STUDY TITLE: BRIDGE Percutaneous Nerve Stimulation for Cesarean Delivery Pain Control

NCT04365465

Study Protocol Approved: 02/02/2022

Specific Aims

Aim 1. Assess feasibility/acceptability of a protocol designed to test effectiveness of NSS2-BRIDGE® in postpartum women with and without OUD. In a randomized, placebo-controlled trial, postpartum women will be assigned to one of three interventions: active device + standard therapy, placebo device + standard therapy, or standard therapy alone. Standard therapy consists of multimodal analgesia including regular doses of acetaminophen and non-steroidal anti-inflammatory drugs. The refined trial study design will generate definitive evidence on the effectiveness of the device for postpartum pain, because it will include a natural history/standard therapy arm to evaluate the potential impact of placebo effect.

Aim 2. Analyze data from 60 women using these devices for postpartum pain.

Data from this pilot study will be used to support a grant application to conduct a fully powered trial to test if NSS-BRIDGE® attenuates postpartum pain in women with and without OUD. Such a study is important to determine the feasibility of using a device intervention that will differentially impact postpartum pain relief in women at high and low risk for severe peripartum pain.

A. PROJECT OVERVIEW

BRIDGE Device: Alternative Postpartum Analgesia

ABSTRACT

Pregnancyassociated mortality involving opioids have more than doubled over the past decade. Persistent postpartum pain (up to 20% of women) places many at risk for opioid misuse/abuse and death. Pregnant women with opioid use disorder (OUD) experience worse pain during and after childbirth. These pain exacerbations can result in exposure to higher doses of opioids for breakthrough pain, potentially triggering subsequent relapse/noncompliance with medically assisted therapy. For these women, alternative therapies – both pharmacological and non-pharmacological – are greatly needed, to avert the risks and consequences of opioid exposure and misuse/abuse. In this pilot investigation of 60 postpartum women (20 active device, 20 placebo device, 20 non-intervention/natural history) with OUD, we will use the NSS-BRIDGE® device to test the hypothesis that this alternative treatment modality reduces postpartum pain and opioid requirements. The NSS BRIDGE® is a disposable, percutaneous nerve field stimulator device that stimulates the nerves of the ear, cranial and occipital nerves and spinal cord. Our preliminary data suggests the NSS-2 BRIDGE® successfully reduces postoperative pain and opioid requirements by 67% after major abdominal surgery (laparotomies, colectomies, Whipple procedures). This project will directly result in a feasible and acceptable trial protocol that investigates the effectiveness of NSS-2 BRIDGE® for postpartum women with OUD. Findings will significantly advance our understanding of alternative pain management in pregnant and lactating women with OUD. Objectives. 1) Assess feasibility/acceptability of a protocol designed to test effectiveness of NSS2- BRIDGE® in postpartum women with OUD; 2) Analyze data from 60 OUD women using these devices for postpartum pain. INCLUSION OF SPECIAL POPULATIONS This project represents a collaboration with an underrepresented community, specifically pregnant women with OUD. The investigators will build a relationship with patients and investigators from the Pregnancy Recovery Center (PRC), an outpatient buprenorphine treatment program for pregnant/postpartum women. These relationships will incorporate patient perspectives into the study design and will enroll participants. The proposed work represents a new direction for the investigators in that it expands investigators' existing work with pregnant populations by adding a special category: patients with OUD. Further, the PI is deepening current pain/analgesia research themes by adding a new dimension focused on alternative pain management.

B. RESEARCH PLAN SPECIFIC AIMS BRIDGE Device:

Alternative Postpartum Analgesia Pregnancy-associated mortality involving opioids have more than doubled over the past decade. Persistent postpartum pain (up to 20% of women)2-6 places many at risk for opioid misuse/abuse and death. Pregnant women with opioid use disorder (OUD) experience worse pain during and after childbirth. These pain exacerbations can result in exposure to higher doses of opioids for breakthrough pain, potentially triggering subsequent relapse/noncompliance with medically assisted therapy. Complementary and alternative medicine approaches have been used successfully for pain management in non-obstetric populations. However, we currently

