Official Title of the study: ADDRESS: Activity Dependent Rehabilitation via Transcutaneous Electrical Spinal Stimulation to Restore Upper Extremity Functions in Spinal Cord Injury
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Study Protocol:

Spinal cord injury and other spinal dysfunctions have a lifelong, high impact on individuals, families, and society. It is estimated that there are between 250,000 and 500,000 new cases of spinal cord injury each year, worldwide. Spinal cord injury is currently incurable. Existing treatment options are less than satisfactory and are limited to preventing secondary complications and maximizing residual function through rehabilitation. Paralysis of the upper limbs results in a significant loss of independence in daily activities and a decrease in quality of life. Tetraplegic patients suffering from a cervical spinal cord injury prioritize the recovery of their arm and hand function to enhance quality of life.

Stimulation of the spinal cord may induce the growth and reorganization of neural pathways, leading to the reanimation of paralyzed limbs. To date, epidural stimulation with surgically implanted electrodes is demonstrating tremendous success for patients with spinal cord injury. Growing evidence suggests that electrical spinal stimulation modulates the excitability of spinal circuitry, enabling the weak but remaining descending drive (signal pathways from the brain) to resume control of movements. Utilizing epidural stimulation can enhance conscious motor control in both the legs and hands of human subjects. Even in cases of clinically complete spinal cord injury, initiation of voluntary leg movements and gains in postural control are observed in human subjects. In addition, epidural stimulation results in tonic and rhythmic motor patterns in the lower limbs of humans lying supine, as well as improvements in bowel, bladder, and sexual function.

Recently, a non-invasive technique for spinal stimulation, specifically transcutaneous electrical spinal cord stimulation, has been demonstrated to be effective in improving motor function in both healthy individuals and patients with spinal cord injuries. The effects of this novel technology on upper extremity motor function have not been tested. This research study employs a prospective, experimental, randomized crossover design to assess the safety and efficacy of transcutaneous cervical electrical stimulation in improving upper limb function in patients with cervical spinal cord injury.

Electrical cervical stimulation has been shown to be effective in improving upper limb function in animal studies conducted in our laboratory. By other groups, transcutaneous electrical spinal

cord stimulation has been demonstrated to be effective in improving lower extremity motor function in both healthy individuals and patients with spinal cord injury. Transcutaneous spinal stimulation was applied to the skin via external electrodes placed midline on the spinous processes of the vertebrae. A novel, well-tolerated, and painless transcutaneous electrical enabling motor control strategy was used for neuromodulation. Previously, no adverse effects have been reported with transcutaneous electrical spinal cord stimulation. Patients described a non-disturbing tingling sensation beneath the electrodes.

The purpose of the study is to implement and test transcutaneous spinal stimulation in patients with cervical spinal cord injury (traumatic or degenerative etiology) in combination with a rehabilitation program. We aim to enhance both arm and hand sensorimotor functions.

Our primary objectives are:

1. To establish a novel, non-invasive therapeutic stimulation approach in patients with cervical spinal cord injury.
2. To determine transcutaneous stimulation locations and parameters that are safe and effective for augmenting hand motor and sensory function.
3. To evaluate both immediate and lasting improvements in hand motor and sensory function via transcutaneous cervical spinal stimulation.

Our secondary objectives are to document and analyze other potential benefits of electrical neuromodulation, including a decrease in spasticity, an increase in bowel and bladder control, and an improvement in mobility.

Inclusion Criteria. Individuals who

1. has cervical (C7 or higher) spinal cord injury with a duration of at least 1 year duration
2. are between 21 and 70 years of age
3. has difficulty with hand functions in activities of daily living (e.g., dressing, grooming, feeding)
4. has a stable medical condition without cardiopulmonary disease or frequent autonomic dysreflexia that would contraindicate participation in upper extremity rehabilitation or testing activities
5. are capable of performing simple cued motor tasks
6. has the ability to attend 2 to 5 weekly physical therapy sessions and testing activities
7. has adequate social support to be able to participate in weekly training and assessment sessions for the duration of 6 months within the study period.
8. has the ability to read and speak English

will be included in the study.

