The Effects Upon the Bladder of Transcutaneous Tibial Nerve Stimulation in Acute Traumatic Spinal Cord Injury

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The Effects Upon the Bladder of Transcutaneous Tibial Nerve Stimulation in Acute Traumatic Spinal Cord Injury

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STUDY PROTOCOL

1. BACKGROUND AND RATIONALE

There are over 1 million people living in the United States with spinal cord injury (SCI) with devastating functional impairments including paralysis and bowel/bladder dysfunction.[1] Over time after SCI, reorganization of the spinal reflexes occurs and it is suspected that these synaptic alterations cause detrusor sphincter dyssynergia (DSD). It is estimated that DSD occurs in 75% of suprasacral spinal cord injuries with up to 50% developing serious urologic complications with current management strategies.[2] Neuromodulation techniques, such as transcutaneous tibial nerve stimulation (TTNS), currently improve bladder function and reduce DSD in chronic SCI, but little is known about their efficacy in acute spinal cord injury.[3] There is currently a gap in our knowledge about the effects of TTNS on the bladder in acute spinal cord injury. We hypothesize that TTNS can improve neurogenic bladder parameters during acute SCI and that development of a feasible protocol during acute rehabilitation will maintain these results and decrease the incidence of DSD.

We believe we can use existing TTNS technology to help neurogenic bladder in SCI. First, we need to determine the safety and feasibility of a 2-week TTNS protocol in acute SCI during inpatient rehabilitation. Second, we will examine the effects on the bladder of this protocol as seen on urodynamic studies (USD) before and after the protocol, as well as on 2-month follow-up. We will perform an observational study of TTNS and UDS on all 4 common neurologic categories of acute SCI admitted to TIRR Memorial Hermann and consenting to the study. Patients enrolled in the study will have baseline urodynamics performed, and then randomized to a control trial (RCT) of a 2-week protocol of TTNS to test for safety and efficacy during inpatient rehabilitation to evaluate bladder changes based upon pre- and post- urodynamic testing, as well as 2-month follow-up. A subset of those in the experimental TTNS group will also have a 1-month follow-up in which they will have a maintenance session of TTNS in clinic.

We will concurrently test novel high density (hd) surface electrodes during the urodynamic studies to see if there is correlation between the electrical activity seen by the hd surface electrodes and the pressure recordings of the bladder. We believe this has the potential to develop into a non-invasive outcome measure in neurogenic bladder. We will be recording bladder activity with high density EMG surface electrodes during session 1, session 5, and session 10. These are the same types of electrodes used in the UDS. Surface electrodes will adhere to the skin and placed above and below the pubic bone, placed by the research assistant. Recordings will last the entire stimulation session.

We will be looking at urine growth factors and inflammatory markers. These markers have been investigated in patients with SCI in the past, however due to technical errors, the conclusions have been withdrawn. These technical errors have since been corrected and the biomarkers are being utilized to characterize other bladder pathologies, including returning to look at neurogenic bladder in SCI. They are currently being used to explore the treatment efficacy of BOTOX in the neurogenic bladder in SCI at TIRR, in which I am involved as a co-investigator.

1.1. General Introduction

The EMPI 300 PV and the newer model, the EMPI Continuum, are electric stimulation units used for the rehabilitation of those with paralysis. It is currently used at TIRR Memorial Hermann on nearly every patient with paralysis for the purposes of motor and sensory recovery. The proposed protocol is using the device in a new way, to stimulate the nerves of the legs which is known to effect the bladder in a process described as "neuromodulation."

The status quo as it pertains to the management of neurogenic bladder in SCI is anticholinergic medications to inhibit bladder activity, increase bladder capacity, and decrease detrusor pressures.[4] However, management of neurogenic bladder requires further improvement, with an estimated 75% of suprasacral SCIs developing DSD and up to 50% developing serious urologic complications.[2] Ongoing research regarding the neuromodulation of chronic neurogenic bladder is promising, demonstrating equal efficacy to current management without non-compliance and adverse medication side effects, with improved quality of life.[5-8] Although neuro-modulation techniques are currently used for chronic neurogenic bladder, little is little known about the effects of neuromodulation of the bladder in the acute phase of SCI recovery. The proposed research is innovative, in our opinion, because it represents a substantive departure from the status quo by using transcutaneous tibial nerve stimulation in the acutely injured to improve bladder function. Rehabilitation horizons for neurogenic bladder management which have previously been unattainable through current efforts including the prevention of detrusor sphincter dyssynergia and related autonomic dysreflexia, maintenance of bladder capacity and compliance, and reduction in oral medication use with improved quality of life are also likely to become attainable.

Electric stimulation is currently being used in acute neurorehabilitation. The candidate has published reviews on the current state of acute rehabilitation in SCI, describing the use of FES and NMES in acute SCI for motor/sensory recovery, decreasing spasticity, and improving neuropathic pain.[9, 10] There has been little published regarding the effects of electric stimulation upon the bladder in acute SCI. Sievert et al. performed invasive sacral neuromodulation in acute SCI in spinal shock (atonic bladder seen on UDS, but time from injury was not reported), with the hypothesis that early intervention would prevent the development of pathologic reflexes leading to DSD.[11] 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 maintained normal bladder capacity, reported improved quality of life scores, and the detrusor did not develop hyperactivity.[11] Although the mechanism of action is unclear, it appears to be afferently mediated, requiring electrically induced nerve conduction to prevent the abhorrent reflexes from forming which cause detrusor overactivity and DSD.[12] Less invasive, transcutaneous electric stimulation performed directly over the bladder for 30 sessions over a 5 week period in acute SCI (as early as 2 months) produced continued beneficial results based on UDS after 2 years.[7] Based upon an extensive review of the literature on neuromodulation of neurogenic bladder and the clinical experience of our research team, we believe a TTNS protocol over a 2 week period will show significant improvements in UDS outcomes.

