A randomized, controlled trial of transcutaneous tibial nerve stimulation to treat overactive bladder and neurogenic bladder patients

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Abstract

Introduction: We aimed to determine if transcutaneous tibial nerve stimulation (TTNS) is effective at treating overactive bladder (OAB) symptoms among neurogenic and non-neurogenic patients.
Methods: We conducted a randomized, double-blind, sham-controlled study. Adult patients were recruited from one of two groups: 1) women with OAB; and 2) patients with neurogenic disease and bladder symptoms. The intervention was stimulation of the posterior tibial nerve, for 30 minutes, three times per week for 12 weeks at home using transcutaneous patch electrodes. The primary outcome was improvement of the patient perception of bladder condition (PPBC). We used ANCOVA (with adjustment for baseline values) and followed the intention-to-treat principle; we reported marginal means (MM) and a $p<0.05$ was considered significant.
Results: We recruited 50 patients (OAB n=20, neurogenic bladder n=30); 24 were allocated to the sham group and 26 to the active TTNS group. Baseline characteristics in both groups were similar. At the end of the study, there was no significant difference in the PPBC between sham or active groups: 13% (3/24) of sham patients and 15% (4/26) of active TTNS patients were responders (p=0.77), and the marginal mean of the end-of-study PPBC score was 3.3 (95% confidence interval [CI] 2.8–3.7) vs. 2.9 (95% CI 2.5–3.4), respectively (p=0.30). Similarly, there were no significant differences in secondary outcomes (24-hour pad weight, voiding diary

parameters, or condition-specific patient-reported outcomes). The results were similar within the OAB and neurogenic bladder subgroups.
Conclusions: TTNS does not appear to be effective for treating urinary symptoms of people with OAB or neurogenic bladder dysfunction.

Introduction

Overactive bladder is a condition characterized by "urinary urgency, often with frequency and nocturia, with or without urgency urinary incontinence"(1). Approximately 16% of adult women meet the clinical definition for overactive bladder, and approximately 1/3 of them will have urgency incontinence(2). Similar symptoms can arise as a result of neurogenic lower urinary tract dysfunction. These symptoms, whether idiopathic or neurogenic in origin, are important given the wide-ranging impact on quality of life, mental health(3), and finances(4). While behavioral and medical therapy is effective[5,6], they have low long-term persistence and undesirable side effects.(5)

Neuromodulation of the lower urinary tract has been studied for over a century.(6) 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. Sacral neuromodulation and peripheral percutaneous tibial nerve stimulation (PTNS) are accepted third-line options for refractory overactive bladder patients(7) and have been used in select groups of patients with neurogenic bladder dysfunction.(8)

Transcutaneous tibial nerve stimulation (TTNS) is a modification of the percutaneous technique. Instead of using a needle, patch electrodes are placed on the skin over the tibial nerve. The potential advantages include a lack of serious treatment related side effects, a non-invasive approach, the ability to self-administer the treatment at home, and a low per-treatment cost. However, recent systematic reviews have identified the need for further high quality evidence to support this modality.(9) Our objective was to carry out a randomized, double blind, sham controlled pilot trial of TTNS among women with overactive bladder and patients with neurogenic disease and overactive bladder symptoms.

Methods

Study participants

We recruited two specific patient populations. The first group was adult women with the clinical diagnosis of overactive bladder (based on the ICS definition) who had failed behavioral measures and a trial of medical management. The second group was adults with a relevant neurologic disease who had failed behavioral therapy and a trial of medical management and had

urgency with or without urge incontinence. All women had to have a baseline Patient Perception of Bladder Condition (PPBC) ≥2 ("my bladder condition cause me some minor problems"). Exclusion criteria for both groups included those with: prior neuromodulation, bladder related medication change in the prior 2 months, predominate stress incontinence, or intravesical onabotulinum use in the prior year. Safety exclusions included implanted pacemaker/ defibrillator, history of epilepsy, potential for pregnancy during the study, bilateral skin disease affecting the lower legs, or bilateral metallic lower limb implants.

