RESEARCH PROTOCOL

STUDY TITLE: Lidocaine patches prior to percutaneous nerve evaluation

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Study Sites:

- University of Louisville Hospital

- UofL Physicians – Urogynecology; Springs Medical Center Office
- UofL Physicians – Urogynecology Associates; 4431 Churchman Avenue, Louisville, KY

Background/Problem Statement

Sacral neuromodulation (SNM) is an accepted therapy for refractory urinary urgency and frequency, urgency urinary incontinence, non-obstructive urinary retention, and fecal incontinence[1]. A common indication for SNM is overactive bladder (OAB). OAB is defined as a syndrome of urinary urgency, usually accompanied by urinary frequency and nocturia, with or without urgency urinary incontinence, in the absence of infection or other pathology.[2] OAB affects approximately 34 million adults in the United States, substantially affecting their quality of life.[3] The initial treatment for OAB consists of diet and behavioral modifications, pelvic floor physical therapy, bladder training, and a trial of anticholinergic or beta-agonist medications. However, long-term adherence to these interventions is poor due to side effects and poor effectiveness.[4]

Sacral neuromodulation (SNM) is a third-line treatment option for OAB that can have a particular impact on this population and success rates as high as 82% can be expected at 5 years.[56] SNM is typically administered with a test stimulation followed by permanent battery/pulse generator placement if successful. Successful test stimulation is defined as a reduction of one or more micturition symptoms of ≥50% compared to baseline. Test stimulation can be performed as a staged procedure in the operating room or as a percutaneous sacral nerve evaluation (PNE) performed in the office. Though a patient is anesthetized in the operating room, discomfort with placement is a larger concern with office based PNE procedures – making increased comfort with this procedure essential.

Lidocaine is frequently used for analgesia with PNE placement. This is often performed with injectable lidocaine, however, other forms can be considered to improve patient comfort and clinical success – namely through topical lidocaine patches. Up to 5% (35 mg) of lidocaine patches are absorbed topically, producing analgesia within 30 minutes with a half-life of 6 to 8 hours[7]. Transdermally absorbed lidocaine appears to have a very low rate of systemic absorption resulting in local analgesia and not anesthesia, a characteristic not shared with lidocaine infiltration. The exact mechanism of this differential effect is unknown, however, it is hypothesized that the lidocaine patch produces analgesia without blocking all the sensory and motor inputs in large, myelinated A-β sensory fibers [7]. The value of this relatively rapid onset medication with analgesic effects and without the associated discomfort of infiltration can be increased comfort for patients. The ability to potentially detect adverse sensation more sensitively in the office may also make this method of analgesia more effective.

Objectives

Primary outcome will be:

- VAS pain scores measured on a 10 point scale before and after PNE procedure

Secondary outcomes will be:

- Patient Overall Satisfaction after PNE placement
- Volume of injectable lidocaine used
- Rate of successful PNE
- Progression to permanent SNS implantation.
- Amplitude of perineal stimulation

Our null hypothesis is that there will be no significant difference in change in VAS score between patients in the lidocaine patch group and the patients in the control group.

We hypothesize that patients in the lidocaine patch group will experience significantly less pain at the time of PNE as measured by change in VAS pain score when compared with the control group.

Study Design/Methodology

Patients who have been scheduled for a PNE procedure will be will be consented for the study on the day of the procedure and screened for participation prior to the procedure by phone. Participants will be randomized with a stratified block randomization scheme (with a random block size of 4, 6, and 8 participants). Randomization sequence will be generated by statistician collaboratorr. All data will be recorded in the RedCap software and be maintained in that password-protected format until analysis. Data analysis will be performed by researchers associated with the IRB for this study. De-identified data will also be sent to statistician collaborator for analysis. The trial is powered to detect a change in VAS pain score of 1.5 points or more on a 10 point scale, a value that is taken to be the minimum clinically meaningful change for the VAS instrument.[8,9] Data on identification key will be deleted at the conclusion of this study. Patient enrollment will conclude when 34 subjects, 17 of each group, have been enrolled in the study. Sample size was determined using G*Power so that we have 80% power to detect a difference between groups of the minimum clinically meaningful effect size of 1.5

points or greater using the two-sample test at α=0.05 and an assumed standard deviation for VAS score of 1.5 points.