Concurrently, we will be testing new hd surface electrodes and correlate the electrical activity found to the pressure recordings during UDS. This harmless, non-invasive technology may provide a useful, quick, feasible, outcome measure in neurogenic bladder.

We will be looking at urine growth factors and inflammatory markers to characterize neurogenic bladder in SCI. They are currently being used to explore the treatment efficacy of BOTOX in the neurogenic bladder in SCI at TIRR.

1.2. Rationale and justification for the Study

We have selected a neuromodulation technique, TTNS, that has been used safely in chronic SCI with good results for improving quality of life and bladder parameters as seen on UDS, specifically cystometry, and we are applying it during the acute period during inpatient rehabilitation. The hypotheses are 1) TTNS will be a safe and feasible modality that can be used during acute rehabilitation and 2) a 2-week protocol of TTNS will be an effective protocol to improve bladder parameters, reduce oral bladder medication usage, and reduce the frequency of DSD and detrusor hyperreflexia (DH) at 2-month follow-up UDS.

High density surface electrodes are currently being studied in the bladder of animal models. There is a wealth of data recorded from the electrical activity of the bladder and the pelvic muscles. The hypothesis is that there will be a correlation between UDS outcomes and the high definition surface electrode recordings that may allow its use as a non-invasive, novel, and feasible outcome measure.

Studies have shown that cytokines and chemokines responsible for autocrine, paracrine and endocrine signalling are also released by non-immune cells in the bladder such as urothelium and detrusor cells. [Bouchelouche et al, 2004; Bouchelouche et al, 2006a; Bouchelouche et al, 2006b] The urinary bladder relies on a broad array of cytokines, chemokines and growth factors to effect biochemical changes within its organ in response to disease and therapeutic intervention. But not all these chemokines/cytokines and growth factors can serve as urinary biomarkers or surrogates of treatment response as they have to fulfil the key requirement of being present in detectable amounts in urine that can be assayed using standard methods.

The detectable amount of nerve growth factor (NGF) in the NGB patients combined with its known role in neuroimmune interactions makes NGF an ideal candidate for a urinary biomarker. It has been proposed that after neurologic injury, the bladder releases NGF into the urine in response to the injury. NGF and its receptors may also amplify other immunoinflammatory and neuronal pathways contributing to bladder inflammation and symptoms associated with UTI.

Other proteins have been consistently detected in the urine of subjects with SCI or other neurological diseases like MS or impairments like diabetes. The chemokines and cytokines include: interleukin IL-5, IL-6, IL-1Ra, sIL-2Rα, CC chemokines including MCP-1, MIP-1 β, RANTES(Regulated upon Activation, Normal T Expressed and Secreted), CXC chemokines including GRO-α/ CXCL1, IL-8, and IP-10 and growth factors including vascular endothelial growth factor (VEGF), epidermal growth factor (EGF), platelet derived growth factor (PDGF-AA), VEGF, and PDGF.

a. Rationale for the Study Purpose

Neuromodulation techniques have been safely used for improving neurogenic bladder in chronic SCI for many years. However, bladder neuromodulation is rarely performed in acute SCI, and it is not common in acute rehabilitation. There has been little published regarding the effects of electric stimulation upon the bladder in acute SCI. Sievert et al. performed invasive sacral neuromodulation in acute SCI in spinal shock (atonic bladder seen on UDS, but time from injury was not reported), with the hypothesis that early intervention would prevent the development of pathologic reflexes leading to DSD.[11] 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 maintained normal bladder capacity, reported improved quality of life scores, and the detrusor did not develop hyperactivity.[11] Although the mechanism of action is unclear, it appears to be afferently mediated, requiring electrically induced nerve conduction to prevent the abhorrent reflexes from forming which cause DH and DSD.[14] Less invasive, transcutaneous electric stimulation performed directly over the bladder for 30 sessions over a 5 week period in acute SCI (as early as 2 months) produced continued beneficial results based on UDS after 2 years.[7]

Gaps in the knowledge which we intend to fill are:
1) Safety and feasibility of TTNS in acute SCI during inpatient rehabilitation
2) Efficacy of a 2-week TTNS protocol in SCI based on UDS findings on 2-month follow-up.
3) Analysis of bladder medication usage in those with and without TTNS, frequency of DSD, and evaluation of morbidity at 2-month follow-up

The rationale for the use of the hdEMG electrodes is to attempt to develop a novel outcome measure for neurogenic bladder that is practical, feasible, and non-invasive.

b. Rationale for Doses Selected

Based upon an extensive review of the literature on neuromodulation of neurogenic bladder and the clinical experience of the mentorship team, we believe a TTNS protocol over a 2 week period will show significant improvements in UDS outcomes. Tibial nerve stimulation protocols use submotor current intensity with a duration of 200 μs and frequency of 10Hz.[13,14] Increasing the treatment frequency dramatically shortens the time required for response while maintaining efficacy, varying from 6-12 sessions.[14]

c. Rationale for Study Population

Participants will include 4 groups of acute tSCI ages 18-65, 10 in each group, based on the common neurologic categories of spinal cord injury:

