbidity. In addition, opioid reduction could potentially lessen the national crisis of opioid addiction. The BRIDGE device has recently been approved by the U.S. Food & Drug Administration for use in accupuncture.

Background & Significance

Liver transplantation has become the standard treatment for many metabolic and end-stage liver diseases but remains one of the most complex abdominal surgeries. As such, liver transplantation is a growing field with more than 7,500 liver transplants performed in the US in 2016. Many of the complications associated with liver transplantation that lengthen hospitalization are related to postoperative pain control. Opioid medications are the standard of care and foundation for post-liver transplantation pain control and are associated with many side effects including prolonged post-operative ileus, delayed return of bowel function leading to a longer interval before reinitiating enteral nutrition, nausea, and extended time to getting up and out of bed.

Postoperative pain management has been a challenge since the field of surgery was invented. Nonetheless, acupuncture has been around since ancient times to help control pain of many types, as have opioid-based medications. Modern scientific approaches have validated the use of acupuncture, electroacupuncture, and transcutaneous electric acupoint stimulation (TEAS) for reducing pain scores and opioid use after surgery. A meta-analysis by Wu and colleagues found that acupuncture and related techniques caused lower utilization of opioid pain medications in the postoperative setting, with the most significant opioid reduction seen in patients treated with TEAS. The stimulation of the external ear may have particular benefit. A study by Greif et al. evaluated electrical stimulation to a point 3cm

anterior to the auricular tragus, a site often used by German anesthesiologists to reduce pain requirements. They found that those patients having auricular stimulation were able to tolerate more painful sensory stimulation before needing rescue narcotics.

A potentially more effective approach to auricular neurostimulation involves field stimulation of multiple points across the ear with alternating current. The BRIDGE device (Innovative Heath Solutions, IN, USA) is an externally placed, FDA-cleared device that delivers percutaneous electrical stimulation with alternating frequencies to branches of cranial nerves (V, VII, IX, and X) through the external ear via a field effect (Fig 1). Preliminary, unpublished animal data indicates that neurostimulation with this device leads to a significant decrease in baseline firing of amygdala neurons and pain perception through attenuation of spinal neurons and neurons in the central amygdala. Clinically, the BRIDGE device has been shown to reduce pain and symptom associated with opioid withdrawal. In that study, there was an 85% reduction in symptoms after just one hour of stimulation. The cymba concha region of the external ear receives 100% of the afferent auricular vagal nerve distribution through the auricular branch of the vagus nerve. Vagal nerve stimulation (VNS) thus is one possible mechanism of the anti-nociceptive effects noted. In humans, the implantable VNS is documented to improve a variety of pain conditions and overall wellbeing. VNS also has demonstrated anti-nociceptive effects by inhibition of sensory neurons in the brainstem based on animal models.

There is now increasing data on non-invasive transcutaneous VNS of the auricle. Human studies indicate increased pain threshold and reduced pain sensitivity through activation of central pain modulation mechanisms. A fMRI study in healthy adults revealed reduced activity in limbic brain regions and improved wellbeing. A central relay station for several cranial nerve signals including cranial nerves V, VII, IX, and X is the brainstem nucleus tractus solitarius (NTS). All of these cranial nerves have projections to the external ear where stimulation occurs. The NTS integrates afferent input and relays information to other brain regions such as the periaqueductal gray (PAG), hypothalamus and limbic regions (amygdala etc) which process behavioral and emotional responses to sensations. The PAG is a major pain center in the CNS and integrates somatic and autonomic responses to pain stimuli. Stimulation of PAG suppresses nociceptive transmission from the spinal cord and PAG. Notably, descending pain inhibition is involved in the anti-nociceptive effects of electroacupuncture in rats.

Auricular neurostimulation is a potential novel and non-invasive method of pain control following liver transplantation in a growing patient population with the probability of significant impact on economics and morbidity. We propose a pilot study to investigate the effects of auricular neurostimulation in patients receiving a liver transplantation. We will investigate the effects of auricular neurostimulation with this novel device and compare it to the current standard of care for pain management following liver transplantation.