Study design

This was a single center, randomized, double-blind, sham-controlled study, which we carried out from January 2016 to March 2019. We used a parallel groups (with equal 1:1 distribution), and a superiority design was used. Participants were recruited from a tertiary functional urology practice. During visit one, patients were assessed with a history and physical exam. They completed the relevant patient reported outcome measures (PROM) and were asked to complete a 24 hour pad test(10) and 3-day voiding diary (based on their voiding/catherization patterns) for the next study visit. During visit two (conducted within the next 1-2 weeks), the voiding diary and pad test was returned, and the patient was randomised to either active TTNS treatment or sham by study staff not involved in the outcome measurements. Randomization was done using a random number generator, and both the study investigator and patient were unaware of the group assignment. Separate randomisation sequences for the overactive bladder group, and the neurogenic bladder group were used. Patients were provided with an EV-906 digital TENS machine. If they were randomised to active TTNS treatment, the patient placed the skin surface electrodes posterior and 5-10 cm above the medial malleolus of the same leg, just behind the medial tibial edge. As per previous studies involving TTNS for neurogenic bladder and overactive bladder(9) and similar to PTNS(11), patients used the bipolar stimulation setting, with a frequency of 10 Hz, 200ms pulse, and the patient was instructed to titrate the amplitude of the current to their maximum non-painful tolerance or toe twitch, and maintain this for 30 minutes. If they were randomised to sham treatment, they were instructed to place the patch electrodes on the lateral side of the lower leg and use the same settings as the active treatment group, but without instructions to increase the amplitude of the current beyond their sensory threshold. This was designed to prevent any meaningful stimulation of the tibial nerve, while still delivering a tingling sensation to simulate active treatment. Patients performed the first treatment in the clinic under supervision, and then were asked to continue to do this at home three times per week for 12 weeks. A telephone followup was done at 2-3 weeks to assess treatment compliance, potential complications, and the effectiveness of our allocation concealment (by asking the patient which group they believed they were assigned to). Patients were asked to keep a weekly treatment log documenting their treatment sessions. At their final visit, they completed the same PROMs, and returned a treatment log, a new 3-day voiding diary and a 24hr pad test. While maintaining

allocation concealment, the study investigator also assigned a physician perception of benefit score based on their subjective comments regarding their symptoms; a global change score of 7 (a very great deal better) to -7 (a very great deal worse) was used.

Institutional ethics approval and trial registration was obtained prior to commencing the study and all participants provided written consent.

Outcomes

The primary outcome was the PPBC question, which is a commonly used endpoint in overactive bladder studies. It is an ordinal scale from 0 ("My bladder does not cause me any problems at all") to 5 ("my bladder causes me many severe problems"). It is a valid, reliable and responsive single question(12), and has been used in neurogenic patient populations previously(13). We specified *a priori* that responders were patients whose PPBC score improved by ≥2 points during the study. Secondary outcomes included 24 hour pad weight (which is a stable, reliable and responsive measure of the degree of urinary incontinence(10)), 24 hour urinary frequency and functional capacity (based on 3-day voiding diary(14)), and additional population specific PROMs. Patients with overactive bladder completed an OAB related quality of life tool (OAB-q SF) which has both a symptom bother scale and a quality of life (QOL) score; they were transformed into a scale ranging from 0-100.(15) Patients with neurogenic bladder completed the Neurogenic Bladder Symptom Score (NBSS, with scores ranging from 0 to 72) (16) and the Qualiveen-SF (a measure of neurogenic bladder related QOL).(17) For all PROMs, a higher score is a worse outcome.

Statistical analysis

The hypothesis was that TTNS would improve our outcome measures compared to sham patients. Using previous PTNS studies as a guide(11), we estimated 20% of sham patients and 60% of actively treated patients would be responders. Using the Chi-square test, a two-sided alpha of 0.05, and 80% power, 27 patients per group would be required.

Data is presented as medians and interquartile ranges (IQR). We followed the intention-to-treat principle for the primary analysis set (all randomized subjects were included). Results from the 12-week PPBC, pad tests, voiding diary and population specific PROMs were compared between the TTNS group and the sham group. Voiding diary parameters were summarized for the 3 days. The analysis was carried out on de-identified data and the assessor was blinded to the identity of the allocation groups. Analysis of covariance (ANCOVA) was used to assess for the differences between outcomes; results are reported as marginal means with 95% confidence intervals (CI) for each group. ANCOVA allowed for adjustment for the baseline values, and therefore accounts for potential differences between groups that exist prior to randomisation. Effect sizes were estimated with the partial Eta squared. Differences in

proportions were tested with logistic regression (also with adjustment for the baseline values). A two-sided p-value <0.05 was considered significant, and the analysis was carried out with SPSS version 25.