- Tetraplegia, complete
- Tetraplegia, incomplete
- Paraplegia, complete
- Paraplegia, incomplete

The age range for this study was selected because age-related changes that may alter the urodynamic studies in adults increases over the age of 65.[15] Consecutive patients meeting the inclusion/exclusion criteria admitted to inpatient rehabilitation for tSCI will be asked to enroll. There are approximately 200 acute tSCI patients admitted to our institution annually, the majority of which satisfy the inclusion criteria. The distribution of the 4 neurologic classifications required is similar to the published data from the Model Systems.[16] Inclusion criteria include

ages 18-65 years old admitted to inpatient rehabilitation within 6 weeks of injury with a neurologic level of injury rostral to T10 (T9 and above). This is a significant neurologic level because the bladder remains innervated at these levels, without damage to the spinal cord neurons innervating the bladder. The RCT is 10 sessions over 2 weeks, thus discharge within 2 weeks is undesirable. Because our institution serves a large geographic region, routinely providing care to five different states, the ability to return to outpatient clinic for follow-up is considered inclusion criteria. Although there is no clear definition of "acute" SCI, most studies range from 2- 14 weeks post injury.[15-19] The European Multicenter Study about Spinal Cord Injury has published a time schedule for the stages of SCI, in which our time frame would be considered acute.[17] The 6 week time period was chosen as the upper limit to ensure recruitment of patients within the time frame of the grant period. We anticipate most subject recruitment within 4 weeks of injury given current admission trends.

d. Rationale for Study Design

Specific Aim 1: Safety and feasibility of TTNS in acute SCI during acute rehabilitation. This has been demonstrated in chronic SCI.
Specific Aim 2.1: 2-week RCT of TTNS to compare UDS outcomes to controls on 2-month follow-up.
Specific Aim 2.2: Those that receive a TTNS maintenance dose 1 month after discharge will have better urodynamic outcomes than both the control and those in the TTNS that did not receive the maintenance dose.

2. HYPOTHESIS AND OBJECTIVES

2.1. Hypothesis

Hypothesis 1: TTNS will be a safe and feasible modality that can be used in acute tSCI patients during inpatient rehabilitation. They will have non-significant differences in morbidity, mortality, and functional outcome measures during their admission compared to controls.

Hypothesis 2.1: Those that receive TTNS will show significant improvements in bladder parameters on post-UDS compared to both baseline UDS and the control group. Improvements may be seen in the following UDS parameters:

- volume at first involuntary detrusor contraction
- maximum detrusor pressure (cmH20)
- bladder capacity (maximum volume infused)
- frequency of detrusor sphincter dyssynergia

Hypothesis 2.2: On 2-month follow-up, those that received TTNS will have sustained bladder improvements compared to control with less occurrence of DSD on UDS. Those that receive a maintenance dose of TTNS will have better urodynamics than those that did not.

2.2. Primary Objectives

Primary Objective 1: Monitor for safety of a 2 week TTNS protocol in acute SCI.
Primary Objective 2: Compare the effects upon the bladder of a 2-week TTNS protocol in acute SCI versus control group upon completion of the TTNS protocol with UDS as well as on 2-month follow-up UDS.

2.3. Secondary Objectives

Secondary Objective 1: Identify the neurologic bladder category of acute SCI based on baseline UDS in which TTNS is effective. Subjects will be stratified into the randomized trial based on areflexic bladder versus not-areflexic bladder.

Secondary Objective 2: Identify the effects of a maintenance dose of TTNS one month after completion of the 2 week trial.

Secondary Objective 3: Compare the findings of hdEMG surface electrodes above the pubic bone to the urodynamic study findings of the detrusor.

Secondary Objective 4: Characterize other bladder pathologies, including neurogenic bladder in SCI, by analysing urine growth factors and inflammatory markers.

2.4. Potential Risks and Benefits:

a. End Points - Efficacy

Specific Aim 1: No efficacy requirement for the safety and feasibility studied in specific aim 1.

Specific Aim 2: Upon completion of the randomized control trial, we expect to observe significant improvements in UDS measures comparing baseline to post- UDS in the TTNS group and at the 2-month follow-up. The UDS outcome measures we expect to improve are:

- Increase in bladder capacity by 50% or 100ml [13]
- Increase in volume at first detrusor contraction by 50% or 100ml [13]
- Decrease in maximum detrusor pressure by 25% [18]

We also expect to see decreased frequency of DSD in those that received TTNS compared to the Control group. We do not expect beneficial UDS changes in the Control group

Anticipated benefits include improved bladder capacity, decreased detrusor pressure, decreased detrusor-sphincter dyssynergia, improved morbidity, and decreased bladder medication usage.

b. End Points - Safety

We expect the rates of morbidity to be the same between those who participate and those who do not in both Aims of the research. Risks can be divided into the risks involved in having urodynamic studies and the risk of having electric stimulation.

<u>Urodynamic Study Risks</u>:
Some complications of urodynamic cystometry may include, but are not limited to, the following:

- Urinary Tract infections (UTIs)
- Autonomic Dysreflexia (symptoms of increased adrenaline response which may include increase blood pressure, headache, sweating, and flushing).

UTIs are a risk any time a foreign object is introduced into the urethra and or bladder. To mitigate this risk, skilled urology nurses will be using sterile technique to insert the catheters.

