TITLE:

SHAM CONTROLLED TRIAL OF RAPID INDUCTION PERCUTANEOUS TIBIAL NERVE STIMULATION

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Study Protocol and Statistical Analysis Plan

Sham Controlled Trial of Rapid Induction Percutaneous Tibial Nerve Stimulation

Principle Investigator:
Kenneth Peters, MD

Co Investigator:

Larry Sirls, MD

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I. Background and Rationale

Overactive bladder (OAB) is a common condition with a prevalence ranging from 5.9% to 16.9% in the United States and has been found to increase with age.[2-5] OAB has a negative impact on health related quality of life (QoL),[6, 7] and OAB patients have more anxiety and depression than controls.[8, 9] Primary treatment for OAB include behavioral modifications, such as decreased caffeine intake and timed voiding, and pelvic floor physical therapy. Second line therapy includes anticholinergic medicine/beta-3 adrenoceptor agonists. Unfortunately, compliance and adherence to these medications decreases over time likely due to side effects and/or efficacy.[10-14]

Per AUA/SUFU guidelines, PTNS is a third line recommendation for OAB along with onabotulinumtoxinA (BTX) injection and sacral neuromodulation.[15] The overall objective success (defined as ≥ 50% decrease in urge or urge urinary incontinence (UUI) and 25% reduction in daytime and/or nighttime frequency) of PTNS has been published and ranges from 60% to 71%.[16-19]

In the single sham-controlled trial (SUmiT: n=220), Peters et al reported that 54.5% of PTNS subjects had moderately or markedly improved bladder symptoms on global response assessments (GRA) compared to 20.9% of sham subjects ($p < 0.001$)[1]. PTNS subjects also had statistically significant improvements in frequency, nighttime voids, voids with moderate to severe urgency and UUI episodes compared to sham. Furthermore, significant improvements in bladder symptoms on GRA and quality of life (QoL) as measured with the Overactive Bladder Questionnaire (OABq) were observed after 12 but not 6 treatments, providing support for a 12-week treatment course.[1] In another randomized, placebo controlled trial, Finazzi et al[19] showed 71% response rate in the PTNS group compared to 0% in the sham, placebo group.

Most PTNS studies use induction protocols of one 30-minute treatment a week for 12 weeks (1x12) that provides 6 hours of PTNS time.[1, 16, 17, 20] The SUmiT trial showed statistically significant separation of the treatment arm over the sham only after the 10 week mark, or after 5 hours of stimulation. [Personal communication with Kenneth Peters, MD.] There is interest in speeding up treatment by providing more frequent treatments, providing a longer stimulation time, or both, to more rapidly reach the 6-hour stimulation mark. Finazzi-Agro et al reported a randomized, placebo controlled trial with 12, 30-minute PTNS sessions, 3 times a week with a 71% response rate.[19] Yoong et al placed patients on a truncated 1x6 (one 30-minute treatment for 6 weeks) treatment induction course with a calculated positive response rate of 69.7% after induction.[18] Because the 1x6 course (3 hours of stimulation total) yielded a shorter median time to return of symptoms of 3 weeks (interquartile range of 2), however, they have since concluded a 1x12 course is more cost effective.[21] There is also early data from an implanted chronic tibial nerve stimulation lead study that shows a minimum of 8 hours of tibial nerve stimulation a day results in significant improvement in incontinence episodes per day at one week (L. Sirls, personal communication, abstract submitted to SUFU).

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Overactive bladder is a prevalent condition affecting up to one of every 6 adults.[5] Because PTNS is a minimally invasive option there is much interest in increasing its overall use. Our study will test the concept of whether the PTNS effect is dose (total time of treatment) sensitive, and whether expanding the dosage of each treatment, i.e. from 30 minutes to 2 hours, will provide significant clinical improvement after a one week induction course.

