Official Title of the Study: Locomotor Function Following Transcutaneous Electrical Spinal Cord Stimulation in Individuals With Hemiplegic Stroke

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PROTOCOL TITLE: Locomotor function following transcutaneous electrical spinal cord stimulation in individuals with hemiplegic stroke

PRINCIPAL INVESTIGATOR:
Elliot J. Roth, MD
Physical Medicine and Rehabilitation
312-238-4864
eroth@sralab.org

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STUDY SUMMARY:

Investigational Agent(s) (Drugs or Devices)	Biostim-5 Spinal Stimulator
IND / IDE / HDE #	
Indicate Special Population(s)	☐ Children ☐ Children who are wards of the state ☐ Adults Unable to Consent ☐ Cognitively Impaired Adults ☐ Neonates of Uncertain Viability ☐ Pregnant Women ☐ Prisoners (or other detained/paroled individuals) ☐ Students/Employees
Sample Size	45 persons with stroke
Funding Source	Shirley Ryan AbilityLab & Frankel Foundation
Indicate the type of consent to be obtained	☒ Written ☐ Verbal/Waiver of Documentation of Informed Consent ☐ Waiver of HIPAA Authorization ☐ Waiver/Alteration of Consent Process
Site	☒ Lead Site (For A Multiple Site Research Study) ☐ Data Coordinating Center (DCC)
Research Related Radiation Exposure	☐ Yes ☒ No
DSMB / DMC / IDMC	☐ Yes ☒ No

OBJECTIVES:

- To determine whether transcutaneous spinal cord stimulation combined with ambulation training modulates corticospinal locomotor networks in individuals with hemiplegic stroke
- To determine whether transcutaneous spinal stimulation combined with ambulation training improves locomotor function in individuals with hemiplegic stroke
- To determine whether transcutaneous spinal stimulation combined with ambulation training improves symmetry of gait in individuals with hemiplegic stroke
- To determine whether ambulation efficiency improves with transcutaneous spinal stimulation and locomotor training in individuals with hemiplegic stroke

Our hypothesis is transcutaneous spinal cord stimulation combined with ambulation training in persons with hemiplegic stroke will lead to improved: modulation of corticospinal networks, locomotor function, symmetry of gait, balance and efficiency compared to ambulation training alone.

BACKGROUND:

The use of epidural stimulation has been performed with implanted electrode systems and demonstrated effectiveness in human and animal models after spinal cord injury, but this will be one of the first studies to investigate the efficacy of a painless and non-invasive method of spinal cord stimulation with individuals with hemiplegia due to stroke. This is significant because the transcutaneous epidural stimulation carries less risk (compared to implantation procedure) and more individuals suffer from the consequences of stroke compared to spinal cord injury.

The use of epidural spinal-cord stimulation was shown to generate locomotion patterning in humans after a complete spinal cord injury[1]. The intervention may be effective, but the invasive and involved procedure is not realistic for incorporation into routine rehabilitation services. Recent efforts have induced step-like patterns in patients with a motor complete spinal cord injury using non-invasive spinal cord stimulation. Even more promising is that these individuals were able to demonstrate *voluntary* step-like patterns with continued training.[2] These results reflect the potential for neuroplasticity modulation through non-invasive spinal stimulation during locomotor training for individuals with a disruption between supra and spinal connections.

We would like to explore the use of this device with patients with a single, stroke history that resulted in hemiplegia. The results of this study will help us understand how transcutaneous electrical stimulation may improve balance and ambulation in individuals with a stroke. The number of people diagnosed with a stroke in the United States is 795,000 per year. Projections estimate that by 2030, there will be an additional 3.4 million adults with a stoke.[3] This is a significant number of people that may benefit from this training paradigm.

References:

1. Dimitrijevic MR, Gerasimenko Y, Pinter MM. Evidence for a spinal central pattern generator in humans. Ann NY Acad Sci 1998;860:360-376.
2. Gerasimenko YP, Lu DC, Modaber M, et al. Noninvasive reactivation of motor descending control after paralysis. Journal of Neurotrauma. 2015. 32:1968-1980. Doi:10.1089/neu.2015.4008.
3. Benjamin EJ, Blaha MJ, Chiuve SE, et al. Heart disease and stroke statistics – 2017 update: a report from the american heart association. Circulation. 2017;135:e1-e458. Doi:10.1161/CIR.0000000000000485

STUDY ENDPOINTS:

Primary endpoint:

- Changed locomotion symmetry reflected by altered symmetry in spatio-temporal parameters, and kinematic measures during walking.