Results

We screened 150 patients for eligibility, and of these 50 patients were randomized to either sham treatment (n=24) or active PTNS (n=26) (Figure 1). Our study population was primarily middle-aged women who had used oral therapies; most had tried pelvic floor muscle exercises and pad weights were a median of 40g (Table 1). The median PPBC was 4 ("my bladder condition causes me severe problems"). Recruitment was terminated December 31, 2018 (predetermined end date). The baseline characteristics of the neurogenic bladder cohort and OAB cohort alone were similar (online supplement, table s1a, s1b). The majority of the neurogenic bladder patients had multiple sclerosis (73%, 22/30), and only 10% (3/30) of the neurogenic bladder patients used intermittent catheters with the remainder being able to void spontaneously.

For the primary outcome of PPBC at the end of the 12-week treatment period, 13% (3/24) sham patients, and 15% (4/26) active TTNS patients met our definition of responders (p=0.77). The marginal mean of the final PPBC score, (which is corrected for the baseline PPBC) was 3.3 (95% CI 2.8-3.7) versus 2.9 (95% CI 2.5-3.4) respectively (p=0.30). The effect size was very small (0.02). There was no missing data for our primary analysis or the PROMs, and <10% of voiding diary or pad weight data was missing. Secondary outcomes are shown in Table 2, and there were no statistically significant differences between sham and active TTNS. Exploratory analysis of the individual OAB and neurogenic cohorts are similar to the main analysis (online supplement, table s2a, s2b).

There were no adverse events during the study, and no patients reported worsening of their symptoms as a result of the study. Patient compliance was high among the patients who completed the study: the median percentage of required treatments completed during the study period was self-reported as 97% (interquartile range 90%-100%). Our assessment of allocation concealment at 2 weeks revealed that 52% of patients correctly guessed their assigned allocation (26/50), and of those that did correctly guess their allocation, 42% (10/24) were in the active TTNS group, and 58% (14/24) were in the sham group.

Discussion

This randomized, sham controlled clinical trial found that TTNS was not effective at improving bladder function among non-neurogenic and neurogenic bladder patients with symptoms of overactive bladder. There were no statistically significant differences in our primary outcome (PPBC scale), and no significant improvements in secondary outcomes such as pad weight, voiding diary parameters, or condition specific PROMs. While some of the results did seem to slightly favor the TTNS group, the associated effect size was extremely small, and likely not

clinically significant.

There is good evidence that PTNS is an effective therapy for OAB(18), and a systematic review found promising evidence that it is also effective in patients with neurogenic lower urinary tract dysfunction.(8) Reported success rates for overactive bladder patients using PTNS are 55-80% after 3 months of treatment, and there is evidence of continued efficacy up to 3 years with the use of a monthly maintenance protocol(19). The exact mechanism of action in humans is poorly understood, however tibial nerve stimulation has been shown to modify the somatosensory pathway(20), and alter urodynamic parameters(21) in humans. However, the efficacy of TTNS is not as clear. A recent systematic review identified 10 randomized studies involving TTNS for neurogenic bladder or OAB. (9) An additional randomized trial has since been published which was a non-inferiority study that compared TTNS to PTNS in patients with overactive bladder. (22) All of these RCTs are small (<100 patients, similar to our study), and only 3 compared TTNS to a sham intervention. None of them assessed the effectiveness of their sham intervention at maintaining blinding. The remaining RCTs compared TTNS to a medication or alternative intervention, and in most cases, they did not properly blind patients (for example the TTNS group did not get a matched placebo pill). A properly concealed sham comparator group is essential given the 20-30% placebo response in PTNS studies(11), and OAB research in general. All of the randomized trials identified in Booth's systematic review had either an unclear or high risk of bias. In addition, the urinary incontinence cure rates reported were extremely optimistic (25-45%), given that a rigorous, well-reported randomized trial comparing intravesical onabotulinum toxin and solifenacin for idiopathic urgency incontinence measured urgency incontinence cure rates of 27% and 13% respectively. (23) In gastroenterology, PTNS was touted as a treatment for several disorders of bowel function, and initial small randomized trials reported positive results; however a large, well conducted RCT did not show any benefit among patients with fecal incontinence. (24)

The efficacy of TTNS is likely limited by the increased stimulation that is necessary to activate the tibial nerve compared to PTNS. The ability to reach this increased stimulation is limited by the patient's pain threshold. Novel methods of delivering non-invasive stimulation to the tibial nerve have been described(25,26), and perhaps these will have improved efficacy. Another challenge is determining the optimal treatment parameters, which are often arbitrary and variable among different studies. (9) A large randomized, multi-center trial evaluating TTNS for overactive bladdery symptoms among patients with Parkinson's disease is underway in France, and this will likely provide the strongest evidence yet for or against TTNS for the treatment of bladder symptoms (NCT02190851).

