



Safety, Feasibility, and Efficacy of Transcutaneous Tibial Nerve Stimulation in Acute Spinal Cord Injury Neurogenic Bladder: A Randomized Control Pilot Trial

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Objectives: We investigated whether transcutaneous tibial nerve stimulation (TTNS) in acute spinal cord injury was safe and feasible, and could achieve neuromodulation and improve cystometrogram parameters during acute inpatient rehabilitation.

Materials and Methods: Participants were consecutive acute traumatic spinal cord injury patients admitted for acute inpatient rehabilitation, randomized to a 2-week trial of TTNS v sham stimulation. Primary outcomes were safety and feasibility of TTNS and secondary outcomes were bladder measures based on pre- and post-TTNS cystometrogram by group and within groups, including bladder capacity, detrusor hyperreflexia, pressures, and detrusor-sphincter dyssynergia, as well as filling sensations and desire to void. The principle investigator and subjects were blinded to treatment allocation.

Results: A total of 19 subjects consented to the study and completed the stimulation protocol. Morbidity was similar between groups and compliance was 100% to the TTNS protocol. Based on a lack of rehabilitation interruptions and comments from staff, TTNS was feasible. Post-cystometrogram parameters were significant for lower volumes until sensation in the control group and prolonged volumes until sensation in the TTNS group. The control group had significant changes of increased detrusor-sphincter dyssynergia and decreased bladder capacity. This was not significantly changed in the TTNS group.

Conclusions: TTNS is a safe and feasible modality that can be performed during inpatient rehabilitation of acute traumatic spinal cord injury. Bladder capacity and episodes of detrusor-sphincter dyssynergia significantly worsened in the control group and did not significantly change in the TTNS group, suggesting that TTNS can alter the course of neurogenic bladder via neuromodulation.

Keywords: Neurogenic urinary bladder, spinal cord injuries, transcutaneous electric stimulation

Conflict of interest: The authors reported no conflict of interest.

INTRODUCTION

Neurogenic bladder develops in nearly every person with spinal cord injury (SCI), with an estimated 95% of suprasacral injuries experiencing detrusor hyperreflexia (DH) and/or detrusor-sphincter dyssynergia (DSD) (1). Neurogenic bladder in SCI is associated with multiple complications, including urinary retention and incontinence, urinary tract infections (UTIs), renal impairment, and overall poor quality of life, making improvements in bladder function the number one research priority in those living with SCI (2). The management of acute neurogenic bladder in SCI is addressed during inpatient rehabilitation by maintaining safe bladder capacities via timed voiding, intermittent catheterization, or indwelling catheterization, as well as overactive bladder medications as needed. This conservative approach has dramatically improved morbidities and mortalities related to the upper urinary tracts, but current management efforts do not address the reorganization of the spinal reflexes which lead to DH and DSD (3).

Neuromodulation of the bladder may be able to attenuate this neuroplastic maladaptation. Sievert et al. performed invasive sacral neuromodulation (SNM) in acute SCI in spinal shock with the hypothesis that early intervention would prevent the development

of pathologic reflexes leading to DSD (4). Unlike the controls that experienced the typical sequelae of SCI neurogenic bladder over time, including decreased bladder capacity and frequent UTIs complicated by sepsis and hospitalizations, the group receiving the implanted neuromodulation device with continued use maintained normal bladder capacity, reported improved quality of life scores, and the detrusor did not develop hyperactivity (4).

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Using similar proposed neural pathways, tibial nerve stimulation (TNS) provides afferent electrical stimulation to the spinal micturition center via the L4-S3 nerve roots. The method was first described by McGuire et al. in 1983, using electric stimulation of the posterior tibial nerve to inhibit detrusor activity, as seen in hind limb stimulation in animal models (5). Since the late 1990s, percutaneous TNS (PTNS) has received United States Food and Drug Administration (FDA) approval for the treatment of overactive bladder. Around the same time, implantable devices used for the stimulation of pudendal afferents to reduce detrusor activity were developed and categorized as SNM. This invasive surgical procedure is also FDA approved for treatment of overactive bladder. Benefits of both of these procedures include increased bladder capacity, reduced detrusor pressures, and improved quality of life (6,7). While SNM requires surgery along with routine urologic monitoring, PTNS requires weekly clinic visits for 3 months of 30 min sessions, with the need for future treatment sessions to maintain improved function (8).