Secondary endpoints

- Improved locomotion efficiency in Six Minute Walk Test (6MWT)
- Improved gait speed as measured by the Ten Meter Walk Test (10MWT) at self-selected velocity and fastest (safe) velocity

- Improved gait kinematics reflected by improved symmetry and decreased base of support during walking on the the GAITRite electronic walkway

STUDY INTERVENTION(S) / INVESTIGATIONAL AGENT(S):
A Transcutaneous Spinal Cord Neurostimulator (BioStim-5) will deliver transcutaneous electrical spinal cord stimulation. It provides constant current stimulation with a range of 0-250 mA through self-adhesive electrodes (ValuTrode, Axelgaard Ltd., USA) with a diameter of 3.2 cm placed as cathodes on the skin between the spinous processes of the C4 and Co1 vertebrae. In addition, two 7.5 × 13 cm self-adhesive electrodes serving as anodes (ValuTrode, Axelgaard Ltd., USA) will be placed symmetrically on the skin over the iliac crests. The stimulation waveform will consist of biphasic, rectangular 1-ms pulses at a frequency ranged between 0.2 and 40 Hz, with each pulse filled with a carrier frequency of 5 to 10 kHz. The stimulation intensity will vary from 5 to 250 mA and be determined based on participant threshold and maximum motor outputs.

PROCEDURES INVOLVED:

Study Design: A randomized control trial. We are evaluating the effectiveness of transcutaneous spinal cord stimulation on ambulation among individuals with hemiplegia due to stroke. We will randomly assign participants in the Stroke group into either intervention group A or intervention group B. Intervention group A will receive transcutaneous spinal cord stimulation during the intervention visits while intervention Group B will complete the same interventions without transcutaneous electrical spinal cord stimulation. However, Group B will receive sham stimulation. Healthy control participants will complete assessment visits in order to obtain comparative data for various outcome metrics.

STUDY EQUIPMENT

- **Wearable sensors**

The sensors used will include EMG sensors and Xsens motion capture sensors. The wearable sensors will collect the following information:

- Biometric data, including electromyography (EMG)
- Movement data from the limbs including signals from triaxial accelerometers (ACC) and gyroscopes (GYR)

- **Electronic walkway**

The GAITRite electronic walkway contains sensor pads encapsulated in a carpet and connected to a computer. The system can be laid over any flat surface and automates measuring temporal and spatial gait parameters. The GAITRite electronic walkway for the study shall be a minimum of 14 feet long. The GAITRite data capture was chosen as measurement of the patient's overall gait quality. Patients will be asked to walk at a self-selected speed and a fast, but safe, speed across the GAITRite electronic walkway with and without lower extremity orthotics if safe and appropriate during assessment visits and during treatment sessions to quantify ambulation symmetry.

- **Gravity Eliminated locomotion training**

A custom designed apparatus to allow the lower legs to move in a gravity neutral position. Participants in the Stroke group are positioned in a side-lying position on their non-paretic side. Participants in the healthy control group will be in a side-lying position on their preferred side. Their legs extend off the edge of the mat table. The upper leg is supported

at the shank and the lower leg is placed on a rotating brace attached to a horizontal board supported by vertical ropes secured to the ceiling. In this gravity-neutral position, the participants will be requested to perform rhythmic stepping-like motions.

- **Transcutaneous Spinal Cord Neurostimulator**

A Transcutaneous Spinal Cord Neurostimulator (BioStim-5) will deliver transcutaneous electrical spinal cord stimulation. It provides constant current stimulation with a range of 0-250 mA through self-adhesive electrodes (ValuTrode, Axelgaard Ltd., USA) with a diameter of 3.2 cm placed as cathodes on the skin between the spinous processes of the C4 and Co1 vertebrae. In addition, two 7.5 × 13 cm self-adhesive electrodes serving as anodes (ValuTrode, Axelgaard Ltd., USA) will be placed symmetrically on the skin over the iliac crests. The stimulation waveform will consist of biphasic, rectangular 1-ms pulses at a frequency ranged between 0.2 and 40 Hz, with each pulse filled with a carrier frequency of 5 to 10 kHz. The stimulation intensity will vary from 5 to 250 mA and be determined based on participant threshold and maximum motor outputs.

