[1669332] High-frequency sacral root stimulation to improve bladder and bowel emptying following SCI

Funding Agency: Department of Veterans Affairs

Principal Investigator/Study Chair: Dennis Bourbeau, PhD

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Abstract

This is a 2-year case series study. Study participants will act as their own controls. This study will determine if sacral root stimulation at 600 Hz limits urethral sphincter contractions in individuals with SCI who have already been implanted with a Finetech-Brindley SARS system. The Finetech-Brindley SARS system is an FDA-approved device (Humanitarian Use Device) and we have received an IDE for testing this device at 600 Hz. In an initial visit lasting about 1 hour, we will complete an informed consent process to enroll the participant and collect a urine sample to test for a UTI. In a second visit lasting about 4 hours, we will conduct experiment procedures. Bladder and urethral sphincter pressures will be recorded using standard clinical urodynamics techniques. In a urodynamics laboratory, we will collect baseline data in response to the typical stimulation parameters that the participant uses for their daily bladder management. We will then test 600 Hz stimulation to determine whether this results in reduced sphincter contraction (Aim 1). The Finetech-Brindley device can also be programmed to achieve bowel emptying and return of bowel control is an extremely high priority for individuals with SCI [7]. Therefore, we will leverage the opportunity of this pilot study to determine if 600 Hz sacral root stimulation also has the potential to improve bowel emptying by reducing anal sphincter pressure (Aim 2). Participants will be asked to participate in experiments for both Aim 1 and Aim 2. Study participants who are Veterans will be consented and tested at the Cleveland VA Medical Center. Participants who are not Veterans will be consented and tested at the MetroHealth Medical Center. An IRB protocol for this study has already been approved at the MetroHealth Medical Center.

List of Abbreviations

CRC – Clinical Research Center
DSD – detrusor-sphincter dyssynergia
FES – functional electrical stimulation
LSCVAMC – Louis Stokes Cleveland Department of Veterans Affairs Medical Center
NIDDK - National Institute of Diabetes and Digestive and Kidney
NIH – National Institute of Health
SARS - sacral anterior root stimulation
SCI - spinal cord injury
SCI&D - Spinal Cord Injury & Dysfunction
TDL - Technical Development Laboratory

Contents

Protocol Title:

1.0 Study Personnel

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- Number of potential participating sites: 2

2.0 Introduction

Spinal cord injury (SCI) leads to neurogenic bladder dysfunctions, and often includes difficulty with emptying the bladder due to detrusor-sphincter dyssynergia (DSD). Current bladder management strategies include catheterization, pharmaceuticals, and/or surgery, but these interventions insufficiently meet individuals' needs. The neurogenic bladder can be emptied using sacral anterior root stimulation (SARS) with electrodes implanted on the sacral nerves to produce bladder contractions. However, this emptying can be impeded by reflex contractions of the urethral sphincter. The sacral sensory roots are typically transected (rhizotomy) to reduce these reflex contractions, but this rhizotomy also impairs desirable reflexes (e.g., sexual function) and sacral sensation if present. Experiments in animals have shown that sacral root stimulation at 600 Hz can inhibit urethral sphincter activity, which has the potential. This approach could be used in lieu of the rhizotomy to improve bladder emptying efficiency.

3.0 Objectives

The objective of this study is to test the potential effectiveness of 600 Hz sacral root stimulation to limit urethral sphincter activity in individuals with neurogenic bladder dysfunction (Aim 1). We hypothesize that sacral root stimulation at 600 Hz will result in lower urethral sphincter pressures compared to pressures in response to stimulation at the lower frequencies that are typically used for SARS. We will also test if this stimulation similarly limits anal sphincter activity (Aim 2). Individuals will already have received an implanted SARS device and will have also received a rhizotomy.

4.0 Resources and Personnel

Principal Investigators:

Dennis Bourbeau, PhD
Affiliate: Cleveland VA Medical Research & MetroHealth Medical Center
Responsibilities: Responsible for the overall conduct of study activities, including identifying interested individuals to participate, obtaining informed consent, data

collection and analysis, regulatory oversight, and dissemination of results. Research staff will report directly to him.

Co-Investigators:
Mary Ann Richmond, MD, PhD
Affiliate: Cleveland VA Medical Research
Responsibilities: assist with experiment oversight, be responsible for assuring access to appropriate facilities, and overseeing adherence to good clinical practice.

Hui Zhu, ScD, MD
Affiliate: Cleveland VA Medical Research & Cleveland Clinic Foundation
Responsibilities: Participate in experiment oversight and results interpretation.