Both SNM and PTNS have demonstrated benefits of increased bladder capacity, reduced detrusor pressure, and improved quality of life (6,7). Ongoing research regarding the neuromodulation of chronic neurogenic bladder via TNS is promising, demonstrating equal efficacy to current management without noncompliance and adverse medication side effects, and subsequent improved quality of life (6–8). There is a substantially larger amount of information regarding the efficacy of the invasive PTNS compared to TTNS (6–10). In a multicenter study of neurogenic bladder due to multiple sclerosis, TTNS improved urinary urgency in more than 80% of the subjects, reduced frequency, and had a positive impact on quality of life measures (10).

Although the benefits are known, the use of these modalities in acute SCI have been limited. We hypothesize that we can achieve similar results of efficacy using TTNS delivered by existing equipment in rehabilitation centers. The potential advantages of developing a TTNS protocol for acute SCI neurogenic bladder are numerous and include: 1) mitigating DH and dyssynergia; 2) maintaining safe detrusor pressures and bladder capacities; 3) decreasing the amount of anticholinergic medications for overactive bladder; 4) using a noninvasive modality that can be safely used acutely without interfering with other important rehabilitation efforts; and 5) using readily available and affordable equipment that have the potential to be used in the home setting in a dignified manner by people with SCI and/or their caregivers. The purpose of this study was to demonstrate safety and feasibility of TTNS in acute SCI during inpatient rehabilitation and provide cystometrograms (CMG) evidence of improved outcomes, specifically decreased incidence of DH/DSD, decreased detrusor pressures, and maintenance of bladder capacities compared to controls.

METHODS

From July 2016 to October 2017, consecutive acute traumatic SCI patients admitted to inpatient rehabilitation within 6 weeks of injury, 18–65 years old, were recruited for this study. Patients with prior central nervous system disorder, peripheral neuropathy, and premorbid genitourinary diagnoses were excluded. Subjects on a ventilator were excluded due to difficulties performing the CMG. Those with a neurologic level of injury below T9 were excluded due to possible lower motor neuron injury of the detrusor.

Upon consent, baseline CMG was performed followed by stratified randomization by a computer algorithm to ensure that subjects with areflexic bladder were equally distributed in the two

arms of the study (Fig. 1). The principle investigator and the subjects were blinded to treatment allocation. The CONSORT 2010 guidelines for randomized clinical trials were followed. The clinical trial was approved by the Institutional Review Board and is registered with clinicaltrials.gov: NCT02573402.

The urodynamic methodology complied with International Continence Society recommendations (11). Cystometry was performed with the patient supine through a double lumen 7 Fr. catheter with computerized analysis of the results and using normal saline at 25–30°C with a filling rate of 40 mL per minute. Measurements included: volume at first involuntary detrusor contraction (ml); maximum detrusor pressure (cm H₂O); bladder capacity (maximum volume infused [ml]); frequency of DH, and dyssynergia. DH was defined as a nonvolitional increase in detrusor pressure of at least 6 cm H₂O. DSD is defined as the presence of involuntary contractions of the external sphincter during detrusor contractions. Factors that may affect the bladder including medication use in the prior 24 hours prior to the CMGs and presence of an indwelling catheter were recorded and used in the analyses. All CMGs were reviewed by the urologist co-investigator (C.P.S), blinded to the treatment allocation. At the time of the CMGs, deep tendon reflexes in the legs were performed and clonus was evaluated at the ankles. Pain scores were recorded and the Penn spasm frequency scale (PSFS) was administered.

