TMU-Joint Institutional Review Board

Title:

Non-invasive Nerve Stimulation for Inhibition of Bladder Incontinence in Spinal Cord Injured Subjects.

NCT number: NCT03877432

Date: 2020/10/29

Taipei Medical University

Certificate of TMU-JIRB Approval

Issue Date: 2020/10/21

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Protocol Title: Non-
invasive nerve stimulation for inhibition of bladder incontinence in spinal cord injured subjects
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Study Site:Taipei Medical University Hospital
Application Form:Version 3.0 / 2020.09.02
Protocol Version/Date:Version 2.1 / 2020.10.05

The amendment of above study has been approved by the TMU-Joint Institutional Review Board in meeting #109-10-3(date:2020/10/20), duration of validity is from 2020/10/21 to 2021/06/28, and must be monitored by TMU-JIRB.

According to Ministry of Health and Welfare and the relevant regulations, follow-up procedures and requirements are as below:

1. Continuing Report: Frequency of the report of this trial/study is every 12 month, and should be submitted to TMU-JIRB for review 2 months prior to expiry date (2021-04-28) or the trial/study must be pending.
2. Final Report: The report should be submitted to TMU-JIRB for review once completed TMU-JIRB may withdraw the approval of the trial/study if the report didn't submitted within 3 months from the date of validity and will suspend PI from new application for 3 months per TMU-JIRB SOPs.
3. SAE: Serious Adverse Event(s) (SAE) Report: SAE report(s) should be submitted to related authorities according to "Regulations for Good Clinical Practice" as well as "Procedures for Reporting Serious Adverse Drug Reaction" by MOHW.

Chairman:

Chung Ming Chen

臺北醫學大學暨附屬醫院
聯合人體研究倫理委員會
Taipei Medical University
Joint Institutional Review Board

Study Protocol and Statistical Analysis Plan

➢ Study Aim

Neurogenic bladder is among the most common complications associated with spinal cord injury, multiple sclerosis and stroke. Neurogenic bladder frequently leads to urological complications, such as incontinence, urinary tract infection, renal damage and subsequent renal dialysis or transplantation. “Turning off” the bladder (i.e. reducing reflex voiding and spasticity of the bladder, decreasing bladder pressures and increasing bladder capacity) has the potential to reduce the number and severity of these complications. Current methods for improving bladder function in persons with neurogenic bladder, including pharmacologic and surgical interventions, are incompletely effective.

The objective of this work is to decrease bladder hyper-reflexia using non-invasive cutaneous nerve stimulation of the S2-S4 dermatome nerve. To examine outcomes following SCI, investigators will test dermatome ES with individuals using intermittent catheterization to estimate the clinical impact on bladder capacity and continence.

➢ Inclusion Criteria

- Uprasacral SCI
- Neurologically stable
- Skeletally mature, over 18 years of age
- At least six (6) months post SCI
- Able to understand and comply with study requirements
- Able to understand and give informed consent

➢ Exclusion Criteria

- Active sepsis
- Open wound or pressure sores on cutaneous area
- Significant trauma, erosion or stricture of the urethra
- Pregnancy
- Individuals who can not speak

➢ Study Protocol

Anticholinergic medications may mask the effects of dermatome ES. If subjects take

anticholinergics (medicines to make participants' bladder relax, such as Ditropan, Oxybutynin, Detrol LA, Detrol, Tolterodine Tartate, Tofranil, Imipramine, Urimax, Xanodine, Enablex, Darifenain) participants will be asked to stop them for two weeks before the study. This may make it more likely that participants' bladder will leak and participants may need to use a pad or wear a catheter and leg bag to collect this leakage.

Urologic data collection will occur in the urodynamic laboratory for a single trial for ~2 hours. A dual-lumen Foley catheter will be inserted into the bladder via the urethra and the bladder will be emptied (volume recorded). One lumen of the catheter will be connected to a pressure transducer and amplifier to record bladder pressure, and the second lumen will be used to control bladder volume by filling and emptying with sterile saline. A balloon catheter inserted in the rectum will be used to determine detrusor pressure by subtracting rectal from vesical pressure. Surface electromyogram (EMG) electrodes will be applied to the anal sphincter to monitor pelvic floor activity. Infused volumes will be measured both via a force transducer and infusion pump. Signals will be monitored on an urodynamic system. Besides, two surface electrodes (1 cm x 1 cm) will be placed on the approximately cutaneous area of S2-S4 dermatome. Investigators expect to obtain bilateral area stimulation. The electrodes will be connected to the stimulator.

