A Randomized Trial of Transcutaneous Nerve Stimulation for Overactive Bladder Patients

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Statement of Objective

To determine the efficacy of transcutaneous tibial nerve stimulation (using skin patch electrodes) for the treatment of women with clinical symptoms of overactive bladder.

Background

Overactive bladder is a clinical diagnosis characterized by "urinary urgency, often with frequency and nocturia, with or without urgency urinary incontinence"[2]. Approximately 16% of adult women meet the clinical definition for overactive bladder, and approximately 1/3 of them will have urgency incontinence[3,4]. While a small proportion of patients do see their symptoms resolve after a year, for the vast majority this is a chronic condition[4,5]. Although it is not inherently dangerous, overactive bladder is an important condition given its wide-ranging impact on overall quality of life and mental health[3]. The magnitude of impact across different domains of quality of life is similar to chronic diseases such as diabetes[6]. In addition, the financial impact is substantial; in the United States this has been estimated at $12 billion annually[7].

Hypothesis

I 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 overall bladder symptoms.

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 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 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 more detail in Appendix 2.

Inclusion criteria

1. Female, >18 years of age, with the clinical diagnosis of overactive bladder (based on the current ICS definition[2]).
2. Failure of behavioral measures and pharmacologic therapy to adequately control overactive bladder symptoms.
3. Baseline patient perception of bladder condition score of 2 or higher.

Exclusion criteria

1. Current or previous percutaneous 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. Abnormal sensory function of the lower limb
12. 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[26,27]. We will use the EV-906 Digital TENS machine (from Everyway Medical Instruments Co Ltd, Health Canada License #73631). 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[25,28,29] and similar to percutaneous tibial nerve stimulation[23], 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 nonpainful tolerance (between 0.5-10mA). For patients undergoing sham treatment, they will have the patch electrodes placed on the lateral side of the lower limb, and told 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: The patient perception of bladder condition (PPBC) is a commonly used measure for global response in overactive bladder studies. It is an ordinal scale from 0-5 (Appendix 3). It is a valid, reliable and responsive single question asking the patient to select the degree of problems associated with their bladder condition[30]. Patients will be categorized as responders (score improvement by 2 points between screening visit 1 and end of study visit 3) or nonresponders.

Secondary outcome measures:

1. OAB related quality of life (OAB-q SF) Valid, reliable, and responsive tool for assessing symptom bother and OAB related quality of life[31].

2. 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[32].
3. Quantification of urinary incontinence with 24hr pad weights. This is stable, reliable and responsive measure of the degree of urinary incontinence[33,34].
4. 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.

Data Analysis and Sample Size

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.

Using previous percutaneous tibial nerve stimulation studies as a guide[23], 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.

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Appendices

A randomized trial of transcutaneous posterior tibial nerve stimulation for refractory overactive bladder patients

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1. Key randomized controlled trials of percutaneous tibial nerve stimulation
2. Schedule of visits for study patients
3. Patient perception of bladder condition (PPBC)

Appendix 1. Randomized controlled trials evaluating percutaneous tibial nerve stimulation.

Study	Sample	Design	Intervention/Control	Outcome
OrBIT[1]	100 adults with urinary frequency >8/day and OAB	Randomized controlled trial. Intention to treat.	PTNS (Urgent PC): 0.5-0mA, 20Hz, unilateral needle electrode, weekly 30 minute sessions x 12 weeks. Control: Tolterodine 4mg OD x 90 days	Intervention: 80% global response assessment moderate or markedly improved Sham: 55% global response assessment moderate or markedly improved. P<0.01
SUmiT[2]	220 adults with OAB	Randomized controlled clinical trial. Intention to treat.	PTNS (Urgent PC): 0.5-10mA, 20Hz, unilateral needle electrode, weekly 30 minute sessions x 12 weeks. Control: Sham group with identical setup but no active electricity.	Intervention: 55% global response assessment moderate or markedly improved Sham: 21% global response assessment moderate or markedly improved. P<0.001
PTNS versus placebo[3]	35 women with urodynamic DO and wet OAB	Randomized controlled trial. Intention to treat.	PTNS (Urgent PC): 0.5-10mA, 20Hz, unilateral needle electrode, 30 minute sessions 3x/week x 12 weeks. Control: Sham group with identical setup but no active electricity.	Intervention: 71% global response assessment moderate or markedly improved Sham: 0% global response assessment moderate or markedly improved. P<0.001
PTNS vs Oxybutynin vs Combination for OAB[4]	70 women with OAB	Randomized controlled trial.	PTNS (Urgent PC): 0.5-0mA, 10Hz, unilateral needle electrode, weekly 30 minute sessions x 12 weeks. Comparator 1: Oxybutynin SR 10mg PO OD x 12 weeks Comparator 2: Both PTNS and Oxybutynin x 12 weeks	Significant reduction among all groups, and no difference between groups based on ICIQ-SF score.

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Appendix 2. 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
OAB-q SF Questionnaire	X			X
3 day Voiding diary	Diary Provided	Completed diary returned & new one provided for Visit 3		Completed diary returned
24hr Urinary Pad test	Supplies Provided with instruction	Pads Returned & new ones 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

Appendix 3. Patient perception of bladder condition. Scored 0 (no problems) to 5 (severe problems).

(PPBC)

Which of the following statements describes your bladder condition best at the moment? Please mark ‘‘X’’ in one box only.

My bladder condition does not cause me any problems at all.

My bladder condition causes me some very minor problems.

My bladder condition causes me some minor problems.

My bladder condition causes me (some) moderate problems.

My bladder condition causes me severe problems.

My bladder condition causes me many severe problems.