The subjects were randomized into TTNS and sham control groups in a 2:1 ratio. Those in the TTNS groups received 30 min of TTNS for 10 days within a 16-day period (12). TTNS was applied to the right leg with the negative electrode behind the internal malleolus and the positive electrode 10 cm. superior to the negative electrode, verified by big toe flexion with rising current intensity. Stimulation frequency of 10 Hz and 200 μsec duration was used with current intensity lowered until absence of toe flexion for 30 min at constant stimulation (12,13). A commercially available neuromuscular electric stimulation unit commonly used in SCI rehabilitation for skeletal muscle activation was used for TTNS. Numeric pain scores were recorded before, during, and after the trial sessions to see if pain was affected by TTNS. Those in the control group received sham stimulation in which the electrodes were placed and the stimulator was activated until toe flexion, but then it was immediately reduced to zero intensity. At every session, the response of toe flexion was recorded, and a percentage was calculated based on the toe flexion responses during the ten sessions. The display on the device was covered in both arms to prevent subjects from reading the current intensity.

The Electronic Medical Record was reviewed for admission and discharge American Spinal Injury Association (ASIA) exams, as well as safety outcomes. Safety outcomes included possible risk of skin irritation with electrode use and electric stimulation as well as the pain scores recorded during TTNS. Possible concerns for other adverse events were recorded, including differences in functional outcomes, UTI rates, deep venous thrombosis, and urgent transfers to the acute care hospital. Feasibility was defined as the combination of compliance, lack of interruptions of the normal therapy schedule, and lack of negative feedback from staff regarding the TTNS protocol.

Statistical Methodology

The primary aim of this pilot study was to evaluate the safety and feasibility of the TTNS protocol in acute traumatic SCI during inpatient rehabilitation. As such, we planned to use a convenience sample in a 2:1 ratio for TTNS and control groups. For the secondary aim, with

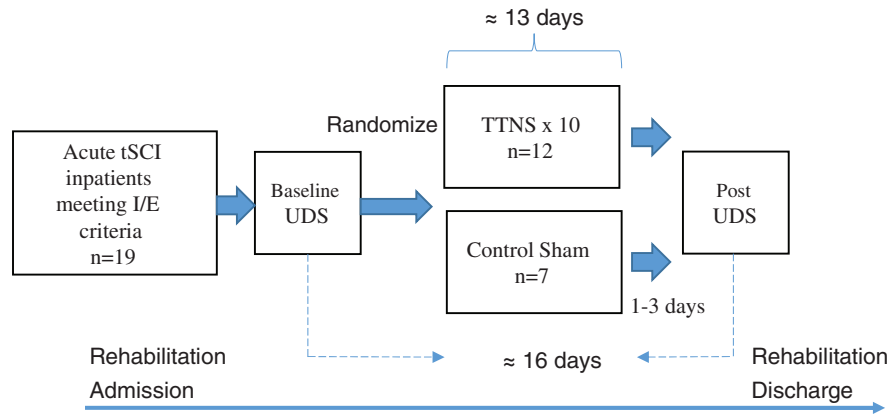


Figure 1. Study design. tSCI, traumatic SCI; I/E, inclusion/exclusion; UDS, urodynamic study; TTNS, transcutaneous tibial nerve stimulation. [Color figure can be viewed at wileyonlinelibrary.com]

12 TTNS and 7 control subjects, we will be able to identify an effect size of 1.5 between control and TTNS group with 80% of power at an alpha level of 0.05 by two-sample two-sided *t*-test. The secondary aim is not an efficacy confirmation, but provides the necessary parameters in study design for further trials.

Wilcoxon rank sum and Fisher’s exact tests were performed on continuous and categorical data, respectively, to identify differences between controls and TTNS groups. Multilevel linear mixed modeling was performed to identify changes within group over time in the CMG parameters, controlling for time and subject variability. Stata 14.0 (StataCorp, 2015) was used for the analyses.

RESULTS

There were 7 control subjects and 12 TTNS subjects. Baseline demographics including age, gender, SCI neurologic level and severity, and days from injury are similar between the groups

(Table 1). Baseline physical exam (Table 2) and CMG data (Table 3) were similar between groups.

There was no significant difference in complete vs. incomplete injury regarding presence of first sensation (*p* = 0.170), first desire (*p* = 0.181), involuntary contraction (*p* = 0.37), and areflexic bladder (*p* = 0.37). In the incomplete group, there were six subjects with a strong desire to void compared to one with complete injury (*p* = 0.006).

After the TTNS trial, physical exams were similar between groups (Table 2). There were no differences in reflexes and spasticity between groups and within groups after the trial. One subject in the control group had a cast on her right leg at baseline and reflexes could not be performed. Reflexes were also not checked on one subject in the TTNS group because the CMG had started.