Autonomic Dysreflexia (AD) is a unique phenomenon which occurs when there is an injury or

lesion between the sacrum (bottom) and the pons (top) within the spinal cord. It may occur in any SCI with a neurologic level of T6 (middle spine) and above. It occurs whenever there is a noxious stimulus below the neurologic level of injury, with a mounting stress response that may cause elevated blood pressures, sweating, flushing, and/or headaches. In this setting, the distention of the bladder during the study and/or the catheter insertion/placement may be the noxious factor. To mitigate AD:

- Filling rate will be 40ml/min, rather than 50ml/min.
- Blood pressure will be monitored every 3-5 minutes. An elevated SBP >20mmgHG from baseline indicates AD.
- Staff will be monitoring for sweating, flushing, and asking about headaches during the study.
- Should the patient have AD, we will stop filling for 5 minutes, reposition the patient and/or catheter as needed, and examine for any other noxious stimuli.
- After 5 minutes, we will resume the filling at 20ml/min.
- Should the AD persist, the study will stop and we will follow the AD protocol, which includes checking BP every 3-5 minutes, loosening clothes, sitting the patient up, emptying the bladder, examining the patient for impacted bowel, and examining the skin for lesions. Should the protocol fail in lowering the BP and the patient requires medication management to lower the BP, a code will be called to better address the situation.

It is not routine to perform UDS acutely due to evolving bladder reflexes. However, it is possible to perform UDS during the acute phase of injury. Bellucci et al. successfully performed UDS on 60 acute SCI patients with injuries less than 40 days prior to the study, without reported morbidity secondary to the UDS.[19]

Electric Stimulation Risks:

Electric stimulation is commonly performed on the extremities of those with spinal cord injury at the study institution. There are few adverse reactions to electric stimulation. The common ones include:

- Pain with electric stimulation: in these cases, the intensity is reduced until it is comfortable.
- Skin irritation: it is common for redness to occur on the skin at the site of the surface electrode. This typically dissipates within an hour of removing the electrode. In some cases, the redness remains the next day. In these cases, they are likely sensitive to the adhesive used and a hypoallergenic skin electrode will be used.

3. STUDY POPULATION

3.1. List the number of subjects to be enrolled.

Consecutive patients meeting the inclusion/exclusion criteria admitted to inpatient rehabilitation for tSCI will be asked to enroll. Children and pregnant women will be excluded.

3.2. Criteria for Recruitment

- Initial screening will be performed via documentation provided in the EMR.
- Patients will be approached on the inpatient unit by the principle investigator or the research assistant to answer remaining questions and to consent the patient.
- They will be given an IRB-approved consent form to review and to sign.
- Those with tetraplegia will unlikely have the ability to sign and we will have a 3rd party attest

to the consent.
- Because of the time constraints of the study, they will have 1 day to decide upon whether they will participate or not.

3.3. Inclusion Criteria

The subject must meet all of the following inclusion criteria to participate in this study:

- 18-65 years old
- Enrollment within 6 weeks of injury
- Neurologic level rostral to T10 (T9 and above). This is a significant neurologic level because the bladder remains innervated at these levels, without damage to the nerve cell bodies of the bladder within the spinal cord.
- Discharge setting and transportation available for follow-up appointments

3.4. Exclusion Criteria

Subjects meeting any of the exclusion criteria at baseline will be excluded from participation:

- Subjects with pacemakers, defibrillators, insulin pumps, and similar devices will be excluded from the study
- History of peripheral neuropathy
- pre-SCI symptoms of peripheral neuropathy (numbness and/or tingling in feet, sharp/jabbing/burning pain in feet, sensitivity to touch, lack of coordination, muscle weakness, etc.)
- Known injury to the lumbosacral spinal cord or plexus, or pelvis with associated neuropathy
- History of genitourinary diagnoses (i.e. prostate hypertrophy, overactive bladder, cancer, etc.)
- Pregnancy
- History of central nervous system disorder (i.e. prior SCI, stroke, brain injury, Parkinson's disease, MS, etc.)
- Ventilator dependent respiration
- Significant autonomic dysreflexia during baseline urodynamic study.
- Non-English speakers

3.5. Withdrawal Criteria

Possible reasons for discontinuation of study intervention:

- Significant autonomic dysreflexia during baseline urodynamic study
- Intolerant to electric stimulation
- Unable to make follow-up appointment

3.6. Subject Replacement

Subjects who drop out will be replaced by screening the inpatient unit and asking for informed consent from those who meet the I/E criteria.

4. TRIAL SCHEDULE

Study Schedule with columns of 6-month intervals

Study Startup	xxxx		

Recruitment	xxxxxxxxxxxxxx	xxxxxxxxxxxxxxxx	
Baseline UDS	xxxxxxxxxxxxx	xxxxxxxxxxxxxxxxx	x
Specific Aim 2 RCT	xxxxxxxxxxxxx	xxxxxxxxxxxxxxxxx	xx
Post UDS	xxxxxxxxxxx	xxxxxxxxxxxxxxxxx	xxx
2-month UDS	xxxxxxxxx	xxxxxxxxxxxxxxxxx	xxxxxxxxxxxxx

