Feasibility and Effectiveness of Home-based Telerehabilitation Program for Recovery of Upper Limb Functions in Incomplete Spinal Cord Injury

NCT04977037

Version Date: 03/15/2022

Project Title: Feasibility and Effectiveness of Home-based Telerehabilitation Program for Recovery of Upper Limb Functions in Incomplete Spinal Cord Injury

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Population: Male and female adults (>18 years of age) with cervical spinal cord injury

Study Site: UTHealth, Department of Physical Medicine and Rehabilitation NeuroRecovery Research Center at TIRR Memorial Hermann

Study Duration: 2 years

Subject Duration: Approximately 2-months per subject

1. Purpose:

The overall purpose of this project is to evaluate a telerehabilitation project that uses remotely supervised, home-based therapeutic program to improve upper-limb voluntary movement in adults with tetraplegia caused by incomplete spinal cord injury (iSCI).

2. Background

Spinal Cord Injury affects 2.5 million individuals worldwide and often leads to severe disability duo to functional limitations in the sensory and motor systems. In 2020, number of new cases are reported as 17,810 each year and total number of individuals living with SCI were ranging between 250,000-368,000 (Center 2020) For those that survive the injury, the damaging effects not only impact the individual but there is also significant burden to family members. Many people with cervical SCI have limited mobility in lower and upper limb functions and require assistance in feeding, grooming, bathing, dressing and toileting (Kloosterman, Snoek et al. 2009, Rudhe and van Hedel 2009). Rehabilitation programs aims to improve patients physically, cognitively, emotionally and in terms of social wellbeing. However, many patients are inactive and access to rehabilitation services are often limited due to lack of energy, reduced mobility, transportation costs, service costs and/or restricted availability (Cowan, Nash et al. 2013, Chamberlain, Meier et al. 2015, Hamilton, Driver et al. 2017, Maher, McMillan et al. 2017, Borg, Foster et al. 2020).

With growing financial constraints on healthcare systems, alternative cost-effective and efficient methods of rehabilitation are needed. In the past decade, development of new technologies has paved the way for their use for clinical purposes, especially to enhance patient's access to specialized treatment services. In this context, telerehabilitation has emerged to be an alternative to in-clinic services. Telerehabilitation is the delivery of rehabilitation services via communication technologies, and has the potential to manage multiple components of health including functional independence, self-care, and self-management (Brennan, Mawson et al. 2009, Dorsey and Topol 2016, Richmond, Peterson et al. 2017). The use of telerehabilitation in spinal cord injury is emerging, however there is still lack of information on feasibility and effectiveness of specialized rehabilitation programs aiming to improve upper-limb motor functions in adults with tetraplegia.

Currently there is no cure for people with SCI. Moreover, for many years SCI has been considered irreversible. Particularly therapeutic approaches aiming to increase hand-movement dexterity should include the corticospinal tract (CST) as damage to the CST causes severe deficit in hand movements (Isa et al., 2014; Anderson et al., 2004). Recruitment of motor descending pathways via non-invasive stimulation of motor cortex might reinforce neuroplastic mechanisms (Martin 2016) and enhance motor recovery (Bunday and Perez 2012). In this context, transcranial direct current stimulation of cortical neurons may be a promising non-invasive technique to facilitate motor recovery. Our preliminary findings and literature has shown that is safe and effective as an add-on intervention to standard rehabilitation protocols in recovery of upper limb motor functions ((Yozbatiran, Keser et al. 2016, Cortes, Medeiros et al. 2017, Yozbatiran, Keser et al. 2017, de Araujo, Ribeiro et al. 2020)

There is evidence that treatment intensity has a profound effect on motor recovery. High-dosage, high-intensity repetitive training of arm movements or functional tasks can provide better functional outcome (Whiteneck, Gassaway et al. 2011, Backus, Gassaway et al. 2013, Jones, Evans et al. 2014, Brazg, Fahey et al. 2017, Francisco, Yozbatiran et al. 2017, Wouda, Lundgaard et al. 2018) However, many patients do not receive high doses of rehabilitation therapy for reasons that include cost, difficulty traveling to the location where the therapy is provided, shortage of regional rehabilitation care, and poor adherence with assignments. Furthermore, even when patients can access in-clinic rehabilitation therapy, the amount of therapy provided is limited, averaging 32 arm movements per session (Lang, Macdonald et al. 2009). In this regard, through telerehabilitation systems clinicians have the possibility of delivering long rehabilitation trainings at patient's homes.

In summary current options for treatment of upper extremity functions in persons with tetraplegia have been limited to in-clinic therapy programs. We suggest that alternative delivery of rehabilitation services should be investigated to provide therapy. Therefore, in the proposed study we aim to investigate the feasibility and clinical effectiveness of remotely-supervised home-based telerehabilitation protocol aiming to improve arm and hand functions in adults with tetraplegia.

3. Objectives:

Specific Aim 1: to determine feasibility and adherence of remotely-supervised home-based upper-limb telerehabilitation program

Specific Aim 2: to determine functional activity level in changes of measurements of upper-limb motor function, grip strength and health-related quality of life.