One subject declined to repeat the post-TTNS CMG, leaving 11 remaining in the TTNS group for the CMG measurements. There were more subjects with the first/strong desire to void in the control group than in the TTNS group (Table 3). In those with sensation, controls had a significantly lower volume to achieve sensation

Table 1. Baseline Demographics.

	Control (<i>n</i> = 7)	TTNS (<i>n</i> = 12)	<i>p</i> -Value
	Mean (SD)		
Age	48.3 (12.9)	36.3 (13.5)	0.08
Neurologic level number*	8.1 (5.3)	7.7 (6.2)	0.97
Days from injury	19.9 (6.2)	20.8 (9.3)	0.83
Admission FIM motor	16.4 (5.6)	16.7 (5.1)	0.72
Admission FIM bladder	1	1	
Admission FIM cognition	29.1 (5)	27.8 (5.6)	0.77
	Frequency (%)		
Male	2 (29%)	8 (67%)	0.17
Complete Injury	3 (43%)	8 (67%)	0.38
Motor Complete	4 (57%)	10 (83%)	0.31
Tetraplegia	4 (57%)	6 (50%)	1
ASIA category			0.62
ASIA A	3 (43%)	8 (67%)	
ASIA B	1 (14%)	2 (17%)	
ASIA C	2 (29%)	2 (17%)	
ASIA D	1 (14%)	0	

*This is a continuous scale beginning at C1 and starting at 1, increasing as moving caudal. FIM, functional independence measure; ASIA, American spinal injury association; AIS, ASIA impairment scale; AIS A, complete injury; AIS B, motor complete; AIS C and AIS D, motor incomplete with less than half (C) or half or more (D) of the muscles below the level of injury functional.

Table 2. Physical Exam Data.

	Control (n = 7) Mean (SD)					TTNS														
	Pre-TTNS trial					Post-TTNS trial					Pre-TTNS trial (n = 12)					Post-TTNS trial (n = 11)				
Days from injury	19.9 (6.2)					24.6 (6.7)					20.8 (9.3)					37.2 (10.12)				
Numerical pain scale	2.8 (3.5)					2.8 (3.4)					2.3 (2.5)					1 (1.9)				
	Frequency (%)																			
Presence of Foley	3 (43%)					4 (57%)					5 (42%)					4 (36%)				
Clonus R	1 (14%)					2 (29%)					1 (8%)					2 (18%)				
Clonus L	1 (14%)					1 (14%)					1 (8%)					1 (9%)				
Babinski R	3 (43%)					4 (57%)					5 (42%)					7 (64%)				
Babinski L	3 (43%)					4 (57%)					5 (42%)					4 (36%)				
	Scores																			
	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4
PSFS	2	0	3	2	0	2	3	0	2	0	2	5	1	2	1	0	8	2	1	0
PSFS Severity	2	2	3	0	0	2	4	1	0	0	2	7	2	0	0	0	8	2	1	0
	Deep tendon reflexes (count)																			
Patellar R	1	4	1	0	0	0	2	2	3	0	7	2	2	0	0	5	1	2	3	0
Patellar L	2	4	1	0	0	0	2	2	3	0	7	2	2	0	0	5	1	2	3	0
Achilles R	4	0	1	1	0	2	2	1	1	1	7	2	2	0	0	7	1	1	1	1
Achilles L	5	0	1	1	0	1	2	3	1	0	7	2	2	0	0	7	1	1	1	1

R, right; L, left; PSFS, Penn spasm frequency scale.

than the TTNS group. Likewise, the first desire to void was also a significantly lower volume in controls than the TTNS group.

Data from the trial sessions were compared between groups (Table 4). The 10 sessions were generally completed in less than

14 days, and the TTNS group had a significantly shorter time to complete the session than the control group. Pain scores were similar between the groups before, during, and after stimulation. Toe flexion was achieved similarly between groups, and the

Table 3. Cystometrogram Data.