lack knowledge on the role of these therapies for pain management in pregnant and lactating women with OUD. For these women, alternative therapies – both pharmacological and non-pharmacological – are critically needed, to avert the risks and consequences of opioid exposure and misuse/abuse. To address this need, we will identify the therapeutic effectiveness of an alternative medicine device on postpartum pain management. Our longterm goal is to identify appropriate therapies for pregnant and lactating women. Our objective in this proposal is to implement a pilot, randomized placebo-controlled and natural-history (no intervention arm) trial that tests the effectiveness of the NSS2-BRIDGE® device in postpartum (after vaginal and cesarean delivery) women with OUD. The NSS2-BRIDGE® device is a disposable, percutaneous nerve field stimulator device that stimulates the nerves of the ear, cranial, and occipital nerves and spinal cord. Our preliminary data suggests that the NSS2-BRIDGE® successfully reduces postoperative pain and opioid requirements by 67% after major abdominal surgery, such as laparotomies, colectomies, and Whipple procedures. Our global hypothesis is that postpartum women with OUD respond favorably to alternative pain management interventions, specifically the NSS2-BRIDGE®. This project will result in data that supports funding applications for a larger study that investigates the effectiveness of NSS-2 BRIDGE® for postpartum women with OUD. This work shifts current postpartum pain approaches with an innovative multimodal pain treatment strategy that integrates complementary medicine tactics. It is a first step toward postpartum pain management that eliminates opioids entirely. UPMC Magee Womens Hospital is one of the largest, managing 8,000-10,000 deliveries annually, and is ideally suited for recruitment. The investigators, Magee-Womens Hospital, University of Pittsburgh, and Dept of Anesthesiology have robust existing research infrastructure that is fully equipped to implement all aspects of this proposal. Aim 1. Assess feasibility/acceptability of a protocol designed to test effectiveness of NSS2-BRIDGE® in postpartum women with OUD. In a randomized, placebo-controlled trial, postpartum women will be assigned to one of three interventions: active device + standard therapy, placebo device + standard therapy, or standard therapy alone. Standard therapy consists of multimodal analgesia including regular doses of acetaminophen and non-steroidal anti-inflammatory drugs. Interviews will be conducted with 15-30 women with OUD from the Pregnancy Recovery Center, an outpatient buprenorphine treatment program for pregnant and postpartum women, to incorporate patient perspectives into the study design. The refined trial study design will generate definitive evidence on the effectiveness of the device for postpartum pain, because it will include a natural history/standard therapy arm to evaluate the potential impact of placebo effect. Aim 2. Analyze data from 60 OUD women using these devices for postpartum pain. Data from this pilot study will be used to support a grant application to conduct a fully powered trial to test if NSS-BRIDGE® attenuates postpartum pain in women with OUD. Such a study is important to determine the feasibility of using a device intervention that will differentially impact postpartum pain relief in women with OUD. This study is innovative because it employs novel theoretical concepts to perinatal pain research, by incorporating alternative therapies to postpartum multimodal analgesia protocols. It is significant because it advances scientific knowledge on the role that auriculo-nerve stimulation has in reducing postpartum pain and the requirement for opioids among postpartum women at high-risk for severe pain and opioid misuse. Treatment services, technologies, and preventative interventions that drive the field of acute pain management will be changed as a result of these investigations. Future Directions. These new directions will result in funding applications to the National Center for Complementary and Integrative Health (NCCIH), whose strategic research mission it is to, “stimulate research on the use of complementary approaches to pain and symptom management.” SIGNIFICANCE This proposal is significant because indiscriminate use of standard analgesics, including opioid SIGNIFICANCE This proposal is significant because indiscriminate use of standard analgesics, including opioids, has been a critical barrier to progress in pain control and recovery, especially in pregnant and postpartum women with OUD. Postpartum women with OUD are at higher risk for severe pain requiring treatment with opioids for breakthrough pain10-13. This proposal is significant because it advances scientific knowledge on the role that percutaneous auricular nerve stimulation has in reducing postpartum pain and opioid needs among postpartum women at high risk for severe pain and opioid misuse. Treatment services, technologies, and preventative interventions that drive the field of acute pain management will be changed as a result of these investigations.