Kenneth Gustafson, PhD
Affiliate: Faculty at Case Western Reserve University / VA Without Compensation (WOC) appointment
Responsibilities: contribute to protocol refinement, interpretation of results, and dissemination of findings.

Research Nurse: TBD

Study Coordinator: TBD

5.0 Study Procedures

5.1 Study Design

In this 2-year case series study, we will enroll 8 participants, male or female, who have SCI and who already use implanted sacral root anterior stimulation to manage their bladder. Participants will act as their own controls.

If a participant is a Veteran, then they will complete study visits at the Cleveland VA Medical Center. If they are not a Veteran, then they will complete study visits at MetroHealth Medical Center for which we already have an approved IRB protocol.

During an initial study visit, expected to take about one hour, we will obtain informed consent. Then a sample of urine will be collected and tested to determine if they have a urinary tract infection.

In the days following this initial visit, subjects will be prescribed an antibiotic, which they will pick up from Pharmacy, to take in the days before and after participation in this study to prevent a urinary tract infection. We will contact subjects in the days leading up to the second visit to remind them of the antibiotic.

A second study visit will then occur 2-30 days later and last about 4 hours. Stimulus waveforms for urethral sphincter inhibition will be tested in the clinical laboratory in a single session. We will not need to conduct new surgeries or implant procedures. The primary outcome measure is urethral sphincter pressure, and additional outcome measures include bladder pressure, rectal pressure, and bladder volume as measured in clinically standard urodynamics examination. The primary outcome measure for Aim 2 is anal sphincter pressure.

Clinical Impact

This study represents the first attempt to limit urethral sphincter contraction via 600 Hz stimulation of sacral roots in human participants. This approach using 600 Hz sacral root stimulation has successfully demonstrated voiding in chronic spinalized dogs, but has not been tested in humans. The Finetech-Brindley external controller has been modified to be capable of producing stimulation up to 600Hz. An Investigational Device Exemption has been obtained from the FDA to test this approach in human participants. Thus, one significant advantage of our study is that we will use this modified external controller to communicate with the already-implanted components of the system without new surgical procedures or significant risks. A second key advantage is that, because they have had a posterior rhizotomy, we can determine the stimulation parameters for activating and potentially limiting sphincter activity directly via the motor nerves, without confounding effects from sacral spinal reflexes. If this project is successful, these parameters can be applied in a future project to individuals who can have a stimulator implanted without rhizotomy, to determine if reflex activation of the sphincter can also be reduced. We understand that future work without rhizotomy will include the influence of reflex pathways, and this study may help us understand that influence by having this negative control. A future project would also then refine this approach by combining 600 Hz stimulation to reduce sphincter pressure with 20 Hz stimulation to evoke bladder contraction.

This project could have a high impact for individuals with neurogenic bladder dysfunction. It would help to address one of the highest priorities of individuals with SCI – restoration of bladder function - and help to address some of the biggest costs and health risks associated with managing neurogenic bladder by potentially improving bladder emptying without the need for catheters. There is a high potential for clinical translation because this approach takes advantage of existing technologies.

If this project demonstrates evidence of urethral sphincter pressure reduction in response to 600 Hz stimulation, then we will propose in a subsequent project to apply 600 Hz stimulation to individuals with SCI in whom sacral reflexes are intact. We would implant a SARS device without the rhizotomy, and determine if reflex contractions of the sphincter can be prevented during bladder emptying. In this way, we plan to achieve efficient, catheter-free, on-demand bladder emptying using sacral root stimulation without the need for a posterior rhizotomy.

5.2 Recruitment Methods

Eight participants will be enrolled, both men and women. Participants will be recruited from a pool of approximately 50 individuals who have already been implanted in Cleveland with the Finetech-Brindley SARS system. Individuals who are already implanted with the SARS system receive regular follow-up contact regarding their system. Our clinical colleagues will ask them about their interest in this study. Individuals who express interest will then be contacted by our study team for study enrollment. We conservatively estimate that at least 50% of these individuals can be reached for follow-up and 50% of those individuals will be willing to participate in this study. We have already received confirmation from 4 such individuals of their interest in participating in this work. Therefore, we are confident that we will not have difficulty recruiting for this study.

Study subjects will be compensated $75 for their participation via Greenphire ClinCard. This compensation rate is consistent with subject honoraria at our local site. They will receive Payment after each visit, including $25 if they complete the first visit and $50 if they complete the second visit. If the participants do not have a private vehicle, transportation will be provided to them.