Strengths of our study include a sham group in which we confirmed adequate allocation concealment. We used multiple validated subjective and objective outcomes and had high adherence to the study protocol; patients did not appear to have issues with adherence to the treatment protocol. Limitations of our research include the generalizability of our results, as for

the most part our study population had urgency incontinence and had failed prior oral treatment; TTNS may have better efficacy among patients with less severe symptoms, or among less refractory patients. Our overall sample size of 50 patients is modest. While we hoped to recruit more patients, investigator-driven research supported by small grants does not allow multi-site participation. Many patients declined participation because of the travel and appointments associated with a clinical study, or because they opted to directly pursue third line therapies. The proportion of patients who responded to active treatment was 15%, and the 95% confidence interval for this proportion is 4 to 35%; this range is much lower than originally hypothesized responder proportion of 60%, therefore despite the small sample size, we do not feel that this treatment would be efficacious with our current protocol, even with a larger sample size. To power a study to detect a difference between 13% and 15% would require over 9000 patients, and this difference would be unlikely to be clinically relevant. The small size of our two patient subgroups (OAB and neurogenic bladder symptoms) means these groups aren't appropriately powered to demonstrate differences, and therefore we can't definitely conclude there isn't a more clinically relevant effect in one of these cohorts, and our sample size precluded any meaningful post-hoc subgroup analysis.

Conclusions

In a randomized, sham controlled clinical study of TTNS in patients with overactive bladder symptoms with or without an associated neurogenic condition, TTNS did not show efficacy in improving patient's perception of their bladder function or improving objective parameters such as pad weights or voiding diary parameters. Given the heterogenous results reported in the literature, further study is necessary to determine whether specific patient populations might benefit from TTNS, or if novel ways of delivering non-invasive tibial nerve stimulation can improve efficacy. Conducting non-industry-sponsored clinical trials in academia continues to be a challenge, and the trade-off between a tightly controlled patient population and recruitment feasibility is an important consideration when designing pilot studies.

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Figures and Tables

Fig. 1. CONSORT flowchart of participants in the study.