INNOVATION

Current postpartum pain management strategies use conventional medications while permitting opioids for severe breakthrough pain. These modalities focus strictly on one component of pain: the sensory dimension. However, pain processing is complex, consisting of sensory, affective, and higher processing dimensions. Existing strategies have

not been successful in minimizing the need for postpartum opioids, because they have neglected to address cortical pain processing, nor have they emphasized pre-emptive strategies to prevent pain in patients at risk for severe postpartum pain, such as women with OUD. Recent studies have shown promising results for postoperative acute pain management and significant opioid medication reductions, using percutaneous auricular nerve stimulation (NSS BRIDGE® device). These advances offer a novel solution to effectively treat pain and reduce postpartum opioid use, by leveraging central sensitization modulating properties Therefore, this research is innovative, because it employs novel theoretical concepts to postpartum multimodal pain management strategies, by: 1) emphasizing alternative approaches that have neurobiological underpinnings (vide infra); 2) targeting central nervous system processing of acute postpartum pain; and 3) by tailoring therapies to severe pain risk by focusing on postpartum women with OUD. Advancements in multimodal acute pain management strategies that are possible with this new approach are several. First, it validates the role of risk-stratified postpartum analgesia approaches that incorporate treatment of multiple aspects of pain. It opens investigations on the discovery of novel pain therapeutic agents that work through CNS pathways, so that opioid-free and/or non-opioid based postpartum pain management strategies in vulnerable women (like those with chronic pain or substance use disorder) can be pursued. APPROACH The study design is a randomized control trial with the following arms: 1) active device; 2) placebo device; 3) non-intervention (active control). The primary outcome, pain with movement, will be measured over the first 72 hours after delivery. The devices will be placed while women are still feeling good pain relief from labor epidural analgesia (after delivering vaginally) or from spinal or epidural anesthesia (after delivering by cesarean). By applying the devices while women are still relatively pain-free, a preventative approach to pain management in women at high-risk for severe postpartum pain (women with OUD) is taken. Investigators – We have assembled a strong team of talented investigators with expertise in specific areas, including obstetric pain pathophysiology (Lim), clinical standards for obstetric pain management (Lim), complementary pain treatments (Chelly), OUD (Krans), and clinical research in pregnancy (Krans, Lim). Our team is uniquely suited for this project, as we have developed and shown feasibility/acceptability for rigorous assessments of sensory and affective dimensions of pain over time in a cohort of perinatal women14. Rationale for using auriculo-nerve stimulation by NSS-BRIDGE to control acute postpartum pain and opioid requirements. Embryologically, the ear starts to develop by week 3 but the external part only starts development by week 5-6 (Figure). There are 6 hillocks, with 1-3 from the first branchial pouch and 4-6 from the second branchial. The 1st branchial arch is innervated by the trigeminal nerve (V). The 2nd branchial arch is innervated by the facial nerve (VII). The 3rd branchial arch is innervated by the glossopharyngeal nerve (IX). The 4th and 6th branchial arches are innervated by the vagus nerve (X). The stimulation of these nerves in an adult by percutaneous auricular nerve field stimulation (NSS-BRIDGE® device) generates impulses that is transferred to the respective nerve nucleus in the brainstem and the spine. In addition, the stimulation of the branches of the cervical plexus result in a modulation of the spine ascending and descending tracts. The results are complex interactions between several nuclei of the limbic system. The figures illustrate the complex interaction between the nucleus of the limbic system as the result of the stimulation the auricular branches of the vagus and trigeminal nerves. These complex interactions result in CNS modulation of pain processing. The NSS-BRIDGE® (NSS-2) device is a disposable auricular electrical nerve stimulator. The device produces an alternative stimulation of the auricular branches of the vagal (X), trigeminal (V), glossopharyngeal nerves (XI), facial nerve (VII) and the superficial cervical plexus for 5 days. The signals generated are initially processed in the corresponding spinal cord and the brainstem nucleus of these nerves, including the limbic system, a complex system established to modulate the pain pathway15-17. Single neuron recordings using electrophysiology techniques have demonstrated device-modulated pain pathways by dampening the firing of neurons in the central nucleus of the amygdala and spinal cord. The central nucleus of the amygdala is also the output nucleus of the amygdala and has major projections to the forebrain and brainstem through which it also influences spinal neurons. Accordingly, the nociceptive signals enter the spinal cord from afferent signals (somatic or visceral), known to be modulated by brainstem nuclei including the rostral ventrolateral medulla (RVM) and periaqueductal gray (PAG). These nuclei get input from the nucleus tractus solitarius (NTS), which is directly affected by the impulses generated by the use of the NSS-2. The result is reduced transmission of the pain impulses from visceral and/or somatic structures to supraspinal areas. Stimulation by NSS-2 causes a significant reduction in spinal neuron and a significant decrease in both somatic and visceral pain. Indeed, randomized, controlled trials in non-obstetric populations show NSS-2 mediated reductions in abdominal pain compared to placebo in adolescent with irritable pain syndrome. The NSS-2 is approved by the FDA to treat opioid

