A Randomized Trial of Transcutaneous Nerve Stimulation for Neurogenic Bladder Patients
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Specific Aim
To determine the efficacy of transcutaneous tibial nerve stimulation (using skin patch electrodes) for the treatment of patients with neurogenic bladder symptoms.

Hypothesis
We hypothesize that the study protocol of transcutaneous tibial nerve stimulation performed at home during 30 minute sessions, 3x/week, for 12 weeks will be associated with a statistically significant improvement in neurogenic bladder symptoms.

Background: Significance & Innovation
A variety of neurologic diseases can lead to bladder dysfunction, including multiple sclerosis, Parkinson's disease, stroke, dementia, cerebral palsy, and spinal cord injury(1). This neurogenic associated bladder dysfunction significantly impacts patients quality of life(2,3). Treatment consists of conservative measures, and often the use of anticholinergic medications. Anticholinergic medications have been primarily studied for the more common indication of overactive bladder(4). In small clinical trials and case series, these medications have demonstrated improvements in urgency incontinence, and urodynamic parameters (such as bladder capacity and detrusor pressure) among neurogenic bladder patients(5). However, anticholinergic medications have a number of undesirable side effects, including dry mouth, constipation and cognitive changes(5,6). This is particularly bothersome in the neurogenic population which commonly use other medications associated with dry mouth(7), have neurogenic constipation(1) and have existing cognitive impairments. These anticholinergic side effects have been shown to significantly limit medication compliance among both the general population(8), and neurogenic bladder patients(9). Even with anticholinergic medications, many patients have residual and bothersome urinary symptoms(3). The recently introduced mirabegron is an alternative oral medication that works through stimulation of the beta 3 receptor in the bladder(10), and studies are underway evaluating its efficacy in the neurogenic bladder population.

Neurogenic bladder patients who find anticholinergics ineffective or intolerable are a challenging population to treat. The recently updated European Association of Urology guidelines for neurogenic bladder list intradetrusor onabotulinumtoxinA and sacral neuromodulation as potential treatment options for neurogenic bladder patients. While onabotulinum toxin injection is well established and commonly used for neurogenic bladder dysfunction(11), it is not appropriate if a patient is unable or unwilling to perform self catheterization in the event of urinary retention. The risk of urinary retention is considerably higher among patients with neurogenic dysfunction(12) compared to the overactive bladder population. The side effective profile and limited efficacy of anticholinergics, and the potential risk of catheterization with intravesical onabotolinium toxin creates a need for neuromodulation treatment modalities.

Neuromodulation of the lower urinary tract has been studied for over a century(13). The application of low level electrical energy either directly to the sacral nerve roots, or through a peripheral nerve originating from the sacral spinal cord, is thought to mediate somato-visceral interactions within the sacral spinal cord, reset somatic afferents and modulate the micturition reflex(13). The ability of sacral neuromodulation to prevent neurogenic bladder systems in the acute setting of a spinal cord injury has been reported(14), and this underscores importance of studying neuromodulation in patients with neurologic disease.

One form of neuromodulation is percutaneous tibial nerve stimulation, which involves placing a small needle above the medial malleolus in order to directly stimulate the posterior tibial nerve. In animal

models, the stimulation of the tibial nerve has been shown to suppress detrusor overactivity(15), and to alter neuronal metabolic activity in the sacral spinal cord(16). The exact mechanism of action in humans is poorly understood, however there is evidence that percutaneous tibial nerve stimulation can modify the somatosensory pathway(17), and alter urodynamic parameters(18) in humans.

The clinical evidence for the efficacy of percutaneous tibial nerve stimulation for overactive bladder has been well reviewed in a recent systematic review and the AUA/SUFU overactive bladder guidelines(19,20). Variable definitions of success have been used (such as clinical parameters, urodynamic outcomes, and validated patient reported outcome measures), with general success rates of 55-80% after 3 months of treatment, and evidence of efficacy up to 3 years with a monthly maintenance protocol(21). The RCT evidence is summarized in Table 1 below. Across all clinical trials and the systematic review, no serious treatment related adverse effects were seen, and minor adverse events were limited to transient skin irritation, leg cramps or toe/foot pain.