	Control (n = 7)		TTNS	
	Pre-TTNS trial	Post-TTNS trial	Pre-TTNS trial (n = 12)	Post-TTNS trial (n = 11)
Maximum detrusor pressure (cm H ₂ O)	33 (11.1)	44.4 (21.5)	30.6 (21) □	38.1 (21.4) □
Bladder capacity (mL)	571 (81.3) ¥	459.6 (156.4) ¥	580 (45.7)	552.6 (110)
Freq. detrusor hyperactivity (count)	3 (3.7)	1 (1.5)	0.83 (1.4)	1.5 (1.8)
Freq. of Detrusor-Sphincter Dyssynergia (count)	0.29 (0.76) €	1 (1.5) €	0.17 (0.39)	0.55 (0.8)
	Frequency (%)			
Detrusor areflexia	3 (43%)	3 (43%)	7 (58%)	4 (36%)
Bladder medication	0	0	0	0
Spasticity medication	5 (71%)	4 (57%)	3 (25%)	4 (36%)
First sensation perception	4 (57%)	5 (71%)	6 (50%)	4 (36%)
First desire perception	4 (57%)	5 (71%) *	4 (33%)	2 (18%)*
Strong desire perception	3 (43%)	5 (71%) ^	4 (33%)	1 (9%) ^
Involuntary contraction	4 (57%)	3 (43%)	5 (42%)	6 (55%)
	Subgroup analysis of those with sensation/contraction: means (SD)			
First sensation (mL)	102.5 (115.5)	111.2 (47)~	201 (117)	360.8 (131)~
First desire (mL)	144.8 (90.7)	133.8 (41)	229.8 (105.2)	426.5 (78.5)
Strong desire (mL)	262.2 (261.9)	305.8 (162) √	344 (41.8)	482 √
First involuntary contraction (mL)	225.8 (168.2)	144.7 (149)	304.2 (81)	265.7 (116)

Between group differences: **p* = 0.04; ^*p* = 0.01; ~*p* = 0.01; √*p* = 0.05.

Within group differences: □*p* = 0.043; ¥*p* = 0.02; €*p* = 0.009.

Table 4. TTNS Stimulation Data.

	Control (7)	TTNS (12)	<i>p</i>
	Mean (SD)		
Days to complete stimulation	14 (0.4)	13 (0.9)	0.001
Toe flexion occurrence (out of 10)	0.71 (0.31)	0.77 (0.34)	0.36
Current mean (mA)	43.6 (29.3)	45.2 (26.7)	0.8

mA, milliamperere.

current required was also similar (for controls, current describes amount required to achieve toe flexion). Adverse events were similar between groups (Table 5). Both control and TTNS subjects had redness after surface electrode placement. After removal of the surface electrodes, the RA ensured this was blanchable erythema indicating no extravasation of red blood cells. Functional Independence Measure (FIM) discharge subtotals of motor, cognition, and bladder, were similar among groups. There were no interruptions of therapy or complaints from staff regarding performance of TTNS. Remarks from the clinical staff included: 1) "[TTNS] looks easy to apply, taking only a few minutes, and it did not interfere with the clinical care of the patients"; and 2) "Based on the ease of use, [TTNS] seems very feasible to implement in the clinical care of SCI patients."

Multilevel linear mixed model regression controlling for time and subject variability was performed on the CMG outcome measures of interest independently. Overall, as days from injury increased by one day, there were increases in DSD frequency (0.06, $p = 0.006$) and maximum pressure (0.73 cm H₂O, $p = 0.014$), while bladder capacity decreased (−3.5 mL, $p = 0.02$). Those with a reflexive bladder significantly decreased bladder capacity by 3.7 mL/day ($p = 0.037$) and increased maximum pressure by 0.82 cm H₂O/day ($p = 0.015$). Controlling for the presence of indwelling catheter did not change the model significantly. Subgroup analysis was significant for increases in DSD and decreases in bladder capacity in the control group (Table 3, Fig. 2). Maximum pressure was increased in the TTNS group.

Further subgroup analyses was performed in the TTNS group based on variables of interest that may have an effect of TTNS on the bladder: areflexic bladder on baseline CMG, mean current applied during TTNS, and mean frequency of toe flexion response. These were not found to be significant, but the interaction of time and toe flexion response to DH frequency was significant (−0.2, $p = 0.047$) (Fig. 3). The subjects in which toe flexion was not achieved 100% of the time increased events of DH, while in those that toe flexion was achieved 100% of the time reduced DH events.