withdrawal symptoms including pain. Participants – Inclusion criteria – Postpartum women will be recruited who are ³18 years of age, admitted to MWH for obstetric delivery, and meet Diagnostic and Statistical Manual of Mental Disorders (DSM-5) criteria for an OUD (e.g. opioid, stimulant or other use disorder). Exclusion criteria – Women will be excluded if they have a fetal or neonatal death, an acute, severe psychiatric condition in need of immediate treatment or pending or legal action that could prohibit or interfere with participation (e.g. incarceration). Recruitment. We intend to recruit 60 women with OUD in the immediate postpartum period to participate in the RCT. We will employ strategies that we successfully used in our previous observational studies including having clinical staff on the labor and delivery unit or postpartum floors alert research staff when potentially eligible women are admitted for delivery. In 2018, 315 pregnant women with a SUD delivered an infant at MWH. Based on our preliminary data, approximately 95% of women will be eligible for recruitment per year or 25 participants per month. Based on a 76% recruitment rate from our previous study, we anticipate that we will easily and successfully enroll our target sample size of 60 women (20 per group) in 12 months or less. Protocol Details: Primary Outcome. The primary endpoint is evoked pain (pain with movement) for the first 72 hours after delivery, measured by 100mm numeric rating scale. Pain data. The affective and sensory dimensions of acute postpartum pain (in hospital) will be gathered per participant every 4 hours by electronic pain diary. To assess and compare these variables, the overall "burden" of these dimensions during the hospital stay and after discharge, will be calculated using the area under the curve (AUC18- 23). The use of AUC is justified by its use in multiple studies as a metric for assessing pain burden, as well as efficacy of pain treatments, over time19-23. Pain burden will be calculated as area under the daily pain Figure. 1A) Relationship between the innervation of the ear, the brachial pouches and the corresponding cranial nerve nucleus. This leads to a complex innervation of the ear (see 1B). 1B) In addition to the trigeminal and vagus nerves, the ear is also innerved by branches of the glossopharyngeal nerve (XI), sensory branch of the facial nerve (VII) and branches of the cervical plexus. In green is the auricular branch of the vagus nerve. In red, the auriculotemporal nerve, a branch of the trigeminal nerve. In yellow, the greater auricular nerve, and in blue, the lesser occipital nerve, both branches of the cervical plexus. 1C) Complex interaction between the nucleus of the limbic system as the result of the stimulation the auricular branches of the vagus and trigeminal nerves B C A level curve (AUC) using the trapezoid rule (AUC = AUC + (X[i]-X[i−1])*((Y[i]+Y[i−1])/2), where X is the number of days since delivery and Y is the reported NRS score of daily average pain)14,24. Analysis plan. The statistical analyses will begin by comparing the baseline characteristics of the population by treatment. Chi-square test or Fisher's Exact test will be used to determine differences in categorical baseline characteristics between the treatments. The analysis for the primary outcome will be based on an intention-to treat principle. ANOVA will be used to determine differences in evoked pain between the three groups. If baseline differences (e.g. age, sex) are observed, imbalance baseline characteristics will be included in the regression model to control for factors not balanced through random assignment. Surveys and Measurements. Several surveys that have are validated and reliable for the constructs they represent will be used in this investigation. The rationale and evidence supporting their use are as follows: • Demographic information. Smoking status (yes/no), number of prior deliveries, race/ethnicity, highest level of education, and household income will be self-reported by subjects. These items relate to social correlates of health that are not obtainable by surveys. If differences in these characteristics are observed between groups, a regression model will control for these factors. • Static, dynamic, and affective dimensions of pain (0-100mm). These pain measures are important assessments of other aspects of postpartum pain that go beyond pain intensity (standard 0-10 pain scale). They will assess 3 aspects of pain: pain at rest, pain with movement, and affective/emotional aspects of pain on a 0- 100mm visual analog scale (VAS). In the hospital, they will be assessed by electronic pain diaries already programmed, trialed, and vetted for their feasibility of use in this population14,25. The pain diaries enhance data capture by sounding a reminder alarm for participants to complete the questions at the appropriate interval. After discharge, the questions will be assessed by email (REDCap) (Figure). • McGill Pain Questionnaire, Short Form (SF-MPQ). The McGill Pain Questionnaire Short Form measures multiple dimensions of pain experience including sensory and affective aspects26,27. The instrument is psychometrically sound, valid, reliable, and has good discriminative capacity28. These measures are necessary to better understand the role that these factors play in pain intensity, quality, and duration, and to assess the relative effectiveness of the device intervention for the affective (vs. sensory) component of pain. • PROMIS Inventories. PROMIS inventories assess core aspects of pain. We will specifically assess neuropathic pain quality (PROMIS-PQ-Neuro), nociceptive pain quality (PROMIS-PQNoci), and pain behavior (PROMIS-PB) over time. The surveys measure external manifestations of pain including social role participation and pain interference (i.e. pain