5.3 Informed Consent Procedures

The PI (Dr. Bourbeau), or other staff authorized to obtain informed consent, will explain the study in person, answer questions, and obtain informed consent for participation in this study. The consent process will take place in privacy in a quiet room. The study goals and an overview of the experiment will be reviewed with each participant. Special care will be taken to inform the participant of all the potential risks of participation and that they may choose to withdraw from the study at any point. HIPAA guidelines will be followed by all study staff. For VA study participants, signed consent forms will be stored in a locked drawer in a locked room (B-E336). Consent will be obtained during the initial visit. The consent form will include contact information for the research team should the subject have further questions during the study.

5.4 Inclusion/Exclusion Criteria

Inclusion:

- Uses a SARS System with rhizotomy for bladder management
- Suprasacral SCI
- Neurologically stable
- Skeletally mature

Exclusion:

- Active, symptomatic urinary tract infection (UTI)
- Active sepsis
- Open pressure injuries on or around the pelvis

- Bleeding diathesis
- Significant urethral trauma, erosion, or stricture

5.5 Study Evaluations

We will use standard clinical urodynamics methods for data collection. We will use an FDA-approved modified external controller to communicate with the already-implanted components of the system, so no new surgeries or other procedures are required. The device has been modified to achieve frequencies up to 600 Hz and this modification was approved by the FDA in an IDE. We will document their normal daily usage device settings for reference, including stimulation amplitude, pulse width, frequency, and on/off cycle duration.

Clinical Urodynamics and Anorectal Manometry Procedure: A standard catheter will be inserted into the bladder via the urethra and the bladder will be emptied. This catheter will be removed and then a second catheter, which can measure bladder and urethral pressures, will be inserted. This catheter will also have a lumen for filling the bladder with sterile saline. A balloon catheter inserted in the rectum will be used to reflect abdominal pressure and distinguish bladder pressures due to detrusor contraction versus bladder pressures due to abdominal activity. This balloon catheter will measure rectal pressure. It will also have pressure transducers at the anal sphincter to measure anal sphincter pressure. Surface electromyogram (EMG) electrodes will be applied to the anal sphincter to monitor pelvic floor muscle contractions. Infused volumes will be controlled via an infusion pump. EMG and pressure signals will be monitored on a clinical urodynamic system. The participant's bladder will be infused with sterile saline while measuring bladder, urethral sphincter, and rectal pressures.

Sacral Anterior Root Stimulation: We will set the stimulation parameters for the implanted stimulator, including stimulation amplitude and frequency, using a modified Finetech-Brindley external controller unit. The frequency will be set either to 600 Hz or to the low frequency that the participant typically uses for emptying their bladder, which is usually 20 Hz. We will use the participant's own power transmission coil. The receiver coil and electrodes will already have been implanted. The pulse width will not be changed from the participant's normal setting.

Aim 1: Determine if 600 Hz sacral root stimulation limits contraction of the urethral sphincter.

During visit 2, in a single session, we will first administer SARS using the stimulation parameters (i.e., frequency, pulse width, and amplitude) that the study participant typically uses to empty their bladder and has been for years. The purpose is to characterize the usual level of urethral sphincter and bladder pressure during their bladder emptying routines and collect these baseline data.

We will also have a frame of reference for stimulation amplitude for testing 600 Hz stimulation.

We will then decrease the stimulation amplitude and identify the threshold amplitude to achieve urethral sphincter contraction at low frequency, which will be compared to the threshold amplitude to evoke bladder contraction. The motor efferents innervating the urethral sphincter are significantly larger in diameter than the motor efferents innervating the bladder, so the thresholds for activating the bladder are higher than for activating the urethral sphincter. These thresholds amplitudes at low frequency will give us additional context for evaluating the recruitment of urethral sphincter and bladder pressures in response to sacral stimulation.

We will then test stimulation at 600 Hz. 600 Hz stimulation will first evoke a brief (~1-2 second) onset respond and then the urethral pressure is expected to return to baseline. The stimulation amplitude will be set to 0 mA and gradually increased to determine the threshold amplitude for evoking an initial onset response of the urethral sphincter. We will continue to increase the stimulation amplitude until we have achieved maximal urethral sphincter pressure onset response. Stimulation will be maintained for up to 10 seconds with at least 30 seconds rest between stimuli. Once this recruitment curve is established, we will repeat stimulation at threshold, 50% maximal recruitment, and 90% maximal recruitment for up to 30 seconds to measure reduction of urethral sphincter pressures.

Aim 2: Determine if 600 Hz sacral root stimulation limits contraction of the anal sphincter.