II. Objectives and Endpoints

a. The primary endpoint will be assessed comparing GRA responses between sham and PTNS groups at one week (± 3 days) post induction. This comparison will also be made for all other visits using t-tests or chi-square tests, as appropriate.

b. Secondary endpoints will include comparisons between sham and PTNS groups looking at variables in the 3-day voiding diary and OABq-SF at one week (± 3 days) post-induction. Voiding diary variables include frequency, nocturia, degree of urgency, and urge incontinent episodes. Changes from baseline will also be analyzed.

III. Methodology

The aim of this study is to determine the efficacy of an accelerated course for percutaneous tibial nerve stimulation (PTNS) induction. The standard 12 weekly induction treatments may be a patient burden and a more rapid induction may speed up symptomatic improvement.

We anticipate enrolling 64 patients, in this randomized trial, 32 in each study arm. Patients will be recruited from Beaumont's Women's Urology Center, as well as private Urology offices. Eligible patients will be consented and randomized into 1 of 2 groups. Patients will be enrolled in the study and randomized:

- After all screening activities have occurred and it has been determined that the patient meets all inclusion criteria without the presence of exclusionary criteria.
- After the patient agrees to enroll and comply with the study protocol, regardless of study group assignment.

Patients will be randomized 1:1 to active PTNS treatment or Sham treatment

The process of randomization will be as follows:

- Randomization will be performed using a table of random numbers. Randomization envelopes will be provided by the study's biostatistician. Randomization assignment will be to either active PTNS treatment or Sham treatment. The randomization envelopes will be securely stored in a locked cabinet. The Research Coordinator(s) will ultimately be responsible for maintaining the confidentiality and security of the randomization envelopes.
- The biostatistician will prepare more envelopes, if necessary.
- After the participant is randomized, staff will complete the ***Subject Enrollment and Randomization Log***. The log may be stored in the locked cabinet with the envelopes. Ultimately the log will be stored in the regulatory binder.

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All patients who enroll will be seen and treated at the Beaumont Urology clinical research suite.

Consented patients will complete the Overactive Bladder Questionnaire Short Form (OAB-q SF), 3-day voiding diary and enrollment questionnaire (demographics, medical history, concomitant medications, etc.) prior to study enrollment. A urinalysis via urine dipstick and pregnancy test (for women of child bearing potential) will be performed at screening. If the urinalysis is positive for leukocytes a urine culture will be sent. Patients with a positive urine culture may be treated per standard of care by the study physician. After treatment is completed, a repeat urine will be checked. If repeat urinalysis is negative, the subject will be allowed to complete the voiding diary and continue with study activities. The diary will be collected and reviewed at the first scheduled treatment visit (within 21 days from screening visit). If the patient meets the eligibility criteria, they will be randomized (1:1) into the sham or accelerated PTNS group.

Our goal is to have patients complete all three treatments within one week (7 days) but as there are always impedances (scheduling conflicts, illness, etc.) we will allow patients to complete all treatments within 2 weeks (14 days) if necessary. Patients will be allowed back-to-back treatments (i.e. two days in a row) if they should elect to do so. Adverse events and concomitant medications will be assessed at each treatment whether sham or active PTNS. GRA will be gathered at each visit beginning with the second induction treatment.

After completing the one-week induction consisting of three active or sham treatments, patients will receive a phone call three days (± 1 day) after the last treatment to assess for any adverse events as well as remind them to start filling out their 3 day diary if they have not already begun to do so. This will also serve as a reminder phone call for their upcoming appointment.

One week post-induction (±3 days), patients will return for an office visit. OAB-q SF, GRA and 3-day voiding diary will be collected. We will also assess for adverse events and concomitant medications at this visit. A blinding assessment questionnaire will be administered as well. A urinalysis will be completed.

At 4, 8, and 12 weeks post-induction (± 7 days), patients will return for follow-up appointments. Non-modified OAB-q SF, GRA and 3-day voiding diary will be collected and a urinalysis completed. Maintenance treatments (sham or active PTNS depending on treatment arm) will be given.Maintenance treatment will consist of a 30 minute treatment per standard of care. We will also assess for adverse events and concomitant medications at each of these visits.