5. STUDY DESIGN (Figure 1)

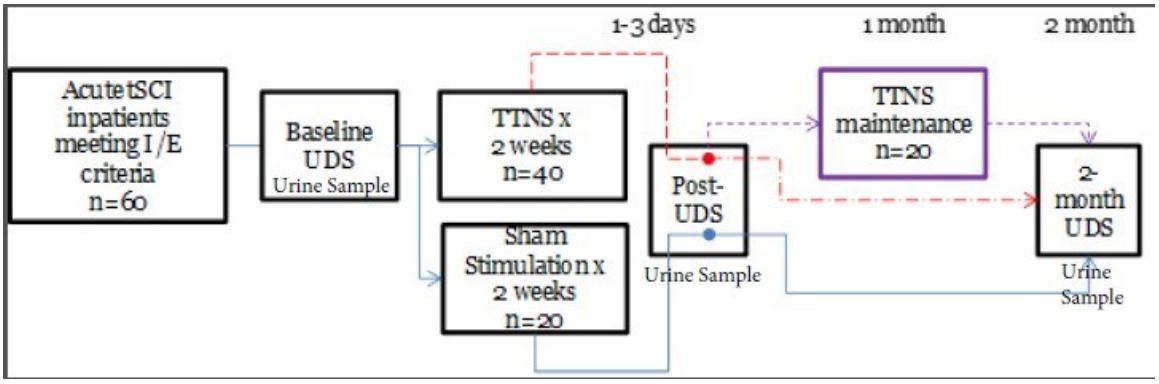

Figure 1. Study Design

- Anticipated number of patients to screen: 80
- Anticipated number of patient to enrol: 70
- Anticipated drop out or loss to follow-up: 10

Approximate time to complete study recruitment: 1 year
Expected duration of subject participation: 4 months

Specific Aim 1: To observe the safety of using TTNS during acute inpatient rehabilitation by prospectively tracking morbidity (infections, burns, and urgent transfers), pain during TTNS (visual analog scale), pain scores recorded per protocol by nursing, and changes in bowel/bladder programs.

Specific Aim 2: To determine the effects of a 2-week TTNS RCT trial as seen in post-UDS and 2-month follow-up UDS.

- Blinded randomized control trial of patients admitted to TIRR with acute SCI who meet I/E criteria and consent to participate in the study divided into three arms:
  - TTNS group: 10 sessions over a 2 week period of TTNS for 30 minutes, with electrode placement and settings as in SA 1. Current intensity may vary from patient to patient and will be documented and used in the analysis. The current intensity per patient will remain the same and should it need to be lowered, it will be recorded and added to the analysis.
  - Control group: control ankle stimulation, 5 sessions per week for 2 weeks, for a total of 10 sessions. Control ankle stimulation will be performed identical to the TTNS group, but after the intensity is set, it will be decreased abruptly to off.
- Pain scores on the visual analog scale will be recorded before stimulation is started, during, and after. This will be recorded for analysis.

Urine sample collected at baseline, discharge and at the follow-up appointments for all groups.

Samples will either be frozen or refrigerated and stored on site until shipped to the lab.
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UDS protocol:
The UDS is performed in the procedure suite at TIRR Memorial Hermann, where nursing staff and technicians routinely perform this study on spinal cord injury patients. Briefly:

- Sterile technique is used to empty the bladder with a lubricated catheter that inserts into the urethra and enters the bladder.
- When the bladder is empty, sterile technique is used to insert lubricated catheters with pressure sensors through the urethra into the bladder and into the rectum while the patient is supine on the procedure table.
- Surface EMG electrodes are placed on the perineal are to record the muscle activity of the pelvic muscles and viscera, including the internal urethral sphincter.
- Infusion of warm saline into the bladder at a rate of 40ml/min begins the UDS, while the computer records the activity of the bladder. Measurements include the pressure of the bladder and the abdominal pressure, as well the capacity and compliance of the bladder.
- The conclusion of the study occurs when bladder capacity is reached and the bladder will be emptied.
- Overall, the UDS will be performed following the guidelines of good urodynamic practices from the International Continence Society.[22]
- During the UDS, we will concurrently test novel high density (hd) surface electrodes to see if there is correlation between the electrical activity seen by the hd surface electrodes and the pressure recordings of the bladder.
    - The surface electrodes will be placed externally above the bladder, below the navel.

TTNS protocol: electrodes 2 inch by 4 inch will be placed according to anatomic landmarks, with the negative electrode behind the internal malleolus and the positive electrode 10cm superior to the negative electrode, verified with rhythmic flexion of the toes secondary to stimulation of the flexor digitorum and hallicus brevis. The intensity level will be set to the amperage immediately under the threshold for motor contraction. If there is not contraction seen, maximal tolerable intensity will be used. In addition, if the patient perceives pain, the intensity will be lowered until comfortable. Stimulation frequency of 10 Hz and pulse width of 200ms in continuous mode will be used.[13, 14]
Recording of the bladder activity with high density EMG surface electrodes will occur during session 1, session 5, and session 10. These are the same types of electrodes used in the UDS. Surface electrodes will adhere to the skin and placed above and below the pubic bone, placed by the research assistant. Recordings will last the entire stimulation session.

- Information gathered:
    - Clinical demographics and Neurologic Exam findings from interview with patients and EMR review.
    - Morbidity information from clinical findings and EMR review.
    - Urodynamic findings will be retrieved from the report generated from the urodynamics machine.
    - TTNS intensity will be recorded for each patient. Pain scores will be collected during the randomized control trial.
    - Skin examination where the electrodes were placed will be performed before and after each trial.
    - Information will be tabulated on an Excel spreadsheet on my personal work desktop, password protected. No paper data will be retained.