This aim has the same design as Aim 1 but will focus on bowel function. Data for this aim will be measured during the same session as Aim 1. We will administer SARS using the stimulation parameters and pattern that the participant typically uses to empty their bowel and has been for years. These data will give us context for evaluating effects on bowel function.

We will then test stimulation at 600 Hz. This testing can be done simultaneously with 600 Hz testing for Aim 1. The stimulation amplitude will be set to 0 mA and gradually increased to determine the threshold amplitude for evoking an initial onset response of the anal sphincter. We will continue to increase the stimulation amplitude until we have achieved maximal anal sphincter pressure onset response. Stimulation will be maintained for up to 10 seconds with at least 30 seconds rest between stimuli. Once this recruitment curve is established, we will repeat stimulation at threshold, 50% maximal recruitment, and 90% maximal recruitment for up to 30 seconds to measure reduction of anal sphincter pressures.

5.6 Data Analysis

Outcomes from urodynamics data will be used to determine the effect of electrical stimulation on limiting urethral and anal sphincter pressures. Distributions of pressures without and with 600 Hz and 20 Hz stimulation will be compared with an ANOVA and a significance level of 0.05. We expect to observe a lower level of urethral and anal sphincter pressure in response to sacral stimulation at frequencies of 600 Hz compared to the low stimulation frequency that participants typically use.

Potential Limitations and Alternative Solutions

If 600Hz sacral stimulation in humans fails to limit urethral and anal sphincter activity compared to what is evoked at low frequency, then we will need to consider alternative stimulation strategies in future studies. We acknowledge that another potential approach using kilohertz frequency stimulation could be considered. Our group and others have tested kilohertz frequency sinusoidal waveforms extensively preclinically to block nerve
conduction. This could be another alternative to the rhizotomy, but it would require development and regulatory approval of a new implantable stimulation system that can safely deliver stimulation in the kilohertz frequency range for human testing [14]– [18].

We do not expect to experience significant technical challenges because (1) we are using a SARS system that study participants have been successfully using for years and (2) we are using research methods that we have successfully used for years to collect these data [19], [20]. We may find that the external controller does not deliver sufficient charge to achieve sphincter reduction at elevated stimulation frequencies. This is unlikely because the amplitude required to avoid contraction at 600Hz frequencies is not significantly higher than the amplitude to achieve activation at lower amplitudes.

5.7 Withdrawal of Subjects

There may be instances that would require investigators to terminate a participant's participation in this study. Investigators will stop the experiment if the participant demonstrates any unresolved physical or psychological discomfort.

6.0 Risks

Tissue Damage – rare. There is a small risk that the neural tissue may be damaged by the application of electrical stimulation. This risk will be minimized by applying stimulation within amplitude and duration parameters that were safe and effective in chronic preclinical experiments.

Urinary tract infection: This risk is uncommon. There is a risk of less than 10% that a subject will develop a urinary tract infection (UTI) following urodynamics in this study. This risk will be minimized by performing catheterization with sterile technique and by taking antibiotics before and after the experiment as

prescribed. If a 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, please contact a member of the study team. Subjects will be advised on how to proceed for medical treatment.

Urethral trauma: This risk is uncommon. There is a small risk, which we 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.

Discomfort during urodynamic testing: Subjects may experience some discomfort from lying down for up to four hours at a time during these procedures. If so, the investigators will assist subjects in changing position to become more comfortable. The investigators will assist subjects in changing position at least every 2 hours, if the procedures last that long, to reduce the risk of pressure injuries.

Reproductive Health/Sexual Activity: The effects on the developing child of using electrical stimulation during pregnancy and the risk of birth defects are unknown. Therefore, women who are pregnant or breastfeeding may not participate in this study.

7.0 Reporting

The investigators have participated in the necessary training activities related to human subject experimentation, protecting study volunteers in research, and passed required computerized training. Because this is a case series study, the primary concern is participant safety. The primary reporting channels within the VA will be used to assure study compliance and review of adverse events if they occur.

8.0 Privacy and Confidentiality

Local and central VA data security standards and protocols will be observed. Research Records will be retained in accordance with RCS 10-1. Electronic data will be stored on a password-protected VA drive (R:/Bourbeau). Physical documents will be stored in a locked drawer in the PI's locked office in B-E336. All data will be de-identified. Data collected during the course of the study will be associated with subjects using distinct alpha-numeric codes and the encoding key will be securely stored.

9.0 Communication Plan

The PI will complete reporting to oversight and regulatory bodies as required by standard procedures for these bodies, including but not limited to, Cleveland VA

Medical Center and its IRB, VA Central Office, and MetroHealth Medical Center and its IRB. PHI/PII will not be shared within this communication.

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