Inclusion criteria:

1. Female patients undergoing sacral neuromodulation for the management of their OAB with SMN trial with PNE without fluoroscopy.
2. No contraindication to the use of lidocaine patch
3. Age >18 years old

Exclusion criteria

1. Patients who are not candidates for SNM therapy
2. Patients with contraindication to SNM including pregnancy
3. Allergy to lidocaine or adhesives
4. Chronic pain as an indication for the PNE procedure

Study design

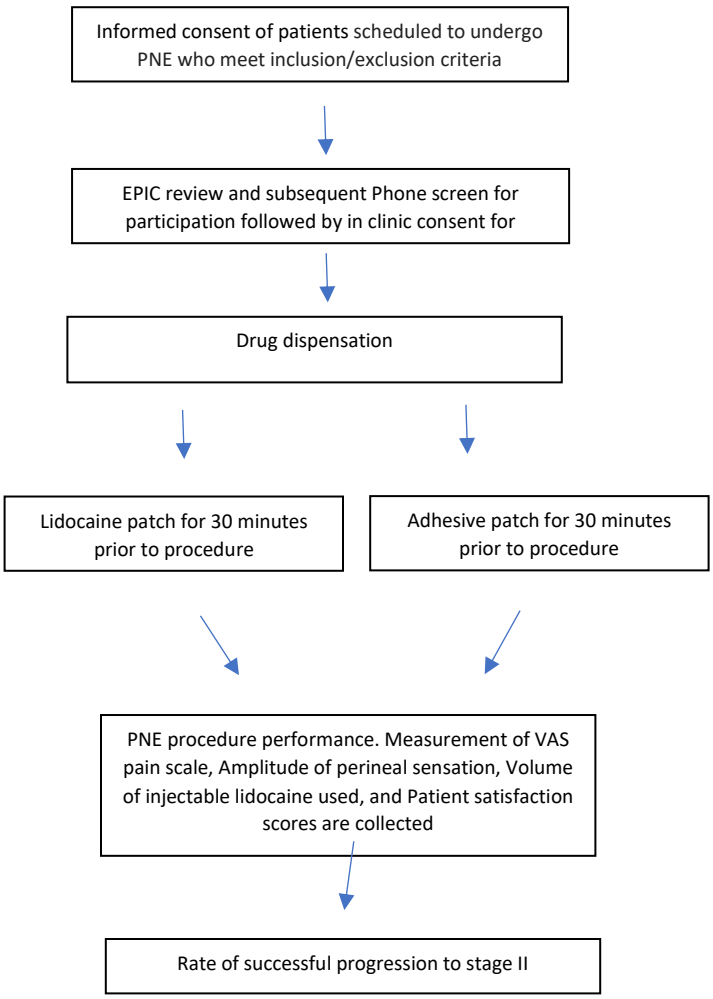
The study design will be a double-blind randomized control trial comparing 4% lidocaine patch placed over the sacrum 30 minutes prior to the procedure to placebo patch. Intervention and control patches will be in envelopes labeled with study number and located within the procedure area. A patch from the envelope corresponding to the patient will be placed by a medical assistant or co-investigator who is not associated with the PNE placement procedure 30 minutes prior to the procedure start. Number of voids and incontinence episodes per day

prior to the PNE procedure will be recorded. A patch (intervention or control) will be removed by a medical assistant prior to provider entering the room in order to secure blinding. 1% lidocaine will be injected into the sacral procedure site for adequate pain relief. PNE procedure will then be performed. If inadequate analgesia is reported by the Patient during the procedure, additional injectable lidocaine will be administered, not to exceed 4.5 mg/kg of injectable lidocaine. The volume of injectable lidocaine used will be recorded. VAS pain scores prior to and immediately after procedure will be recorded. Patient Satisfaction Score, rate of successful PNE, rate of progression to SNS implantation, and amplitude of perineal stimulation of a Likert scale will be collected immediately after the procedure.