5.1. Summary of Study Design

In Specific Aim 1, we will monitor for safety and feasibility of TTNS during acute inpatient rehabilitation of SCI. In Specific Aim 2, the efficacy of TTNS will be studied by randomizing into 2 groups in a 2:1 ratio of TTNS:control. Control will be receiving brief ankle stimulation that will be turned off after the maximal intensity is found. After 2 weeks of stimulation, the RCT will have completed. Half of those in the TTNS group will be randomized to receive one maintenance dose of TTNS in the clinic. All those that participate will have UDS to measure outcomes at 2 months in clinic.

6. METHODS AND ASSESSMENTS

a. Urodynamic Studies will be performed per protocol described above. Data from the study is generated on a graph and printed. The pertinent values will be added to the data spreadsheet and the paper will be discarded.
b. Physical exam will be performed per usual care at TIRR, by the attending SCI physicians. Data will be retrieved from the electronic medical record and placed into the data spreadsheet. Missing data will be requested from the attending physician or directly from the patient.
c. Transcutaneous Tibial Nerve Stimulation (TTNS) will be placed daily by trained research assistants. Electrodes will be removed after the 30 minute session is completed. Pain scores will be collected before, during, and after the TTNS session. Skin inspection will be performed before and after each stimulation session at the electrode sites.
d. Bladder activity will be recorded at session 1, 5 and 10 lasting the whole stimulation session of all groups using the same type of electrodes used in the UDS placed below and above the pubic bone.
e. Urinary levels of NGF, cytokines and chemokines will be measured at baseline, discharge and follow-up appointment. Urine will be collected by sterile catheter or clean catch midstream (CCMS) voided specimen. Specimens will be processed at the time of collection, de-identified with an untraceable number.

6.2. Randomization and Blinding

a. Blinding: The P.I. will be blinded to the study allocation groups. Trained research assistants will apply the electrodes and collect the data during the 30 minute sessions.
b. Randomization: After consent and the baseline UDS, subjects will be assigned a number which will have already been designated as control or experimental group. Stratification will occur based on the UDS findings of areflexia versus no areflexia. The PI will be blinded to this randomization. The research assistant will have access to this file. Unplanned breaking of randomization will occur should rates of morbidity significantly increase. If breaking of randomization is required, the research assistant will provide the randomization file to the PI.

6.3. Contraception and Pregnancy Testing

For females of childbearing age included in the trial, pregnancy testing is typically performed prior to their admission to TIRR, available in the EMR or in the provided charting. Patient contraception is not applicable in acute spinal cord injury as the normal menstrual cycle is impaired in the acute setting and the study will be performed while the patient is admitted to inpatient rehabilitation.

6.4. Study Visits and Procedures

- *Screening Visits and Procedures*

Screening will be performed upon admission to inpatient rehabilitation via EMR. If there is missing information to complete the screen, it will be requested from the attending physician.

Those that meet the I/E criteria will be approached by the PI or research assistant and asked for informed consent. They will have 1 day, if needed, to decide. If the subject decides to participate, they will be scheduled for the baseline UDS in the following days and a urine sample will be collected. .

- *Study Visits and Procedures*

The baseline UDS will be scheduled by our therapy scheduling team and the UDS procedure suite will be prepared to accept the patient. Patients and the PI will be blinded to the randomization. Both groups will have the electric stimulation electrodes placed on their legs and the experimental group will have 30 minutes of the stimulation, with the parameters entered by the research assistant. This will occur for 10 sessions within a 2 week period.

Bladder activity will be recorded at session 1, 5 and 10 lasting the whole stimulation session of all groups using the same type of electrodes used in the UDS by placing them below and above the pubic bone.

Upon completion of the RCT, patients will be scheduled for a post-UDS. This will be similar to the baseline study. A second urine sample will be collected upon discharge.

Patients will then be scheduled for a discharge follow-up appointment that is estimated to be at 2 months. They will be given the Voiding Journal to fill in daily on discharge until their follow-up appointment. Some will be randomized to the maintenance group, 1 month after completion of the RCT. They will come to clinic and have the TTNS applied by the research assistant. The PI will continue to remain blinded. A third and final urine sample will be collected during the followup appointment for all groups.

- *Final Study Visit:*

The final study visit is the 2-month follow-up, in which the patients typically see their attending physician. The 2-month UDS will be scheduled for the same date. Subjects will perform UDS as in the post-UDS. The Voiding Journal will be reviewed with the patient and collected. Missing information will be asked of the patient.

As this UDS is part of the standard care at TIRR Memorial Hermann, recommendations on the management of neurogenic bladder will be given by the PI based on this study and recorded in the EMR. This includes prescriptions for bladder medications, as needed.

- *Post Study Follow up and Procedures*

The data will be statistically analysed in the post-study follow up. Subject participation is not required.

- *Discontinuation Visit and Procedures*

If withdrawal occurs, no evaluation will be required for the final study visit, regardless of the withdrawal reason. There are no safety risks in withdrawing from this study at any point.

7. TRIAL MATERIALS

The electric stimulation device used for TTNS is the Empi Continuum. The control is the Empi Continuum with the stimulation intensity set to zero. Low-binding plastic containers will be used for handling and storing urine. Urine will be processed via protocol for frozen and preserved specimen. The use of ethanol, betamercaptoethanol, and centrifugation will be used to process the urine for storage.