In summary, neurogenic bladder symptoms often have a significant impact on a person's quality of life. A large proportion of people are not well treated with anticholinergic medications, and may not be candidates for intravesical onabotolinium injection. Tibial nerve stimulation is a minimally invasive form of neuromodulation which may be a potential effective treatment, however there is a lack of high quality evidence to support this option. Transcutaneous delivery of electrical current with patch electrodes may be an effective means of tibial nerve stimulation that allows the patient to have the convenience of an at home treatment schedule, with very low associated costs. The objective of this study is to conduct a pilot randomized, sham-controlled, clinical trial to assess the short-term effectiveness of transcutaneous posterior tibial nerve stimulation for patients with neurogenic bladder symptoms that are not adequately controlled with pharmacologic therapy.

Design and methodology

Study design: This is a randomized, double-blind, sham-controlled, clinical trial. The primary intervention is 30 minute sessions, 3x/week, for 12-13 weeks of transcutaneous tibial nerve stimulation sessions carried out at home. The sham intervention will consist of the same treatment schedule, except with the application of transcutaneous nerve stimulation to the lateral aspect of the lower leg, away from the tibial nerve. Patients will undergo a 12-13 week treatment course. The patient and the treating physician will be blinded to the group assignment of the patient. Randomization will be done using a random number generator, and study assignment will only be released at the end of the study. Only the study nurse instructing the patient on placement of the study electrodes will know the patient assignment. The effectiveness of our sham protocol will be evaluated with a question during week 2-3 asking if they think they are in the active or sham group. The study visit schedule is outlined in figure 1.

Figure 1. Proposed study schedule

STUDY SCHEDULE	Visit 1 Screening	Visit 2 Randomization	Telephone Followup	Visit 3 End of study
Visit Windows	*1- 4 weeks prior to Randomization*	*Week 0*	*Every 2-3 Weeks*	*12-13 Weeks*
Documentation of Consent	X			
Medical History and Physical Exam	X			
Inclusion/ Exclusion Criteria Review	X			
Medication and Health Review	X			X
Urine Pregnancy Test	X			
PPBC Questionnaire	X		X (week 6-7 only)	X
Qualiveen-SF/NBSS Questionnaire	X			X
3 day Voiding diary	Diary Provided	Completed Diary Returned & Provided for Visit 3		Completed diary returned
24hr Urinary Pad test	Supplies Provided with instruction	Pads Returned & Provided for Visit 3	Pad test done 1-7 days prior to visit 3	Pads Returned
Randomization		X		
Initial 30 minute treatment session in clinic with nurse supervision		X		
Assessment of treatment masking			X (week 2-3 only)	
Assessment of compliance, review instructions, address any adverse events or questions			X	
Physician assessment of benefit				X

Inclusion criteria

1. >18 years of age, with a clinical condition associated with neurogenic bladder dysfunction (multiple sclerosis, Parkinson's disease, stroke, dementia, cerebral palsy, spinal cord injury)(27).
2. Failure of behavioral measures and/or pharmacologic therapy to adequately control neurogenic bladder symptoms.

Exclusion criteria

1. Current or previous percutaneous/transcutaneous tibial nerve stimulation or sacral neuromodulation therapy
2. Stress predominant urinary incontinence
3. Newly added bladder medication or dose change with the last 2 months (Tamsulosin, Silodosin, Alfuzosin, Terazosin, Baclofen, Diazepam, amitriptyline, imipramine, DDAVP, tolterodine, oxybutynin, fesoterodine, darifenacin, solifenacin, trospium, mirabegron)
4. Intravesical botulinum toxin use within the last 1 year
5. Implanted pacemaker or defibrillator
6. History of epilepsy
7. Unable or unwilling to commit to study treatment schedule
8. Pregnant, or possible pregnancy planned for the duration of the study period
9. Active skin disease of the lower legs (dermatitis, cellulitis, eczema, trauma)
10. Documented allergy to patch electrodes or their adhesive
11. Metallic implant within the lower limb