Serial cystometrograms will be conducted by filling the bladder with saline and recording the volume and pressure in the bladder. A total of 8 serial cystometrograms will be performed: 2 control fills, followed by 4 fills with stimulation, followed by 2 control fills. An initial cystometrogram will be used to verify bladder inhibition: the bladder will be filled until reflexive bladder contractions are elicited and electrical stimulation applied after the onset of a bladder contraction. For serial cystometrograms, stimulation will be initiated 30 seconds prior to, and stopped 30 seconds after, the cystometrogram. When bladder filling reaches the threshold volume at which reflex bladder contraction occurs (a bladder pressure increase greater than 35 cmH_2O sustained for >10 s or any bladder voiding), filling will be stopped. At the end of each cystometrogram, the bladder will be emptied and the volume added to any voided volume to determine total bladder volume.

➢ Potential Side-effects and Handling Methods

1. Elevated blood pressure or Autonomic Dysreflexia (AD)

There is a risk in subjects with spinal cord injury of elevation of blood pressure when the bladder is distended or contracting. This is due to autonomic dysreflexia and the risk is

dependent on the neurological level of spinal cord injury, being of relatively little significance with lesions below T6 but of increasing significance with higher lesions, and is well-known in clinical urodynamic testing. The elevation of blood pressure is occasionally asymptomatic but is usually associated with symptoms such as flushing of the face, nasal congestion, and headache and is well-known to most subjects with spinal cord injury. If ntreated it can result in stroke or death. This risk will be minimized by ensuring that subjects are familiar with the condition and its prevention and management and if necessary providing them with the standard medications used for its management. During urodynamic testing in this study the risk will be minimized by monitoring blood pressure with automatic measurement at least every five minutes, by stopping bladder filling and emptying the bladder in the event of substantial rises in blood pressure, and by utilizing the standard autonomic dysreflexia protocol in place in the SCI outpatient clinic.

2. Urinary tract infection

There is a risk of approximately less than 10% that a subject with SCI will develop a urinary tract infection (UTI) following urodynamics in this study. This risk will be minimized by performing catheterization with sterile technique. If the subject experiences signs or symptoms of a UTI (such as blood in the urine, frequency, urgency, increased spasms, fever, chills, and/or pain in the lower back) after the study, they will be instructed to contact a member of the study team. The subject will be examined and treated, if necessary, with the appropriate antibiotic.

3. Urethral trauma

There is a small risk, which investigators estimate at approximately 2%, that a subject will experience mild trauma to the urethra as a result of catheterization for this study. Such trauma might result in a small amount of bleeding from the surface of the urethra, similar to that seen from the gums on vigorous tooth-brushing. This risk will be minimized by lubricating the catheter with sterile water-soluble gel and by careful catheterization technique. Many individuals catheterize themselves multiple times per day and therefore the risk in these subjects is not significant.

4. Tissue burn

There is a very small risk that skin electrodes for electrical stimulation or recording could cause a tissue burn. This risk is very low because of the level of electrical stimulation and safety testing of the equipment. The safety of the complete electrical set up will be tested and documented before any testing is done. Periodic biomedical safety checks will

be performed for the intended use of all equipment used during these studies.

5. **Skin irritation**

There is a slight risk of skin irritation from the electrodes applied to the skin for electrical stimulation or from the gel used to assist in conducting the electricity. This will be minimized by using electrodes that are not known to be allergenic, and by using gel that is commonly used for other types of electrical stimulation and recording. The electrodes applied to the skin surface do not come into contact with the saline solution or urine.

6. **Exposure to uncomfortable electrical stimulation**

Subjects with incomplete SCI may be exposed, during acute experiments, to stimulation levels that are uncomfortable. This risk is small and manageable because stimulus amplitude will be increased slowly and discontinued if desired. Previous dermatome studies in non-SCI women to determine maximum tolerable stimulation levels have been conducted, therefore investigators do not expect tolerance to stimulation to be a limitation.

7. **Incontinence**

There is a risk of increased incontinence due to increased bladder capacity in patients who are asked to discontinue their usual anticholinergic medication 2 weeks before the study and for the duration of the study. This risk will be managed by describing it to the subjects and by offering them alternative methods of managing incontinence during this period, such as a condom and leg-bag system, pads, diapers, or catheterization.

➢ Statistical Analysis Plan

Investigators will use repeated measures ANOVA to determine the effects of dermatome stimulation on each outcome measure. Investigators will include subject as a factor in our analysis and consider starting levels as potential covariates. The outcome measures will be plotted as a function of day number throughout the trial to look for trends including increases or decreases in stimulation effectiveness. In addition, examination of baseline characteristics such as age, SCI location, etc. against the outcome effects might shed some light on other possible covariates to consider in future studies.