After all study activities are complete, patients will be un-blinded at week 12 marking the end of the study. Those who were in the sham arm will be offered the opportunity to continue on to the open label phase of the study. Subjects in the open label phase will be offered the same accelerated treatments as those in the initial active PTNS treatment group. They will have up to 12 weeks to decide if they would like to continue on to the open label phase. This option will also be offered to those who had been previously randomized to the Sham group prior to the protocol amendment, even if they have completed their visit schedule. The follow up schedule will also be conducted in the same manner. Either of the groups can be offered re-induction per insurance requirements if they elect to do so with their

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physician or can seek alternative treatments (BTX, sacral neuromodulation, etc.) per standard of care.

Our goal is to have patients complete all three open label treatments within one week (7 days) again, as there are always impedances (scheduling conflicts, illness, etc.) we will allow patients to complete all treatments within 2 weeks (14 days) if necessary. Patients will be allowed back-to-back treatments (i.e. two days in a row) if they should elect to do so. Adverse events and concomitant medications will be assessed at each treatment whether sham or active PTNS. GRA will be gathered at each visit beginning with the second induction treatment.

After completing the one-week open label induction consisting of three active treatments, patients will receive a phone call three days (± 1 day) after the last treatment to assess for any adverse events as well as remind them to start filling out their 3 day diary if they have not already begun to do so. This will also serve as a reminder phone call for their upcoming appointment.

One week post- open label induction (±3 days), patients will return for an office visit. OAB-q SF, GRA and 3-day voiding diary will be collected. We will also assess for adverse events and concomitant medications at this visit. A urinalysis will be completed.

At 4, 8, and 12 weeks post-open label induction (± 7 days), patients will return for follow-up appointments. Non-modified OAB-q SF, GRA and 3-day voiding diary will be collected and a urinalysis completed. Maintenance treatments using active treatment will be given.Maintenance treatment will consist of a 30 minute treatment per standard of care. We will also assess for adverse events and concomitant medications at each of these visits.

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	Consent and Screening	Week 1: Induction Treatments (Tx)			3 Day Post Induction Phone Call (± 1 day)	1 Week Post Induction Visit (± 3 days)	4 Weeks Post - Induction Visit (± 7 days)	8 Weeks Post- Induction Visit (± 7 days)	12 Weeks Post- Induction Visit (± 7 days)	Part 2/Week 1 Induction Treatments (Tx)			Part 2/ 3 Day post induction phone call (+/- 1 day)	Part 2/1 Week Post Induction Visit (± 3 days)	Part 2/4 Weeks Post – Induction Visit (± 7 days)	Part 2/8 Weeks Post Induction Visit (± 7 days)	Part 2/12 Weeks Post- Induction Visit (± 7 days)
		Enrollment and Tx 1 (within 21 days of screening)	Tx 2	Tx 3						Part 2 Tx 1 (within 12 weeks of un-blinding)	Tx 2	Tx 3					
Consent	X																
Eligibility	X																
Demographics, medical history	X																
OABq-SF	X					X	X	X	X					X	X	X	X
3-day Voiding Diary		X				X	X	X	X	X				X	X	X	X
Pregnancy test	X																
Urinalysis	X	X				X	X	X	X	X				X	X	X	X
Induction Txs		X	X	X						X	X	X					
Maintenance Treatment							X	X	X						X	X	X
GRA			X	X		X	X	X	X		X	X		X	X	X	X
Blinding Assessment						X								X			
Concomitant Medications	X	X	X	X		X	X	X	X	X	X	X		X	X	X	X
Adverse events		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Case Report Forms/Data Entry/Query Resolution	X	X	X	X		X	X	X	X	X	X	X		X	X	X	X
Un-Blinding									X								

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Schedule of Research Activities
*urine culture required if urinalysis is positive for Leukocytes, positive cultures will be treated by the study physicians per standard of care.