The BRIDGE device 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. The electrodes will be placed percutaneously in the external ear with the help of a transilluminator to visualize the neurovascular

bundles. The BRIDGE device has recently been approved by the U.S. Food & Drug Administration for use in accupuncture.

Design & Procedures

This is a prospective, randomized study to determine the efficacy of the BRIDGE device in reducing pain and opioid use in patients following liver transplantation. Subjects will be randomized in a 1:1 ration to one of the below groups:

Group 1: BRIDGE device will be placed by a physician prior to start of the surgery with standard of care pain control analgesia

Group 2: Subjects will receive the standard of care pain control analgesia

Subjects will be randomized using the blinded envelope method. The manufacturer will provide the researchers with one device per package and each package will have a serial number. The devices will be stored in the manufacturer's packaging and stored in a locked office in the Division of Abdominal Transplant Surgery and in the primary investigators office, only accessible by research coordinators/personnel. A labeled folder for each patient with all questionnaires (0-10 numerical pain scale, BAI, PONV, ASP-POQ-R, and symptom surveys) needed for the entire study will also be stored similarly. A team member will ask the subject to complete the pre-operative questionnaires and hand the device (numbered with serial #) to one of the certified MDs or advance practice providers for placement. A device accountability log will be maintained.

a) Rationale: Neurostimulation via acupuncture, electroacupuncture, and transcutaneous electric acupoint stimulation have proven to be beneficial for pain control in healthy humans when applied to the auricular area. This new device uses field stimulation of the auricular with alternating frequencies and the use of positive and negative current to prevent nerve saturation. This allows better and more effective stimulation to modulate central pain pathways. Preclinical studies have already demonstrated efficacy and clinical studies have demonstrated also demonstrated efficacy and safety. We now propose the use of this technique in to more effectively manage pain after liver transplantation.

b) Experimental Design: After prescreening and informed consent, patients will be enrolled in the trial. The BRIDGE device will be applied after the transplant team determines subject eligible for liver transplantation but prior to the start of the surgical procedure. The 0-10 numeric pain rating scale and Beck Anxiety Inventory (BAI) scores will be measured prior to placement of the device, while VAS, Postoperative Nausea and Vomiting Intensity scale (PONV), Revised American Pain Society Patient Outcome Questionnaire (APS-POQ-R), and daily symptoms surveys will be measured on device days 1-5. All patients will receive a standard pain control regimen while hospitalized.

Selection of Subjects

Patients currently or awaiting listing for a liver transplant will be prescreened by study personnel prior to their clinic. A member of the clinical care team known to the potential subject will introduce the study and/or study personnel once initial eligibility is confirmed. All patients eligible for liver

transplantation will be assessed for eligibility and potential study participation. All transplant patients undergo social and psychological evaluation prior to transplant. The clinical and study team will address any cognitive issues prior to transplant. Subjects that signed consent greater than 1 month prior to transplant will be contacted at the time of transplant notification to confirm continued desire to participate. Patients with liver failure may also experience liver encephalopathy that would impair their ability to consent. For subjects experiencing hepatic encephalopathy we will consent their legally authorized representative prior to transplantation. Subjects will be re-evaluated following the liver transplant procedure for consent appropriateness. We anticipate enrolling 35 participants in each group, for a total of 70 subjects. We will exclude pregnant females form this study as part of clinical standard of care for liver transplantation.

Inclusion criteria:

≥18 years of age but < 70 years of age

Actively listed for isolated liver transplantation

Subject or legally authorized representative able to sign informed consent

Not currently treated with opioids or any medications that may interact with opioids

English speaking

Willing and able to participate and consent to this study

Exclusion criteria:

Diagnosis of acute liver failure or primary sclerosing cholangitis (PSC)

Anticipated that the subject will require a new roux-en-y hepaticojejunostomy

Current use of opioid use or other substance abuse.

Chronic pain disorders

Need for regional anesthesia (regional nerve blocks or epidurals)

Adhesive allergy/sensitivity

Subject admitted to the ICU at the time of transplant

Pregnancy

Subjects who meet eligibility and sign the consent form will be eligible to be enrolled into the study at the time of transplant. All eligible subjects will be recruited from Duke Transplant clinics or during hospital admission prior to transplant.