Patients will follow up in 1 week – as is standard of care with the PNE procedure. Adverse events such as pain or change in sensation will be recorded. Number of voids and incontinence episodes per day after the PNE procedure will be recorded. Overall satisfaction score will be recorded at that time.

In summary, overall questionnaires and data being collected include:

Figure 1: Patient flow and outcomes:



Study has been registered on Clinicaltrials.gov

Participant Recruitment Methods

Subjects will be recruited from the ULP Female Pelvic Medicine and Reconstructive Surgery (FPMRS) practice at the University of Louisville Health Care Outpatient Center (HCOC), Urogynecology Associates office at 4431 Churchman Avenue and the Springs Medical Center. All Patients receiving care at University of Louisville Urogynecology who meet screening criteria will be called prior to their PNE procedure to assess for willingness to participate in this study. Women meeting study criteria will be approached by a member of the research team for consent prior to their PNE procedure. Women interested in the study will have the study explained to them, the consent reviewed, and questions addressed in a confidential manner in a private room. At the time of consent, participants will be informed that their participation in this research is voluntary and that they may discontinue participation without penalty at any time. Participants will not be reimbursed for their participation in this research study.

Informed Consent Process

Patients will be called prior to their procedure to assess if they are interested in participation in this study. If they are interested, they will present with sufficient time prior to their procedure

to review and sign their consent form and have their patch (lidocaine vs placebo) placed (in place for 30 minutes). Consent form is otherwise attached.

Research Procedures

Please see study design/methodology section for further details. In addition all members of the research team will be educated on the study protocol at a division meeting or meeting set up for training purposes. All members of the research team will be able to ask questions at this education session and after the education session to ensure they are comfortable with all aspects of the study protocol. Members of the research staff that will be using REDCap (Research Electronic Data Capture) will be trained on how to use this database.

Minimizing Risks

Potential risk of breach of confidentiality will be mitigated by the redcap software and use of password protected University of Louisville computers for data entry and analysis. No one other than study investigators will be able to access data and it will be deleted at the conclusion of the study. Patient will be assigned a study number during the consent process and it will be associated with a patient identifier in REDCAP. No other location will have this information.

As this study is minimal risk there will not be oversight of the data. As this drug is available over the counter and is not investigational, it will be placed in envelopes at the start of the study and dispensed by investigators and clinic staff.

All expected adverse events are of mild severity.

For this study, the following standard adverse event (AE) definitions are used:

- Adverse event: Any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a medical treatment or procedure, regardless of whether it is considered related to the medical treatment or procedure.
- Serious Adverse Event (SAE): Any AE related to the study drug that results in any of the following circumstances: death, life-threatening, event requiring inpatient hospitalization or prolongation of existing hospitalization, persistent or significant disability/incapacity

AEs are graded according to the following scale:

- Mild: An experience that is transient and requires no special treatment or intervention. The experience does not generally interfere with usual daily activities.
- Moderate: An experience that is alleviated with simple therapeutic treatments. The experience impacts usual daily activities.
- Severe: An experience that require therapeutic intervention. The experience interrupts usual daily activities. If hospitalization (or prolongation of hospitalization) is required for treatment of something related to the study drug, it becomes a SAE.

The study uses the follow AE attribution scale:

- Not related: The AE is clearly not related to the study procedure (i.e., another cause of the event is most plausible and/or a clinically plausible temporal sequence is inconsistent with the onset of the event).
- Possibly related: An event that follows a reasonable temporal sequence from the initiation of study procedures, but that could readily have been produced by a number of other factors.
- Related: The AE is clearly related to the study procedures.