All PTNS or sham sessions will be completed by an experienced Urology Research Nurse. The methods described by Peters et al[1] in the SUmiT study will be utilized.

ACTIVE PTNS GROUP:

Position: Patients will be placed in a comfortable position, sitting or supine. The treatment leg will be propped up comfortably on a foot rest but draped and out of view from the patient.

Needle: A 34-gauge needle electrode will be inserted at a 60-degree angle approximately 5 cm cephalad to the medial malleolus and slightly posterior to the tibia (Fig. 1a in the appendix).

Electrode Pads: A PTNS surface electrode will be placed on the ipsilateral calcaneus as well as 2 inactive sham surface electrodes, 1 under the little toe and 1 on the top of the foot. When the PTNS lead set is connected to the Urgent PC stimulator, a current level of 0.5 to 9 mA at 20 Hz was selected based on each patient's foot and plantar motor and sensory responses.

Duration: This treatment will be maintained 60 minutes. The patient will be given a brief break between sessions. To complete the 120-minute session, the same treatment will be performed on the patient's other foot for 60 minutes.

SHAM GROUP

Since patients in the active arm will feel foot stimulation, the sham arm will mimic this feeling without the tibial nerve being stimulated.

Position: The leg and foot will be draped and out of view from the patient. The patient will be placed in a comfortable position, supine or sitting, for easy access to the sham insertion site; for example, the patient may sit with the soles of the feet together and knees abducted and flexed.

Needle: The medial aspect of the lower extremity will be palpated and the tibial nerve site will be identified approximately 5 cm cephalad from the medial malleolus. A Streitberger needle will be used at the tibial nerve insertion site as described above to simulate needle placement without puncturing the skin. The needle will be taped in place.

Electrode Pads: Three electrodes will be placed on the patient's foot, two active TENS electrodes and one inactive TENS electrode. The TENS "grounding pad" will be a gel electrode pad from a TENS unit device that is placed on the bottom of the foot just below the smallest toe. Another gel electrode will be placed on the top of the foot just above the small toe for conduction. These two electrodes will be connected to the TENS unit lead wires for

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sham stimulation. A third, inactive, gel electrode, will be placed near the medial aspect of the calcaneus to mimic the PTNS treatment. Care must be taken to avoid reflexology areas for major organs as the electrode pads are placed. All TENS electrodes are reusable and may be designated for individual patients.

Test and Therapy: The TENS electrode will be connected by lead wires to the Biostim M7 TENS (Biomedical Life Systems, Vista CA) unit or equivalent set at 20 HZ. The TENS unit will be turned on and stimulation slowly increased to the patient's first sensory level.

Duration: This treatment will be maintained 60 minutes. The patient will be given a brief break between sessions. To complete the 120-minute session, the same treatment will be performed on the patient's other foot for 60 minutes.

IV. Risks and Benefits

PTNS or Sham Treatment

Less frequent (occurring from 1% to 10% of the time):

- Discomfort/pain/pressure/tingling at, or near, the stimulation site, or the subject's lower leg or foot
- Redness/inflammation at, or near, the stimulation site
- Possible worsening of OAB symptoms (Stimulating the nerves can either improve, worsen, or have no effect on symptoms) i.e. increased frequency, urgency, nocturia/ leaking due to the procedure

Rare (occurring less than 1% of the time):

- Skin irritation
- Electrode burn
- Allergic reaction to adhesive pad gel
- Numbness of toes
- Allergic Reaction
- Possible increase in lower extremity pain or pelvic pain

If a patient is required to turn off their InterStim or complete a "washout" period to participate in the study there is a chance they may return to baseline urinary symptoms. This may include but is not limited to an increase in urinary frequency, urgency, and urinary leakage.