Study Interventions

Technical Details

Subjects will prospectively complete the following questionnaires at different time points during the study (see Table 1 for timeline):

Patients will be asked to rate their average level of pain in the past week on an 11-point scale (0-10) at baseline and at every time point as listed in table 1

Beck Anxiety Inventory (BAI): 21-item self-report inventory for measuring the severity of anxiety with high internal consistency. Each of the 21-items is rated on a 4-point Likert scale indicating how much each symptom bothered the patient in the previous month. This is a reliable and validated self-reported measure of anxiety. This will be performed at baseline, visit 7 and visit 10.

Postoperative Nausea and Vomiting Intensity scale (PONV): This is a 4-item questionnaire that is a valid, reliable, and responsive measure of clinically important postoperative nausea and vomiting. This will be performed at baseline, visit 2, 3, 4 and visit 9.

Revised American Pain Society Patient Outcome Questionnaire (APS-POQ-R): This questionnaire measures 6 aspects of patient quality including 1) pain severity and relief, 2) impact of pain on activity, sleep, and negative emotions, 3) side effects of treatment, 4) helpfulness of information about pain treatment, 5) ability to participate in pain treatment decisions, and 6) use of nonpharmacological strategies. This is a reliable, validated, and feasible questionnaire with high internal consistency. This will be performed at visit 3, 4 and 5.

Daily symptom surveys: Post-operative days 0-6, patients will complete a sheet with 16 questions about pain intensity, nausea, vomiting, and mobility. This will be performed at each visit starting at visit 4 through visit 9.

Patients will receive general anesthesia and post-operative analgesia per standard of care for liver transplantation.

Screen failures:

Subjects that are unable to complete visit 2 assessments, within the allotted window, will be a screen failure. Follow-up assessments will not be performed on screen failure subjects. However, subjects randomized to the device may continue to wear the device through the 120 hours regardless of screen fail status.

Auricular Neurostimulation Application:

The electrodes will be placed percutanesously 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 electrodes will be taped and secured behind the ear next to the generator itself which is secured to the skin with adhesive. The entire device may be covered by longer hair. Device placement training of all physicians, research personnel and advanced practice providers will be performed. After completing the baseline assessments above, the BRIDGE device will then be placed on the right ear prior to any premedication.

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.

Bridge Placement Details:

The neurostimulator placement will be performed as directed and per training protocol instructions

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.

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 and advance practice providers.

The device will then be activated.

Device placement will take approximately 5 minutes. The patient will remain at rest for the next 5 minutes. Care will be taken not to interfere with standard pre-operative procedures. If the electrodes become dislodged a qualified practitioner will re-apply them.

Subject will then undergo surgery as per standard of care. The patient's anesthesiologist will be informed ahead of time of the device placement. Anesthesiologist and operative room staff will be instructed to avoid manipulating the device while moving the patient or during the procedure.

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. If the electrodes become dislodged a qualified practitioner will re-apply them.

Intraoperative and Postoperative Protocol

In those randomized to have the BRIDGE device, neurostimulation will be delivered below sensation threshold continuously for 120 hours, the duration of the device battery. The anesthesiology team will be informed 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 the patient or during the procedure. The device does not interfere with any monitoring routinely used in the operating room.

All patients will undergo general anesthesia per standard of care. There will be no intraoperative or postoperative use of regional pain therapies (i.e. epidural anesthesia, tranversus 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, both groups (those with the device and those without) will continue to receive postoperative pain control per standard of care, as determined by the anesthesia and surgical teams. During the hospitalization, the postoperative pain control in all patients (both groups) will be per standard of care (opioids) per the adult liver transplant protocol.

Postoperative ileus will be measured by need for nasogastric decompression for >48 hours; again, these events are routinely documented in the medical record as part of routine medical care. Time to sitting up in a chair and time to walking will be determined based on patient symptom surveys. Diet will be advanced as determined by the primary care team. Once the patients are able to tolerate oral intake, oral opioid medications will be started 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. The patients will receive an information sheet upon discharge with study and device information as well as contact information for study team members.