- **Cosmed K4B^2 Metabolic unit**

Cosmed K4B^2 (K4B2 Cosmed, Italy) is a portable gas analysis system that measures oxygen consumption (VO_2) and Carbon-dioxide production (VCO_2) in a breath by breath fashion. K4B^2 system consists of a portable unit and battery pack that weighs about 2.4 lbs (1100 gm). The portable unit has O_2 and CO_2 analyzers that are bi-directionally connected to a flowmeter and turbine attached to a rubber facemask that is tightly strapped over subject's nose and mouth. K4B^2 requires calibration before every testing session due to usage of heated sensors for measurements. Manufacturer's recommend at least 45 minutes warm up time for unit under ambient temperature (ideally at 20°C) before calibration. K4B^2 calibration involves verifying flowmeter and concentrations of gases with labeled concentrations. K4B^2 acquires heart rate using a telemetric heart rate sensor that is strapped over subject's thorax. The K4B^2 and battery pack can be securely placed in slots on a standard harness worn by subject. This harness allows access to buttons on the unit on upper back and minimal interference to activities like walking. Data extraction and processing is carried using K4B^2 custom software.

VISIT SCHEDULE & DESCRIPTION

Visits 1: Initial screening session

- Obtain voluntary and informed consent
- Inclusion/exclusion criteria checklist reviewed with patient
- Medical history review
    - Patient name
    - Patient date of birth
    - Patient race (voluntary)
    - Patient gender
    - Date of stroke
    - Type and location of stroke
    - Paretic/non-paretic limb
    - Assistive device use
    - Recent surgery/injuries
    - Allergies
    - Therapy history

    - Current medications
    - Emergency contact information
    - Personal contact information
- Evaluation of Physical Function
    - Active and passive range of motion of bilateral lower extremities
    - Assessment of lower extremity spasticity using Modified Ashworth Scale
    - Assessment of gait for ataxia and level of independence with Functional Ambulation Category

A letter detailing the study procedures and risks will be sent to the subject's physician or clinician to request medical clearance for the subject to participate in the study. Permission to contact the participant's physician or clinician to obtain medical clearance will be obtained during the screening process prior to or during Visit 1.

Baseline Assessment Visits

- Standard evaluation of physical function
    - Muscle strength assessment using manual muscle testing of lower extremities
    - Skin integrity screen

- Functional outcome measurements
    - Six Minute Walk Test (6 MWT)

    Participants will complete the 6MWT with wearable sensors and Cosmed K4B^2 Metabolic unit to determine participant's baseline gait efficiency

    - Ten Meter Walk Test (10 MWT)

    Participants will complete at their self-selected speed (SSV) and fastest safe velocity (FV) three times each with and without lower extremity orthotics if safe and appropriate (12 total) with wearable sensors and CosmedK4B^2 Metabolic Unit to determine baseline gait speed and community ambulation assessment without stimulation. Participants will then repeat the assessment up to 12 times with the use of transcutaneous electrical spinal cord stimulation to assess for the immediate effects of stimulation on gait speed.

- Locomotion assessment for inter and intra limb coordination using wearable sensors and EMG sensors. Participants will ambulate along Gait Rite electronic walkway to evaluate baseline gait pattern at both their self-selected and safe fast gait speed without stimulation.

- Spinal Motor Evoked Potentials (MEPs) will be obtained at each of the assessment time points while stimulating the spinal cord between the spinous processes of C4 and the Co1 vertebrae with a single pulse. MEPs are the electromyograph responses of the peripheral muscles to electrical stimulation of the spinal cord. MEPs will be used to test the integrity of the motor pathways of the spinal cord.

Treatment Sessions

Each participant will complete up to 24 treatment sessions over the course of 8 weeks. Each treatment session will:

- Intervention Group A (Experimental):
    - 45 minutes of locomotion training with transcutaneous spinal cord stimulation. However, the amount of time spent in side-lying locomotion training, treadmill

training and overground training will depend on individual tolerance and progression.