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V. Eligibility Criteria

Inclusion criteria:

- Women and men ≥ 18 years of age
- Self-reported failed conservative care of behavioral modifications and / or oral medications
- A score of ≥ 4 on question 1 of the OAB-q symptom bother short form completed by the patient at screening
- Average urinary frequency of ≥ 8 voids per day as recorded on initial 3-day voiding diary
- Self-reported bladder symptoms ≥ 3 months
- On a stable dose of antimuscarinics/beta-3 agonists for ≥ 4 weeks, and willing to remain on the medication for the duration of the study **OR** discontinued antimuscarinics/beta-3 agonists for ≥ 2 weeks
- Capable of giving informed consent
- Ambulatory and able to use toilet independently without difficulty
- Capable and willing to follow all study-related procedures

Exclusion criteria:

- Pregnant or planning to become pregnant during study duration
- Diagnosis of neurogenic bladder
- Botox use in bladder or pelvic floor muscles within past 12 months
- Pacemakers or implantable defibrillators
- Current urinary tract infection
- Active use of neuromodulation in any other form. If patient has InterStim, must be turned off for 2 weeks for a washout period and remain off during the entirety of the study.
- Current use of Transcutaneous Electrical Nerve Stimulation (TENS) in pelvic region, back or legs
- Previous PTNS treatment who received greater than 6 treatments. Those who have received less than 6 treatments will be allowed to screen if the last treatment was at least 6 months prior to screening.
- Use of investigational drug/device therapy within past 4 weeks
- Participation in any clinical investigation involving or impacting gynecologic, urinary or renal function within past 4 weeks
- Current or past history of any physical condition that, in the investigator's opinion, might put the subject at risk or interfere with study results interpretation (i.e. pelvic cancer or pelvic radiation treatment)

VI. Data Analysis

A biostatistician will perform all statistical analyses using SAS or similar statistical software. Descriptive statistics will be calculated. A completer analysis will be conducted for those who finish the study per protocol. The primary endpoint will be assessed comparing GRA responses between sham and PTNS groups at one week (± 3 days) post induction. This comparison will also be made for all other visits using t-tests or chi-square tests, as appropriate.

Secondary endpoints will include comparisons between sham and PTNS groups looking at variables in the 3-day voiding diary and OABq-SF at one week (± 3 days) post-induction.

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Changes from baseline will also be analyzed. This comparison will also be made for all other visits using appropriate statistical tests.

Other statistical analyses will be completed as appropriate.

An intent to treat analysis which will identify any subject not assessed at 12 weeks post-induction as a failure will be conducted; a minimum of 1 induction treatment will be required to be included in the analysis.

Calculating Sample Size:
A sample size estimate of approximately 64 patients, 32 per study arm, was calculated using the Z test with pooled variance using a 58.3% responder rate in the PTNS group and a 21.9% responder rate in the sham group with a 5% significance level and 80% power; this also accounts for a 10% drop out rate. (Peters et al[1] reported 58.3% and 21.9% responder rates for PTNS and sham groups respectively for an as-followed completer analysis and 54.5% and 20.9% responder rates for PTNS and sham groups respectively with an intent to treat analysis. We used the as-followed responder rates in calculating our sample size.)

VII. Data Safety Monitoring Plan

Ongoing safety monitoring will be performed by the study staff, including the Principal Investigator (PI) and co-investigators. The PI will have ultimate responsibility of assuring patient safety. Safety issues will also be addressed in the annual reports to Beaumont's Investigational Review Board (IRB).

Additional data safety monitoring procedures include:

- Research Administration's Clinical Research Quality and Process Improvement Program (CRQIP) will perform in-house monitoring of the first patient enrolled after the completion of visit 1
- An audit of the study records after the first 10 patients are enrolled and at the half way point of enrollment by an RN in the Urology Research Department that is not directly involved with the research study. This will be done to ensure the safety of subjects and lack of significant adverse effects.

As an on-going plan, any adverse effects (prolonged irritation, hemodynamic changes, significant pain, or other deemed significant by clinicians) will be reported to the research nurse and then to the PI at the time of the event. Adverse events, serious adverse events, and unanticipated problems not listed in the risks section of this protocol will be reported per IRB guidelines.

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