DISCUSSION

This randomized control trial has demonstrated safety and feasibility of TTNS in acute SCI during inpatient rehabilitation. There were no differences in morbidity or functional improvements based on safety and FIM scores, respectively. Compliance to TTNS was 100%. Every patient completed the stimulation protocol and tolerated the TTNS sessions without significant changes in pain scores.

We were also able to present CMG evidence that suggests efficacy, as described in the Sievert et al. study (4). The control group progressed to develop the typical findings of SCI neurogenic bladder, including worsening bladder capacity and DSD events. This was not found in the TTNS group. Sensation was also affected by TTNS, with an increased and shortened presence of sensation in the controls compared to the TTNS group. The absence of significantly worsening bladder capacity and DSD, as well as the changes in sensation during CMG suggests neuromodulation effects of TTNS in the acute period of SCI.

Despite their clinical use, the mechanism of action of PTNS and SNM remains unclear. There have been some advances in the theoretical mechanisms. No longer is direct muscle stimulation of the detrusor the predominant theory, especially considering the current used is below the threshold required for motor contraction. The leading theory is that stimulation of the peripheral sensory afferent fibers block competing abnormal visceral afferent signals from the bladder and prevent the reflexive, efferent motor response resulting in detrusor hyperactivity and dysynergia (14). This postulated mechanism can also be achieved with TTNS.

Table 5. Safety Outcomes.

	Control (7)	TTNS (12)	<i>p</i> -Value
	Mean (SD)		
Discharge FIM motor	32.7 (16.1)	33.5 (14.9)	0.87
Discharge FIM bladder	2.1 (1.9)	1.5 (1.2)	0.25
Discharge FIM cognition	33 (3.3)	33.5 (1.5)	0.77
Change in NPS during TTNS	−0.06 (0.13)	−0.01 (0.22)	0.46
	Frequency (%)		
DVT/PE	1 (14%)	0	0.37
UTI	3 (21%)	4 (33%)	0.53
Other infections	0	0	
Cellulitis/burn	0	0	
Pressure injury	1 (14%)	0	0.37
Unexpected discharge	0	0	

FIM, functional independence measure; NPS, numerical pain scale, 0-10; DVT/PE, deep venous thrombosis/pulmonary embolus; UTI, urinary tract infection.

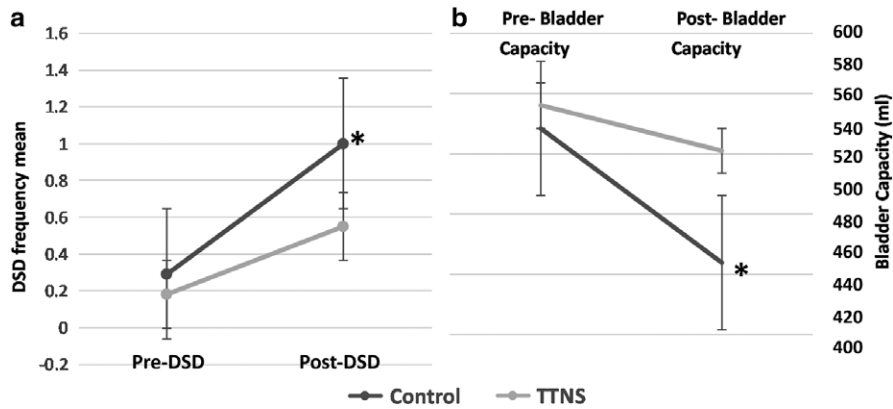


Figure 2. a. DSD means pre- and post-trial in controls (dark) and TTNS (light). b. Mean bladder capacities pre- and post-trial in controls and TTNS. *Differences from baseline, $p < 0.02$.

