Study Protocol: **Effectiveness of Bilateral PTNS compared to Unilateral PTNS for the Treatment of Overactive Bladder/Urge IncoNtinence (BUTTON)**

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Scientific Background

Overactive bladder (OAB) is defined as a syndrome of urinary urgency, usually associated with frequency with or without incontinence (1). This syndrome is estimated to affect more than 16 % of the adult population (2) and has a significant impact on the quality of life of those affected by it (3). The treatment algorithm as recommended by the American Urologic Association includes starting with behavioral modifications then offering pharmacologic therapy if needed (4). Previous data show that adherence to pharmacologic therapy is low due to side effects and thus there is a high discontinuation rate (5). One of the approved treatments with a low side effect profile is percutaneous posterior tibial nerve stimulation (PTNS) (4).

The SUmiT trial, a randomized controlled study for OAB has shown that when compared to sham, PTNS demonstrated 54% improvement in symptoms subjectively as compared to 20% in the sham arm. In addition, PTNS was associated with a better reduction of incontinence episodes and daily number of voids (6).

The OrBIT study which randomized women with OAB to PTNS or extended release tolterodine found a larger number of women receiving PTNS (79.5% vs. 60 %) who reported significant improvement in symptoms (7).

PTNS device has been cleared by FDA for the treatment of overactive bladder and urge urinary incontinence. It however does not state whether stimulation of the posterior tibial nerve should be performed unilaterally or bilaterally. The above studies using PTNS have all involved unilateral percutaneous stimulation of the posterior tibial nerve. We do not yet know whether bilateral stimulation produces a different result from the traditional unilateral stimulation.

A study of sacral neuromodulation, also an approved second tier OAB treatment which stimulates the sacral nerve demonstrated that 76% of patients with bilateral lead implants had more than 50% improvement in overactive bladder symptoms as compared to 58% of those who had unilateral lead placement (8). A percutaneous nerve evaluation pilot study for those who failed sacral neuromodulation revealed that a select group of patients benefited from bilateral stimulation (9). There have been no bilateral PTNS studies for OAB to date. Though the colorectal literature suggests bilateral transcutaneous stimulation of the posterior tibial nerve improves fecal incontinence (10). The aim of our study is to compare the effectiveness of bilateral tibial nerve stimulation versus unilateral tibial nerve stimulation in managing overactive bladder symptoms using PTNS device. The study will not be evaluating the effectiveness of the device itself but rather comparing stimulation of one nerve versus two nerves using a device that is already on the market.

Study Objectives

Percutaneous tibial nerve stimulation (PTNS) is an accepted treatment for overactive bladder that can be accomplished in the office with minimal side effects. It is currently carried out by stimulating one of the posterior tibial nerve unilaterally.

The aim of this study is to determine whether bilateral percutaneous tibial nerve stimulation is more effective than unilateral stimulation.

Patients with a diagnosis of overactive bladder or urge incontinence who have previously failed lifestyle changes and/or pharmacologic therapy will be offered percutaneous tibial nerve stimulation. Enrolled patients will be randomized into two groups. The control group will receive the traditional unilateral treatment of PTNS. The intervention group will receive bilateral PTNS treatment during the study period. Intervention success will be measured by an improvement in the scores on the overactive bladder questionnaire and incontinence impact questionnaire as well as a decrease in the number of daily voids, nocturia episodes as assessed by voiding diaries.

Hypothesis

Bilateral PTNS is more effective than unilateral PTNS at reducing symptoms of OAB.

Primary Aim: Compare improvement of overactive bladder symptoms of participants receiving bilateral PTNS to those receiving unilateral PTNS using the overactive bladder questionnaire (OAB-q).

Secondary Aim(s):

1. Evaluate impact of OAB on quality of life using the incontinence impact questionnaire
2. Compare the number of voids per 24-hour periods
3. Compare the number of nighttime voids
4. Compare the number of incontinence episodes

Study Design and Methods:

This will be a randomized study of patients with overactive bladder not naive to behavioral therapy and/or pharmacotherapy (or unable to tolerate or with contraindications to pharmacotherapy) with or without urge incontinence recruited through the outpatient offices of the Division of Urogynecology at Women and Infants Hospital and University of Pittsburgh Medical Center Magee-Womens Hospital. The patients will be randomized to receiving unilateral or bilateral PTNS for 30 minutes weekly for a total of 12 weeks. Though we considered the use of a sham needle to decrease participants' bias in reporting their results, we have elected not to use a sham needle. Since all participants will be naïve to PTNS, they are unable to gauge the amount of improvement they should have and therefore we can expect reported improvement to be accurate.

Participants will be asked to complete a 2-day bladder diary at baseline and weekly as per routine PTNS care. Participants will also be asked to fill out a validated OAB symptom severity questionnaire (OAB-q) and the incontinence impact questionnaire (IIQ-7) at baseline (+/- 1 week), four weeks (+/- 1 week), eight weeks (+/- 1 week) and twelve weeks (+/- 1 week).

Our primary outcome will be the improvement in symptom severity as measured by the OAB-q score.