Intervention: Transcutaneous electrical nerve stimulation is a safe and effective therapy that has been used by physicians and other health professionals for a variety of conditions such as pain and muscle

rehabilitation(28,29). Two adhesive patch electrodes will be applied to one of the patient's lower limb, and the location used will be based on their treatment assignment (active treatment versus sham). The initial treatment will be carried out in the clinic under the supervision of the investigating physician, with training provided for the patient on proper use of the device by the study nurse. The remaining treatments will be detailed on a calendar for the patient, with telephone contact every 2-3 weeks with research staff to assess compliance. When undergoing active treatment, patients will have the electrodes applied posterior to the medial malleolus, and 5-10 cm above the medial malleolus of the same leg, just behind the medial tibial edge. As per previous studies involving transcutaneous posterior tibial nerve stimulation for neurogenic bladder and overactive bladder(30-33) and similar to percutaneous tibial nerve stimulation(26), we will use the bipolar stimulation setting, with a frequency of 10 Hz, 200ms pulse, and the amplitude will be titrated up to patient's maximum non-painful tolerance or toe twitch in the case of complete SCI(30) (between 0.5-20mA). For patients undergoing sham treatment, they will have the patch electrodes placed on the lateral side of the lower limb, and instructed to keep the current setting stable at 1mA. This will prevent any meaningful stimulation of the tibial nerve, while still delivering a slight tingling sensation to simulate active treatment.

Primary outcome measure: We will use Patient Perception of Bladder Condition question, which is a common used endpoint in overactive bladder studies. Although it has not been formally studied in neurogenic bladder, its face validity is high, and it has been used for this purpose in the past(34). It is an ordinal scale from 0-5 ("My bladder does not cause me any problems at all" to "my bladder causes me many severe problems"). In the general population it is a valid, reliable and responsive single question(35). Patients will be categorized as responders (score improvement by 2 points between screening visit 1 and end of study visit 3) or non-responders.

Secondary outcome measures:

1. Neurogenic bladder symptom score (NBSS): valid and reliable tool for assessing neurogenic bladder symptoms(36).
2. The Qualiveen-SF is a measure of neurogenic bladder related QOL, which has been specifically shown to valid, reliable and responsive in neurogenic bladder(37,38).
3. 3-day voiding diary parameters (daily voiding frequency, functional bladder capacity, mean voided volume, longest time between voids, nocturia, number of urgency incontinence episodes). This is a valid and reliable measure of urinary symptoms(39).
4. Quantification of urinary incontinence with 24hr pad weights. This is stable, reliable and responsive measure of the degree of urinary incontinence(40,41), and will be analyzed for the subgroup of patients with incontinence.
5. Physician assessment of benefit will be completed based on a standard clinical history at study visit 3 (end of study), and graded on a 7 point global response assessment.

Sample size: Using previous percutaneous tibial nerve stimulation studies as a guide(26), we estimate 20% of sham patients and 60% of actively treated patients will be responders. Using the Chi-square test, a two-sided alpha of 0.05, and 80% power, 27 patients per group will be required. Our final sample size, adjusting for a 10% dropout rate, is 60 (30 per group). Our sample size calculation is based on our intention to treat analysis.

Statistical Analysis: Analysis of our primary outcome will be an intention to treat analysis (using the chi squared test) based on the proportion of patients classified as a responder using the change in the patient perception of bladder condition. A secondary analysis, based on a per protocol analysis (for efficacy) will be performed for patients who completed at least 80% of the treatment sessions for at least 20 min each (determined from patient completed treatment diary, and electronic usage log in the TENS device). Secondary endpoints will be analyzed as appropriate using the students t-test or chi squared test. All data analysis will be carried out using SAS 9.2.

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