All patients will receive a phone call on device day 30 by the study coordinator, PI, or co-PI. At this time, the patients will again be asked to complete the numerical pain scale, BAI, symptom survey, and PONV score via telephone, and will be asked if he or she is still requiring narcotic pain medication, or if a refill of the narcotic pain medication was needed.

Device Removal

The study investigators, PI, or co-PI will remove the device after 120 hours of stimulation. The date and time of device removal will be recorded. If the patient is at home after 5 days, then the patient will be asked to remove it and to bring it to the next clinic appointment for proper disposal. 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 device life has expired, time of removal will be recorded.

Risk/Benefit Assessment

Overall risks/ discomforts involved are very minimal – Rare (event rate 1% - < 5%)

Possible risks/discomforts may involve:

Discomfort upon insertion of the electrodes for < 5 minutes - Rare (event rate 1% - < 5%)

Discomfort at the lead placement site > 5 minutes – Rare (1 % - < 5%)

Bleeding at the electrode site if the neurovascular bundle is penetrated - Rare (event rate 1% - < 5%)

Localized discomfort if the electrodes should become dislodged during the wearing of the device - Rare (event rate 1% - < 5%)

Localized dermatitis - Rare (event rate 1% - < 5%)

Drop in blood pressure - Rare (event rate 1% - < 5%)

Syncope (fainting) - Rare (event rate 1% - < 5%)

Adverse effects to supporting personnel

Skin piercing with percutaneous needles - Rare (event rate 1 % - < 5%)

There are numerous, possible direct and long-term benefits to the subjects in this study. The results of this study may provide important insights to the medical field regarding a new, non-pharmacologic therapy that could improve pain control and quality of life for patients undergoing liver transplantation. If effective, a significant decrease or prevention in post-operative opioid use would be a major breakthrough in healthcare. This treatment would then have the potential to be extrapolated to other post-operative settings and populations.

Data Analysis & Statistical Considerations

This randomized study and the subjects will be randomized 1:1 ratio to the treatment groups. The primary efficacy endpoint is opioid usage after surgery in the two groups, and the related secondary endpoint is pain score in the two groups at the end of surgery. Normality possible transformations to attain normality of these variables will be assessed. These variables will be analyzed using either a two-sample t-test or non-parametric Wilcoxon test, depending on whether the outcomes are normal or non-normal. Analysis will be conducted under Intent-To-Treat (ITT), and any missing outcome will be imputed under missing at random (MAR) using multiple imputation methods. In addition, complete case analysis will be conducted. Continuous outcomes, adjusted for covarites, will be examined using regression analysis. Significance of the results will be examined at a two-tailed 0.05 alpha level.

Other secondary outcomes are: postoperative nausea and vomiting, postoperative ileus, postoperative immobility, length of hospital stay, incidence of ileus and time to return of bowel function, time to physical function, complications, and re-hospitalization. Continuous variables here will be analyzed using two-sample t-test or non-parametric Wilcoxon test, depending on whether the variables are normal or non-normal; categorical variables will be compared using chi-squared tests; time to event analysis will be examined using Kaplan-Meier curves. In addition, adjusted continuous outcomes will be examined using regression analysis; adjusted dichotomous outcomes will be examined using logistic regression; and adjusted time-to-event analysis will be examined using Cox proportional models. These analyses are exploratory, and significance will be assessed with and without adjusting for multiple testing.

Adverse events of this trial are infections and complications. Rates of infections and complications between the groups will be examined using Fisher's exact test or Chi-squared test.

Power: At the least (without any research funding) 25 subjects each will be randomized to the treatment groups. At alpha = 0.05 and 80% power and 25 subjects randomized to treatment groups, we should be able to observe effect size of about 0.81 between the two groups on the outcome of opioid usage; if we secure external funding, we should be able to randomize at least 32 subjects to each of the treatment groups. With 32 subjects in each groups, at alpha = 0.05 and 80% power, we should be able to observe effect size of 0.71 between the two groups. If we assume a 20% dropout rate, with the above sample sizes, we would observe effect sizes between .69 and 0.80 (Cohen, 1988).

Analysis will be conducted using statistical software SAS 9.4 (SAS Institute, Inc., Cary, NC).