Secondary outcomes will include change in the number of daily voids, change in nocturia or night time voids, change in number of incontinence episodes as measured by the bladder diary and, impact in quality of life as demonstrated by change in score of the incontinence impact questionnaire, IIQ-7.

All questionnaires collected from participants will be labeled with a unique study number and any participant identifiers on the questionnaires or voiding diary will be redacted prior to saving in a research folder in a locked drawer.

Inclusion criteria

Female patients over the age of 18 who have previously tried and failed, or were unable to tolerate, behavioral therapy. Patients will have to consent to participate in the study. Patients on pharmacologic therapy at the time of recruitment will continue their treatment.

Exclusion criteria

1. Pregnant patients

2. Patients with pacemakers of implantable defibrillators

3. Patients with neurogenic bladder

4. Patients who have received Botox or have an implant for sacral nerve stimulation

5. Patients with uncontrolled bleeding disorder

6. Patients with unhealed ulcers or with leg edema surrounding medial malleolus

Rationale for exclusion criteria

PTNS is an approved procedure that was not previously studied in the pregnant population therefore we will exclude pregnant patients from this study. PTNS is the electrical stimulation of the tibial nerve through a needle and therefore it is unclear how this stimulation would interact with a pacemaker or implantable defibrillator.

While patients with neurogenic bladder may have overactive bladder, the pathophysiology of their urinary frequency and incontinence is different therefore including them in this particular study has the potential to confuse the study results. Botox and Interstim (implantable sacral nerve stimulator) are advanced overactive bladder therapies and are generally offered to those who have failed pharmacotherapy and PTNS and therefore PTNS is unlikely to be effective in participants that have failed more advanced therapies. A needle is inserted through the skin for PTNS and thus PTNS conjures a potential for bleeding. Therefore, those with bleeding disorders will be excluded. Electrical stimulation is sent to the tibial nerve through a needle and therefore leg ulcers and edema can potentially alter the stimulation received by the nerve.

Sample Size calculations

Based on the SUmiT trial results, we expect a decrease in OAB symptom severity of 36.7 with a standard deviation of 21.5 in the unilateral PTNS group. If we estimate that the bilateral PTNS group will show at least 50 % improvement from the unilateral, then we should see an average decrease in in symptom severity of 55 in the bilateral PTNS group.

Our sample size estimate based on 5% significance and 80 % power with a standard deviation of 21.5 will be: 23 per group for a total of 46 participants.

If we expect an attrition rate of about 10%, our goal is therefore to recruit a total of 50 participants with 25 participants in each arm.

Statistical Analysis

Descriptive statistics will be used to assess the balance of baseline characteristics between randomization groups: unilateral and bilateral PTNS groups. The primary analysis will be intent-to-treat. At baseline, for both treatment groups, the Wilcoxon-rank sum test will be used for all continuous variables and Fisher's exact test for all categorical variables. For the analysis of primary and secondary outcomes, we will compare the last measurement to the baseline measurement within and between treatment groups in OABq score, IIQ-7, daily number of voids, number of nighttime voids, and number of incontinence episodes between the unilateral and bilateral PTNS groups using a pairwise t-test (using a Bonferroni adjustment). These comparisons will result in three sub-analyses: the changes of the primary and secondary outcomes within the unilateral PTNS group, within the bilateral PTNS group, and between the groups (taking the differences between the baseline and last measurement between the groups).

Recruitment and enrollment

Patients with overactive bladder or urge urinary incontinence who have failed behavioral or pharmacologic therapy will have all advanced therapy options presented to them as part of their clinical care by their physician. Those who choose to have PTNS will be approached about the study either by the physician or the research coordinator. If the patient meets eligibility and wishes to participate, they will be consented. In addition, patients who present for their first PTNS visit but were not previously approached about this study will be asked about participating in the study and consented if they are willing

Randomization

Randomization has been performed by a member of the staff at Women and Infants Hospital not part of the research team. Randomization has been concealed in opaque envelopes. Assignment of the randomization envelope to each subject will occur after the patient has signed consent.

Intervention

There will be 12 weekly PTNS treatments of 30 minutes. At the first visit, the participant will complete the OAB questionnaire and the incontinence impact questionnaire. This will be repeated at weeks 4, 8 and 12.

Participants will also be asked to fill out a weekly 2-day bladder diary as is routinely done for PTNS which they will bring to their visit. The bladder diaries will be provided to the participants at the initial visit. Participants will be instructed to fill out the bladder diary for 48 hours including all fluid intake, voids and any leakage.

Participants who are randomized to unilateral PTNS stimulation will have one ankle stimulated for 30 minutes weekly for a total of 12 sessions. Participants who are randomized to bilateral stimulation will have both ankles stimulated simultaneously for 30 minutes weekly for a total of 12 sessions.

PTNS stimulation is performed with a fine needle electrode that is inserted just below the skin in the medial ankle. This needle electrode is connected to a handheld stimulator through a lead wire. The handheld stimulator is then used to administer electrical impulses to the needle electrode increasing the current to a level that leads to a motor response and is comfortable to the participant.

References

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