7.1. Trial Product (s)

The Empi Continuum is a multifunction electrotherapy device currently used at TIRR Memorial Hermann for the purpose of motor and sensory recovery in people with paralysis. It has the ability to provide conventional neuromuscular electric stimulation (NMES), transcutaneous electric nerve stimulation (TENS) and Pulsed Galvanic Stimulation electrotherapy. The device has wide-ranging capability and programmability, with stimulation and wave parameters adjusted for the proposed study purpose. The FDA Approved indications for the Empi Continuum are:

As an NMES device, indications are for the following conditions:
• Retarding or preventing disuse atrophy
• Maintaining or increasing range of motion
• Re-educating muscles
• Relaxation of muscle spasms
• Increasing local blood circulation
• Prevention of venous thrombosis of the calf muscles immediately after surgery

As a TENS device, indications are for the following conditions:
• Symptomatic relief and management of chronic, intractable pain
• Adjunctive treatment for post-surgical and post-trauma acute pain
• Relief of pain associated with arthritis

As a Pulsed Current device, indications are for the following conditions:
• Reduction of edema (under negative electrode)
• Reduction of muscle spasm
• Influencing local blood circulation (under negative electrode)
• Retardation or prevention of disuse atrophy
• Facilitation of voluntary motor function
• Maintenance of increase of range of motion

As a functional electrical stimulation (FES) device, the indications for the following condition:
• Stimulation of the leg and ankle muscles of partially paralyzed patients to provide flexion of the foot, thus improving the patient's gait

The high density surface EMG device has been evaluated by the FDA and has been found to be substantially equivalent to other medical devices used in people. FDA letter has been attached.

7.2. Storage and Drug Accountability

There are no special storage needs for the device. They will be stored in the locked office of the PI in a dry, dedicated place. Urine samples will either be frozen or refrigerated and stored on site until shipped to the lab.

8. TREATMENT

8.1. Rationale for Selection of Dose

Bladder neuromodulation in acute rehabilitation is not common. Neuromodulation of the detrusor has been successfully performed as early as 2 months after injury with transcutaneous surface electrodes applied directly over the bladder.[7] Thirty session of electric stimulation over a 5 week period sustained significant improvements in UDS measures at 2 years.[7] Invasive sacral neuromodulation has also been successfully performed early in spinal cord injury, while the bladder is atonic, with beneficial UDS outcomes.[11] Neuromodulation outcomes are typically measured after weeks of stimulation, however improvements in bladder parameters seen on UDS can be seen on initial electric stimulation of the tibial nerve.[13] Stimulation frequency of 10 Hz and pulse width of 200ms in continuous mode will be used.[13,14]

The 2 week period for the randomized control trial was chosen because it is feasible to perform during inpatient rehabilitation. Neuromodulation of the bladder has been shown to be effective after 6-8 sessions, with sessions performed once weekly over 12 weeks or 3 times weekly.[14] The 30 minute stimulation session is commonly used for bladder neuromodulation.[23, 24]

8.2. Study Drug Formulations

NA

8.3. Study Drug Administration

NA

8.4. Specific Restrictions / Requirements

Participants in the randomized control trial will be restricted from using any other form of electric stimulation in the lower extremities until the post-UDS is completed.

8.5. Blinding

Study participants will be blinded to the stimulation parameters of the TTNS. The research assistant will apply the electrodes and the PI will be blinded the stimulation setting as well. Unblinding is expected to occur after the 2 month follow up, at which point both subject and PI will be made aware of their group assignment.

Early unblinding will occur in the case of adverse events, including adverse events unrelated to the research. The attending physician will be made aware of the group in which the patient was

included.

8.6. Concomitant therapy

Medications that may have an effect upon the bladder will be recorded. The medication classes include: 1) bladder medications, 2)anti-spasm medications, 3) anti-depressants/anxiolytics; 4) neuropathic pain medications.

9. SAFETY MEASUREMENTS

9.1. Definitions

An adverse event is any unfavourable and unintended sign, symptom, or disease temporally associated with the use of a medical treatment or procedure that may or may not be considered related to the medical treatment or procedure.

The FDA definition of unanticipated adverse device effect will be used, as followed: *An unanticipated adverse device effect* as defined by FDA regulations at 2CFR 812.3(s) – Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

Skin irritation, inflammation, and electrode burn beneath the electrodes are potential adverse events directly related to the use of electric stimulation.

9.2. Collecting, Recording and Reporting of Adverse Events

The Investigator will be responsible for collecting and reporting adverse events during the UDS. The research assistant and the PI will collect adverse events related to the randomized control trial.

Grading of the severity of the adverse events will be made by the PI, using the Common Terminology Criteria for Adverse Events v4.0 developed by the National Cancer Instiute. The relevant “Burn” category is included below.

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		Grade				
Adverse Event	Short Name	1	2	3	4	5
Burn	Burn	Minimal symptoms; intervention not indicated	Medical intervention; minimal debridement indicated	Moderate to major debridement or reconstruction indicated	Life-threatening consequences	Death
REMARK: Burn refers to all burns including radiation, chemical, etc.						

Reporting procedures for:

- Deaths and life threatening events
- other SAEs
- Other adverse events

The PI will report problems according to the UTHSC-Houston IRB policy, specifically in the event which in the opinion of the PI is both unexpected and related and places subjects or

others at risk of harm.

The PI will report the reportable events to CPHS via iRIS within 7 days, unless the report involves the death of a participant, in which case the report needs to be provided to CPHS within 24 hours.

9.3. Safety Monitoring Plan

The Data Safety Monitoring Plan (DSMP) for the research study includes periodic statistical analysis on rates of morbidity of study participants compared to controls by the PI and the statistician. Because of the rolling recruitment in the proposed protocol, we anticipate the number of recruited individuals will be sufficient for morbidity review quarterly.