- Intervention Group B (Control):
    - 45 minutes of locomotion training without transcutaneous spinal cord stimulation, but with sham stimulation. However, the amount of time spent in side-lying locomotion training, treadmill training and overground training will depend on individual tolerance and progression.

Under all the conditions, the goal is to generate smooth and symmetrical stepping movements. The trained research personnel will provide cues (verbal, visual and tactile) to improve symmetry of gait and avoid compensatory mechanisms. The progression in training refers to gradually increasing gait speed while maintaining improved gait kinematics.

Follow-up Functional Assessment Visits – Mid point, Post, 3 months Post

- Refer to Baseline Assessment Visit for repeat of assessments

SAFETY MONITORING

All visits will be under the supervision of a trained researcher and clinician. Manual assistance or cueing will be provided as necessary for safety and balance. Clinicians will also utilize gait belts and overhead harness systems to ensure patient safety during physical activity. Vital signs will be monitored with use of our wearable sensors before, during and after physical exertion. All subjects will be permitted to stop physical activity or rest at any time during the study. In addition, the following patient reports will be used to assess patient participation and make adjustments as appropriate.

- **Rating of Perceived Exertion (RPE)**

The 15-grade Borg Scale during ambulation training (overground, treadmill and gravity-eliminated) to monitor RPE. The intensity will be adjusted to ensure patients do not exceed a rating of 17 (very hard).

- **Pain scale**

Visual Analogue Scale (VAS) for pain will monitor patient discomfort during non-invasive spinal cord stimulation and locomotion training parameters. This is a 10-point scale. We will stop when the participant states pain that interferes with their safe participation in the research.

AUDIO/VIDEO RECORDING/PHOTOGRAPHY

Video recording and/or pictures of each participant during assessment and training sessions may be taken during the training and testing sessions. These items may be used to help troubleshoot potential issues for fit or functionality of the device. They may also be used for presentations and training of other research personnel. Each Subject may choose to limit if/how these items may be used, as indicated during their Consent process.

DATA AND SPECIMEN BANKING

Data will be collected and kept confidential and compliant with HIPPAA requirements. All personal information and study documentation that can identify participants will be kept secure to protect their privacy and will never be shared at any time with any person or entity. Data collected during the study and shared with others will reference participants only by an alphanumeric code. The “master list” linking personal information to the alphanumeric code will not be shared. All data will be captured in electronic format and stored on the secure and password protected network and devices managed by the Shirley Ryan AbilityLab. Electronic folders will be private with limited access as determined by the PI.

INCLUSION AND EXCLUSION CRITERIA

Inclusion Criteria:

- Participants are 18 years of age or older
- Participants are at least 4 weeks post stroke
- Participants with hemiplegia secondary to a single stroke
- Functional Ambulation Category of 2 or greater - Patient needs continuous or intermittent support of one person to help with balance and coordination.
- Participants are able to provide informed consent
- Participants are not currently receiving regular physical therapy services

Exclusion Criteria:

- Individuals less than18 years of age
- Individuals less than 4 weeks post stroke
- Individuals with ataxia
- Individuals with multiple stroke history
- Currently taking a Selective Serotonin Reuptake Inhibitor (SSRI) or Tricyclic antidepressant (TCA)
- Botox injection in lower extremity within the last 4 months
- Modified Ashworth score of 3 or greater in lower extremity
- Pregnancy or nursing
- Pacemaker or anti-spasticity implantable pumps
- Active pressure sores
- Unhealed bone fractures
- Peripheral neuropathies
- Painful musculoskeletal dysfunction due to active injuries or infections
- Severe contractures in the lower extremities
- Medical illness limiting the ability to walk
- Active urinary tract infection
- Clinically significant depression, psychiatric disorders, or ongoing drug abuse
- Metal implants in their spine
- Active cancer or cancer in remission less than 5 years

VULNERABLE POPULATIONS NA

PARTICIPANT POPULATION(S)

Accrual Number:	Category/Group: (Adults/Children Special/Vulnerable Populations)	Consented: Maximum Number to be Consented or Reviewed/Collected/Screened	Enrolled: Number to Complete the Study or Needed to Address the Research Question
Local	Adults (Stroke Group)	100 consented and screened, goal of 45 to complete the full protocol	45
Study-wide	Single-Center Study	0	0
Total:		45	45