The posterior tibial nerve is a terminal branch of the sciatic nerve with origins in the lumbar and sacral roots (L4-S3), carrying both sensory and motor nerves. Direct stimulation of the S3 nerve root has been shown to decrease overactive bladder in humans (4,15–17). S3 dermatome stimulation has also improved detrusor overactivity, frequency, and nocturia, but has limited use due to the difficulty in applying the electrodes (18–20). TTNS involves the S3 fibers, given that proper positioning of TTNS causes plantar flexion of the big toe or fanning of the other toes. Although the exact mechanism of TNS is unknown, it has been postulated that TNS depolarizes somatic sacral and lumbar afferent fibers, inhibiting detrusor activity (21). Several studies support this postulated theory, including pudendal nerve studies in men, in which the sensory afferents were able to inhibit detrusor activity (21). Our data supports this mechanism, in which beneficial CMG parameters were maintained along with the prolongation of sensory findings. Physical exam reflecting possible neuromodulation of reflexes in the lower extremities, including spasticity, deep tendon reflexes, and clonus, were not different between groups and did not change significantly over time. The placement and settings of the TTNS protocol may be specific to bladder neuromodulation rather than the entire lumbar motoneuron pool.

Based on the work of Sievert et al., we proposed that the efficacy would be greater in those with areflexic bladder, thus we randomized after the baseline CMG to identify and equally distribute areflexic bladders into the two groups. Controlling for areflexic bladder did not change the modeling regarding the outcomes of interest: DH, DSD, maximum bladder pressure, and

bladder capacity. Likewise, much like prior studies, we did not find an association with physical exam and CMG changes (22). The groups were also similar based on their response to initial toe flexion, with similar currents required for similar toe flexion response rates. We did find an association with improved efficacy of TTNS based on achieving toe flexion and DH changes (Fig. 3). In the case of wide adoption of this modality, this is an important observation for instructing on proper electrode placement, stimulation intensity, and overall expected efficacy.

There are several limitations in this study. The control group was a smaller sample size than the TTNS group and may have biased the results. However, physical exam, function, and TTNS stimulation settings were similar between groups, therefore differences in SCI and peripheral nerve function is unlikely to be the cause for worsening bladder outcomes in the control group compared to the TTNS group. The times to reported sensation should be interpreted with caution given the low numbers reporting sensation (range 1–5). Finally, the power analyses were based on similar neuromodulation work in the chronic SCI population, in which the neurogenic bladder is relatively stable compared to the developing neurogenic bladder in acute SCI. This pilot trial provides effect size information for future studies of TTNS in acute SCI neurogenic bladder.

CONCLUSIONS

TTNS is a safe and feasible modality that can be performed during inpatient rehabilitation of acute traumatic SCI. Bladder capacity and episodes of DSD remained stable in the TTNS group compared to worsened findings in the control group, suggesting that TTNS can alter the course of neurogenic bladder via neuromodulation. Furthermore, sensation during filling was significantly prolonged in the TTNS group, supporting the proposed mechanism of action of TTNS of blocking detrusor afferent signals at the spinal cord level with competing signals from TTNS. Further research is necessary to determine the mechanism of action and whether long-term efficacy can be achieved.

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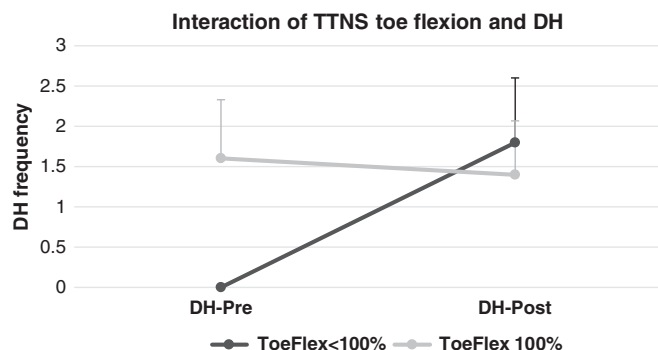


Figure 3. Interaction of toe flexion rate with mean DH and standard error bars. Those with 100% toe flexion response (light) throughout the ten TTNS sessions had decreased DH events after the trial.

Authorship Statements

Drs. Stampas, Zhu, Smith, and Gustafson designed the study. Drs. Stampas and Korupolu performed the physical exams. Drs. Stampas and Smith independently interpreted the CMG tracings. Drs. Stampas and Zhu independently performed statistical analyses for verification of results. Dr. Stampas prepared the manuscript with important intellectual input from all of the authors.

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