Exclusion criteria. Individuals who

1. has an autoimmune etiology of spinal cord dysfunction/injury
2. has a history of additional neurologic disease, such as stroke, MS, traumatic brain injury, etc.
3. has peripheral neuropathy (diabetic polyneuropathy, entrapment neuropathy, etc.)
4. has rheumatic diseases (such as rheumatoid arthritis and systemic lupus erythematosus)
5. has significant medical disease, including uncontrolled systemic hypertension with values above 170/100 mmHg; cardiac or pulmonary disease; chronic contagious disease, such as Hepatitis B and C, HIV; uncorrected coagulation abnormalities or need for therapeutic anticoagulation.
6. has active cancer
7. has cardiovascular or musculoskeletal disease or injury that would prevent full participation in the physical therapy intervention
8. unhealed fracture, contracture, pressure sore, urinary tract infection, or other illnesses that might interfere with upper extremity rehabilitation or testing activities
9. has any condition that would render the patient unable to safely cooperate with the study tests, as judged by the screening physician
10. are pregnant
11. has received botulinum toxin injections in the upper extremity muscles in the prior 6 months
12. has undergone tendon transfer or nerve transfer surgery in the upper extremity
13. are dependent on ventilation support
14. has an implanted stimulator (e.g., vagus nerve stimulator, pacemaker, cochlear implant, etc.).
15. has depression or anxiety based on Patient Health Questionnaire (PHQ-9) (score >9/27) and General Anxiety Disorder-7 item Questionnaire (score >9/21), respectively.
16. has alcohol and/or drug abuse.
17. has cognitive impairment based on the Short Portable Mental Status Questionnaire (SPMSQ) (score >2/10).
18. are unable to read and/or comprehend the consent form.
19. lack of ability to fully comprehend and/or perform study procedures in the investigator's opinion/judgement
20. has a history of severe allergy (i.e., allergic reaction that could not be treated with antihistaminic medication

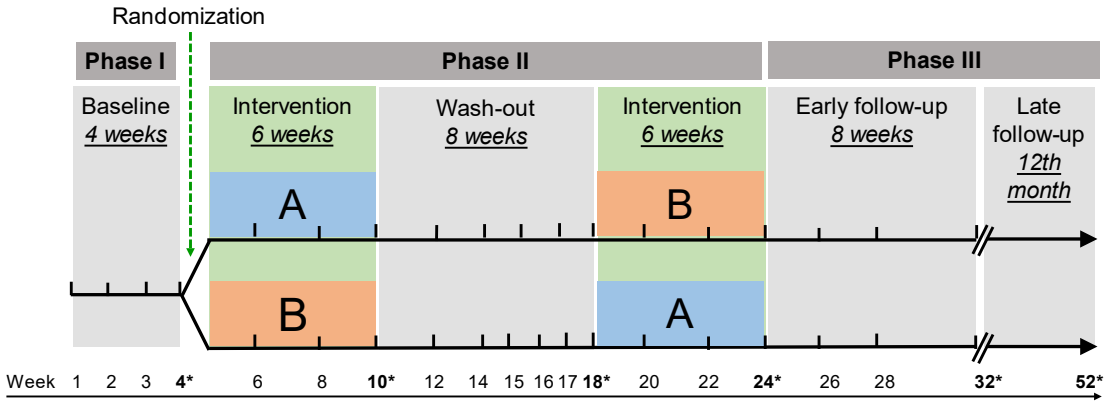
will be excluded.

If a patient inquires about the study, they will then be provided an opportunity to speak with research assistants about the study. This will be done in a quiet and private area, such as a patient's room or office, in order to maintain confidentiality. If the patient contacts us via phone, research assistants will provide information about the study and answer their questions. Research assistants will explain that participation in the study is strictly voluntary, and if the patient chooses not to enroll, their care will not be affected in any way. The research team member obtaining informed consent will explain that participation in the experiment is not required nor connected with the clinical treatment or procedure. No individual incentives will be offered in exchange for participation in the study.

Subjects who meet all the inclusion criteria and none of the exclusion criteria at their pre-screening and initial evaluation visit will be approached by research assistants. (S)he will explain the study and review the consent with the patient. Patients will be assured that participation is voluntary and that they will continue to receive their usual clinical care if they choose not to participate. Subjects will be given 1 week to decide whether they wish to participate in the study.

We will use advertisement flyers/information sheets that will be clearly displayed in the neurosurgery and rehabilitation outpatient departments for all to see. Additionally, subjects will be informed about the study during their routine control visits in the Departments of Neurosurgery and Rehabilitation Medicine by their primary physicians. Notifications may be posted on our departmental and laboratory websites and distributed via listservs that reach this community.

Study design:



Timeline for outcome measurements:
Weeks without asterisk – only GRASSP quantitative prehension and grip & pinch strength measurements will be done
Weeks with asterisk – all outcome measurements will be done

A – Physical Therapy Only
B – Transcutaneous Spinal Cord Stimulation + Physical Therapy

Pre-Screening Phase – Patients interested in volunteering will be evaluated for eligibility by a research assistant. Candidate patients will be asked to provide their oral consent to participate in the screening questionnaires. This includes a yes-no questionnaire and multiple-choice questions by phone or in person.

After completing the screening procedures, eligible patients will provide informed consent. During that visit, one of the research assistants will answer any further questions the candidate patient may have regarding the study. Patients will have 1 week to decide whether they would like to participate in the study.