Expectedness of Adverse Events:

- Uncommon: discomfort over the area the lidocaine patch was placed and discomfort with the PNE procedure itself
- Rare: Allergy to adhesive bandage or lidocaine, lidocaine toxicity

Plan for Analysis of Results

Summary statistics for demographics, procedures variables, and outcome measures will be summarized for each treatment group (lidocaine patch and control patch) using means, standard deviations, counts and proportions, as appropriate. Differences in these variables will be assessed using the two-sample t-test for continuous variables and the Fisher exact test for categorical variables. A two-sample t-test will be used to assess differences in the primary outcome of change in VAS score after procedure between groups. Differences in secondary outcomes will be considered using the two-sample t-test for continuous variables and the

Fisher exact test for categorical variables. Transformations and/or non-parametric methods will be used if continuous data are found to substantially violate the assumption of approximate normality. Multivariate linear/logistic regression models may be used to assess the impact of other variables onto primary or secondary outcomes. Throughout, a significance level of $\alpha=0.05$ will be used, and all tests will be two-sided. Data analysis will be performed by a biostatistician collaborator using the R statistical software.

Research Materials, Records, and Privacy

Data that is to be collected with this study and entered into an encrypted database:

Demographic data

- Name
- Date of birth
- Age
- Weight
- BMI
- Race/ethnicity
- Smoking status
- Indication for PNE
- Contact information
- Randomization assignment

- Study ID number
- Number of voids and incontinence episodes per day prior to the PNE procedure and 1 week after the PNE procedure

Procedural variables:

- Total amount of lidocaine used
- Side of PNE lead stimulated
- Amplitude of stimulation at completion of procedure
- VAS pain score prior to and after the PNE procedure.
- Satisfaction scale immediately post procedure and 1 week after the procedure.

1-week follow up variables:

- Adverse events of PNEs such as uncomfortable change in perineal sensation present at the 1 week post-procedure visit
- Patient satisfaction score immediately after the PNE procedure and at the 1 week post-procedure visit
- Number of days with successful stimulation
- Amplitude of stimulation at time of removal
- Bladder/ fecal diary with symptoms during the PNE trial period

3-month follow up

- Number of patients with a “successful” PNE who underwent an implantation
- Number of patients with a “successful” PNE who planned implantation but had not yet scheduled

- Number of patients with a “unsuccessful” PNE who underwent staged procedure
- Number of patients with a “unsuccessful” PNE and what other treatment options they pursued in the next 3 months

Successful PNE is defined as PNE procedure which resulted in successful wire placement.

Unsuccessful PNE is defined as PNE procedure which did not result in successful wire placement.

Implantation defined as stage 2 procedure after interval PNE results showed >/=50% symptom reduction.

Staged procedure is a stage 1 procedure in the operating room as opposed to being performed as an outpatient PNE

This information will be sourced from the subjects themselves and questionnaire templates for satisfaction score and VAS pain score will be attached to this document as appendices. This information is necessary to display if the intervention results in an increased comfort with the PNE procedure or increased satisfaction with the procedure. Number of voids and incontinence episodes before and after the PNE procedure is recorded to examine if a change in procedural effectiveness occurs with this intervention.

All identifying information and data collected during the course of this study will be kept secure and strictly confidential. For confidentiality, only research team members will have access to the study information and the information entered into the database. Subjects will be assigned

a unique study ID that will be used on all case report forms and database reporting. The database that will be used is REDCap which is HIPPA (Health Insurance Portability and Accountability Act of 1996) compliant, encrypted, and password protected. Any hard copies will be maintained in a locked cabinet in a locked office by a member of the research team.

The research personnel involved in this study are CITI and HIPAA trained. If new research personnel are added to the study, an amendment will be submitted to and approved by the IRB before being allowed to participate in the study

References

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