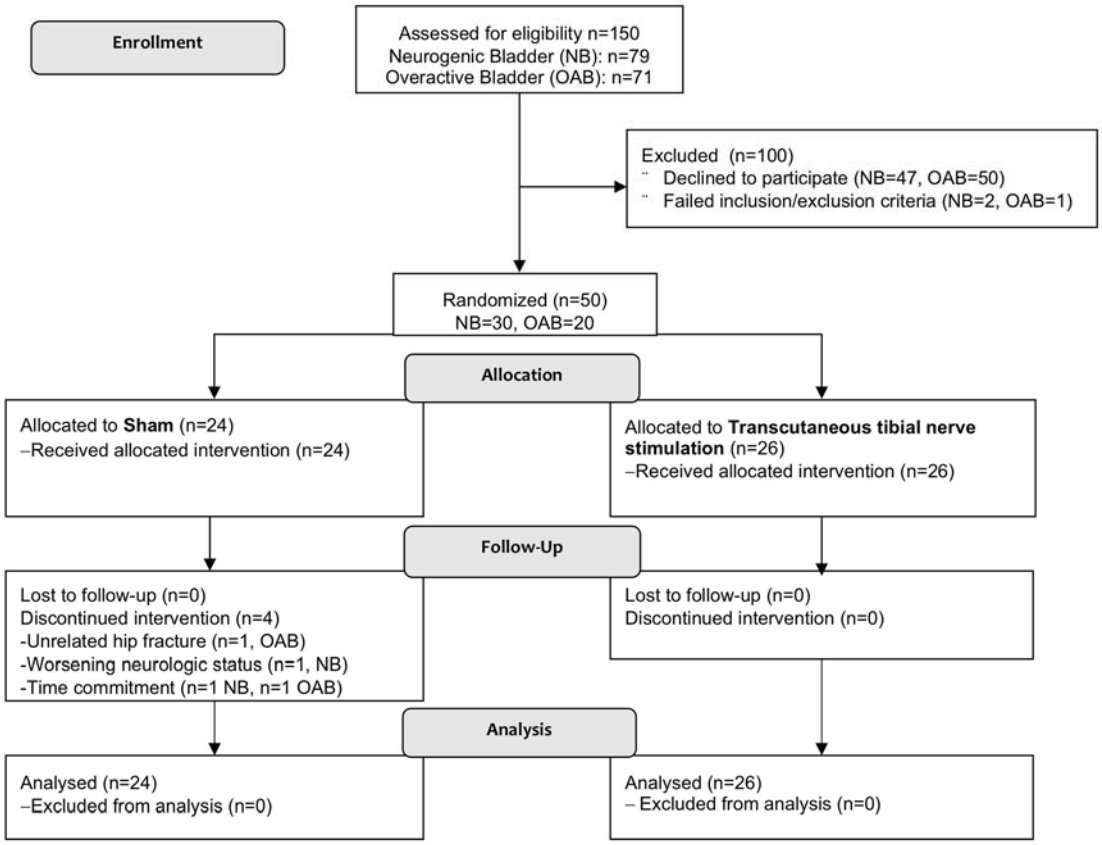

Table 1. Baseline characteristics of participants		
	Sham TTNS (n=24)	**Active TTNS (n=26)**
Male	17% (4)	23% (6)
Age	58 (46–64)	62 (54–68)
Body mass index	29.1 (23.0–33.0)	29.1 (23.7–34.2)
Neurogenic diagnosis (most commonly MS)	58% (14/24)	62% (16/26)
Number of prior oral therapies	1 (1–3)	2 (1–3)
Prior pelvic floor exercises	58% (14)	65% (17)
With therapist	21% (5)	19% (5)
Prior stress incontinence surgery	21% (5)	23% (6)
Prior urodynamic studies	67% (16)	54% (14)
Proportion with detrusor overactivity	50% (8/16)	43% (6/14)
24-hour pad weight (g)	44 (15–532)	37 (18–286)
3-day voiding diary		
Daily frequency	10 (8–12)	9 (7–13)
Functional capacity (mL)	270 (140–396)	325 (268–450)
PPBC	4 (3–4)	4 (3–4)
PROMs for neurogenic cohort (n=30)		
NBSS	39 (31–46)	34 (28-40)
Qualiveen-SF	34 (30–35)	27 (23-33)
PROMs for the OAB cohort (n=20)		
OAB-q bother score	74 (58–97)	67 (67–76)
OAB-q QoL score	79 (54–83)	71 (65–83)

All numbers are median (interquartile range), or percentage (proportion). MS: multiple sclerosis; NBSS: Neurogenic Bladder Symptom Score; OAB-q: overactive bladder questionnaire; PPBC: perception of bladder condition; PROM: patient-reported outcome measures; SF: short form; TTNS: transcutaneous tibial nerve stimulation; QoL: quality of life.

Table 2. Secondary study outcomes measured at the end of the study			
	Sham (n=24)	**Active TTNS (n=26)**	**p**
24-hour pad weights (g)	276 (156–396)	238 (125–350)	0.64
3-day voiding diary			
Functional capacity (mL)	356 (322–390)	321 (292–351)	0.12
Daily frequency	11 (10–12)	10 (9–11)	0.32
PROM: OAB cohort			
OAB-q bother	62 (52–73)	61 (50–71)	0.82
OAB-q QoL	64 (54–75)	57 (47–67)	0.29
PROM: Neurogenic cohort			
NBSS	33 (29–38)	29 (25–33)	0.16
SF-Qualiveen	27 (23–31)	27 (24–31)	0.85
Physician global assessment of improvement	1 (0–2)	2 (1–3)	0.27

Outcomes are reported as marginal means and 95% confidence interval CI from an ANCOVA model corrected for the baseline value of the outcome. Note that the marginal means to developed for comparison purposes and are not comparable to the medians reported in Table 1. NBSS: Neurogenic Bladder Symptom Score; OAB-q: overactive bladder questionnaire; PPBC: perception of bladder condition; PROM: patient-reported outcome measures; SF: short form; TTNS: transcutaneous tibial nerve stimulation; QoL: quality of life.