Specifically, we will focus on the occurrence of UTI. We hypothesize that the rate of UTIs in TTNS group will be similar to the control group. Based on literature, the rate of UTIs ranges from 20% to 50% in acute SCI patients, plus the addition of the incidence of UTI post UDS in acute SCI may be nearly 16%. As a result, we will stop the study if there is evidence to support UTI rate more than 40% in the TTNS group. The stopping rules are based on exact lower 95% Blyth-Still-Casella confidence bounds. If the number of cases of UTI exceed the specified stopping rules: ≥ 8 UTIs in 10 patients, ≥ 13 UTIs in 20 patients, ≥ 18 UTIs in 30 patients, ≥ 23 UTIs in 40 patients, then patient accrual will be paused pending a review by the Safety Monitoring Committee.

10. DATA ANALYSIS

10.1. Data Quality Assurance

The PI will be solely responsible for the accuracy of the data. Single data entry will be performed with plans to check 10% of primary variables as a quality control. Single data entry error rates are slightly higher than 0.5% when performed by trained staff and the minimally improved error rate through double data entry is outweighed by substantial cost savings for single data entry.[25] Data anomalies will be reviewed by the PI and clarification and/or correction will be performed. Incomplete entries will be reviewed and corrected if information is available.

10.2. Data Entry and Storage

Data will be entered on a spreadsheet file located on the TIRR Memorial Hermann password-protected desktop computer of the PI located in a locked office in TIRR Memorial Hermann. After data from reports generated from the UDS are entered into the spreadsheet, they will be filed in a study binder in a locked drawer in the office of the PI with HIPPA information removed.

5 years after manuscript publication, the paper reports will be placed into the shredder bins for destruction.

11. SAMPLE SIZE AND STATISTICAL METHODS

11.1. Determination of Sample Size

Our working hypothesis is that responders to TTNS would increase bladder capacity 100ml or 50%, which requires n=60. Sample size consideration was based on the working hypothesis with at least 80% power to detect an effect size of 1.0, regarding increased bladder capacity

and volume of first involuntary detrusor contraction with TTNS. These values were estimated based on the findings of Amarenco et al. and Chartier-Kastler et al.[13, 18] With an effect size of 1.0, this sample would result in a power of 88.3%. Power analysis was performed using the Proc Power in SAS with the paired sample t-test under assumed pairwise correlation of 0.5.

11.2. Statistical and Analytical Plans

The primary outcome measures for SA 1 are markers of morbidity between the control and experimental groups. This includes differences in rates of infections, skin irritation, urgent transfers, and pain scores. For these comparisons, the analysis will use a proportion test or generalized linear models.

The non-parametric Mann-Whitney U-test or paired t-test (for continuous measures) and McNemar test (for discrete measures) will be used to compare data as two samples come from the same subject. Multivariate analysis will be considered when patients' clinical variables are included as a confounding factor. If significant differences are found, then we will use post-hoc analyses using ANOVA to compare each of the primary end points. We will also conduct pairwise comparisons to identify which pairs of the study arms have different mean outcomes.

The primary outcome measures for SA 2 are the changes in the UDS parameters after 2 weeks of TTNS versus sham stimulation, with UDS performed at the end of the 2-week trial and again on follow-up in 2 months, which will use a similar statistical approach as in SA 1. When the study concerns multiple comparisons among four groups, the Bonferroni method will be used to ensure that the overall type I error remains below 0.05. A p-value of <0.05 is considered statistically significant. All statistical analysis will be conducted using SAS version 9.3 (SAS Institute, Inc. Cary, NC).

The secondary outcome measures include analyses of the differences amongst the 2 groups of neurogenic bladder in SCI according to baseline UDS. This will be analyzed with generalized mixed models (GMMs) which can also afford a multivariate analysis to account for potential confounders.[26] To correct potential selection bias by response, the analysis will be supplemented by weighted estimating approach.[27]

12. ETHICAL CONSIDERATIONS

12.1. Informed Consent

The PI will obtain informed consent from subjects meeting I/E criteria, within 1 week of their admission to TIRR Memorial Hermann. Subjects will have 1 day to decide whether they want to participate.
IRB-approved study participation material will be provided to the subjects.
Non-English speakers will be excluded.

12.2. IRB review

This protocol and the associated informed consent documents have been submitted to the IRB for review and approval, pending.

12.3. Confidentiality of Data and Patient Records

All patient records will remain confidential. Data with Protected health Information (PHI) will be de-identified and given a number assignment found on the Linking Log. The Linking Log is a separate file in a separate folder found on the PI's desktop computer.

Reports generated from the UDS will be de-identified and placed in a binder, stored in a locked drawer in the office of the PI.

13. PUBLICATIONS

We anticipate publication in a peer-reviewed journal within 2 years of beginning this study describing the effects of TTNS in acute SCI upon the bladder. Upon completion of the study in year 3, we anticipate publication of another manuscript within the year to describe the outcomes at 2 months.

14. RETENTION OF TRIAL DOCUMENTS

All records for all participants including CRFs and source documentation will be retained by the PI in a binder locked in his office, and on his desktop computer locked in his office. IRB and regulatory records will be placed in a binder along with the mentioned documents and will be retained by the PI in his office at TIRR Memorial Hermann, locked in a cabinet.

List of Attachments

Appendix 1 **Study Schedule and Study Design**

Appendix 2 **Case Report Form**

Appendix 3 **Sample Voiding Diary Log**

Appendix 4 **Informed Consent Form**

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