Phase I – Initial Medical Assessment and Baseline Measurements

After obtaining informed consent, an initial medical assessment of the included subjects will be conducted by a licensed physician/neurosurgeon of our UW Neurological Surgery Department. Baseline upper extremity functional measurements and health-related questionnaires will be obtained by one of the research assistants/scientists at the UW Department of Rehabilitation Medicine and/or the Amplifying Movement & Performance Laboratory (AMP Lab). John M. Wallace Hall (Room 055, 3737 Brooklyn Avenue NE, Seattle, WA 98105). Initial medical assessment and outcome measurements include:

- A complete physical and neurological exam
- Graded and Redefined Assessment of Strength, Sensibility, and Prehension Test (GRASSP)
- International Standards for Neurological Classification of Spinal Cord Injury (ISNCSCI)
- Hand strength measurement by grip and pinch dynamometry
- WHO-Quality of life – BREF

After the initial assessment, patients will be scheduled for additional hand function measurements up to 2 times per week for up to 4 weeks (no more than four sessions total). These sessions measure the stability of the underlying disability and control for test-retest learning. Each session will last 1-2 hours. These recurrent measurements will include:

- GRASSP test Quantitative Prehension Subscale
- Vital signs (blood pressure, heart rate)
- Hand strength measurement by grip and pinch dynamometry

Phase II – Intervention Phase

After Phase I, patients will be randomized to receive either physical therapy alone (Arm A) or physical therapy plus transcutaneous spinal cord stimulation (Arm B) for 6 weeks. Then, patients will be followed up for an 8-week wash-out period, during which neither study intervention will be administered. During wash-out period, patients will not be allowed to receive treatments that violate exclusion criteria (e.g., botulinum toxin injections or tendon/nerve transfer

surgery in the upper extremity) or new treatments that could affect the study's outcome (e.g., alternative exercise therapies or robotic rehabilitation targeting upper extremity function). However, they can continue to get their regular lower extremity physiotherapy.

Next, the intervention arms will be crossed over, i.e., patients who received the A intervention arm first will receive the B intervention arm, and vice versa, for another 6 weeks. In each intervention arm, sessions will last 2 hours/day, 2-5 days/week.

Transcutaneous Spinal Cord Stimulation Procedure: Transcutaneous spinal electrical stimulation is a non-invasive neurostimulation technique. Stimulation will be delivered through the skin using surface hydrogel electrodes, which are commonly used in practice today.

During the first stimulation session, optimal electrode placement and stimulation parameters will be determined using hand function testing and electromyographic (EMG) testing of the upper extremity muscles. Hand function will be tested by the abbreviated GRASSP test, Quantitative Prehension subscale, pinch and grip force measurements, and Capabilities of Upper Extremity Test (Cue-T). EMG testing will be done using skin surface recording electrodes.

Transcutaneous spinal stimulation paradigms that elicit appropriate muscle activation with the lowest threshold stimulation current will be identified. A painless cutaneous enabling motor control paradigm will be used for this purpose: biphasic or monophasic rectangular pulses of 1.0 ms per phase duration will be delivered at a frequency of approximately 30 times per second (Hz). Within these pulses, a very high carrier frequency of 10 kHz is delivered to avoid painful sensations as the current crosses the skin (i.e., the Russian Method of muscle stimulation). Stimulation intensity will range from 1 to 180 mA. During the initial testing, stimulation will be delivered for a duration of 10 to 30 seconds.

After determining the optimal initial stimulation configuration, we will deliver physical therapy sessions while transcutaneous spinal stimulation is administered for a total of up to 90 minutes. The duration of 90-minute stimulation is determined based on the effect mechanism and safety information reported in earlier clinical studies with spinal stimulation. Time without stimulation will be interspersed to examine the difference in movement with and without stimulation.

Hand and Arm Physical/Occupational Therapy Protocol: The therapy program will include progressive functional task practice for upper extremity motor training (i.e., active assistive range of motion, stretching, strengthening, reaching and grasping exercises, and fine motor skills training). The physical therapy program will be tailored to the patient's specific functional deficits and needs.

For safety monitoring, we will document vital signs (blood pressure, pulse, respirations, temperature), orientation to time and place, and skin examination before and at the end of each

session. For cardiovascular safety, non-invasive continuous blood pressure monitoring will be done during transcutaneous cervical spinal electrical stimulation. Patients will be encouraged to report any abnormal feelings and discomfort throughout the session. After each session, patients will be released if they are deemed stable. If not, they will be referred to a healthcare professional for evaluation and provided appropriate care.

Every two weeks throughout the intervention, we will measure and document the functional improvements observed during stimulation and those that persist beyond the stimulation. At the end of each intervention arm and wash-out period, outcome measurements will be repeated, as described in the study design figure above.

Phase III – Follow-up

After completing the two-arm crossover intervention phase (Phase II), patients will be provided with a home rehabilitation exercise program. Three follow-up visits during the early follow-up period (8 weeks following the last intervention session) and one last follow-up visit at the end of one year of the study will be scheduled, where assessments and measurements will be done as described in the study design figure above, at UW Rehabilitation Department and/or in Amplifying Movement & Performance Laboratory.