behavior), and neuropathic/nociceptive pain quality. They are valid and reliable for the constructs that they assess29-31. Through these measures, an understanding of device-related changes in nociceptive/neuropathic pain and pain behaviors over acute/chronic periods will be gained. • Perceived Stress Scale (PSS). Psychological stress/distress affects pain, post-operative recovery, and depression. It will be measured in these populations using the Perceived Stress Scale.32-36 • Breastfeeding (BF). Breastfeeding (yes/no) will be assessed starting at 24-hours postpartum, and over time to assess the potential impact of the device intervention on enhanced breastfeeding success. • Inpatient opioid use (milligram morphine equivalent, MME). The impact of NSS-BRIDGE® on inpatient opioid requirements will be assessed by measuring oxycodone, hydromorphone and morphine (mg) totals over the first 72 hours postpartum. These medications will be standardized to a single variable, milligram morphine equivalent (MME), using calculation instruments from the Center for Disease Control (CDC)37,38. • Outpatient opioid use (average daily medication use). Similarly, the impact of NSS-BRIDGE® on long term/outpatient opioid requirements will be assessed by daily diaries completed by subjects on average daily pill use. These medications will be converted to a single variable, milligram morphine equivalent (MME), using calculation instruments from the Center for Disease Control (CDC).37,38 Retention Plan. Retention is critical as withdrawals from bad outcomes can bias the results toward good outcomes, and vice versa. Starting at enrollment/consent, subjects will be completely informed of study procedures, including the vital need to complete all procedures in a timely fashion. Subjects will be paid in graduated installments in the schedule noted in the Table. Deliverables and Future Directions. These investigations will directly result in a feasible and acceptable protocol for a larger trial and will inform future studies on alternative therapies in pregnant and lactating women with OUD. In a fully powered trial, the neural mechanisms explaining such effects will be rigorously tested with sensory testing. Future research will focus on the following questions: 1) Mechanisms: How do these modalities work? Does treatment success differ across pain populations, sex, or age? What differentiates responders and non-responders 2) Heterogeneity of treatment effect: Which specific populations benefit the most from alternative treatments? Do women with OUD respond differently to these treatments?