4. Study Design:

The proposed study will use parallel-groups, randomized, sham controlled, double-blinded design in which 36 participants with motor incomplete SCI (AIS B – D level) will randomly assigned to receive tDCS combined with repetitive arm training (RAT) or sham tDCS combined with R-A training. During the first 20-minute participants (n=24) in the experimental group will receive 20 minutes of anodal tDCS (2 mA) on motor cortex contralateral to their trained side followed by RAT for 60 minutes. Participants (n=12) in the control group will receive 20 minutes of sham tDCS followed by RAT for 60 minutes. In the sham stimulation 2 mA of anodal current will be delivered in a ramp up and down fashion for 30 seconds at the beginning and 30 seconds at the end of 20 minutes of stimulation. Treatment will be administered at an intensity of 5 sessions per week for 2 weeks.

The randomization schedule will be provided by project statistician (Dr. Xu Zhang).

Outcome measure:

Feasibility outcome measure: Adherence with therapy will be measured as;
(1) the number of treatment sessions attended by each participant,
(2) number of drop-outs in each group,
(3) participant's perceptions of the use of study implementation (using the tDCS and exercise equipment, numerical rating scale with 'not difficult at all' at 0, and 'very difficult' at 10)
(4) participant's perceptions of usefulness of the intervention (numerical rating scale with 'not at all useful' at 0 and 'very useful' at 10).

The telerehabilitation intervention will be considered as feasible if at least 80% adherence rate is achieved (completed number of sessions ≥ 8 out of 10), if attrition rate is no higher than 10% in each study group, if at least 40 minutes of 60 minutes exercise session is completed and if no serious adverse events took place (other than expected side effects from tDCS).

Clinical outcome measure: Primary clinical outcome measure is GRASSP prehension performance (Kalsi-Ryan et al., 2012). Secondary clinical outcome measures are grip strength and Spinal Cord Injury Independence Measure (SCIM III) (Itzkovich, Gelernter et al. 2007). Assessments will be repeated immediately after completion of 10 sessions and at 4-weeks follow-up.

Brain motor cortex function: Functional near-infrared spectroscopy (fNIRS) device will be used to measure and record to relative changes in oxygenated and deoxygenated hemoglobin from the motor cortex of the brain. This in turn will help examine and understand the effects of a combined tDCS/robotic assisted arm training treatment upon motor-related brain activity. FNIRS emits near-infrared light (740nm/850nm) into the head and acquires the amount of light returning using a detector positioned 3cm from the light source. It is a portable, non-invasive device similar to EEG and has been used in multiple research studies investigating brain function under various task-oriented settings. One major risk the fNIRS device poses is potential eye damage if the infrared light-emitting diodes (IR LEDs) are shined into an individual's eyes for an extended amount of time. This will be mitigated however by ensuring that the investigator leaves the device powered off before placing it on the user's head. An additional minor risk includes a mild discomfort caused by the tightness of the headband and straps. The investigator will adjust the device to provide optimal comfort to the subject. fNIRS will be performed at the baseline, immediately after completion of 10 sessions treatment and at 4-week follow-up.

5. Study Population:
36 adults with chronic incomplete cervical SCI will be recruited from TIRR/Memorial Hermann, local healthcare providers and from support groups in Houston area.

Participants will be included if they have:
(1) diagnosis of a chronic incomplete cervical lesion as defined by the American Spinal Injury Association Impairment scale classification and at least for 6 months post injury;
(2) upper-extremity weakness associated with tetraplegia with minimal residual thumb and index finger movement sufficient to grip small objects such as marble;
(3) age 18 - 70 years;
(4) no brain injury;
(5) no planned alteration in upper-extremity therapy or medication for muscle tone during the course of the study;
(6) no contradiction to tDCS
(7) access to internet at home.

Subjects will be excluded if they have:
(1) prior history of seizure;
(2) modifications in chronic use of neuroactive medication (e.g., neurostimulants, anticonvulsants, or antidepressants) during study period (between baseline and follow-up);
(3) any joint contracture or severe spasticity in the affected upper extremity, as measured by a Modified Ashworth Score ≥ than 3 out of 4.

6. Study Procedures:

Baseline Assessment (Duration: two to three hours): For both SCI subjects and healthy volunteers, the baseline assessment can be on the same visit as screening and will be performed in the Motor Recovery Laboratory by an evaluator blinded to subject's group assignment. Subjects (SCI) will be evaluated for upper extremity motor functions. Arm and hand functions will be assessed with Graded Redefined Assessment of Strength, Sensibility and Prehension (GRASSP), ASIA upper extremity scale (motor and sensory), grasp and release test and independence in daily functions will be assessed with SCIM-II.
Caregiver training: On the day of in-clinic baseline assessment, caregiver/family member who will be delivering the therapy at home will be trained on intervention protocol (localization of primary motor cortex to deliver the tDCS, operating the tDCS machine, operating the laptop and videoconference system, using special exercise equipment). Then they will take the tDCS device, exercise equipment and lap top computer home.

Treatment at home (Duration: two hours): Home-treatment sessions will start on the following week (Monday through Friday) and continue for two-weeks (total 10 treatment sessions). During each treatment session primary motor cortex (C3 or C4 according to international EEG system) will be stimulated with anodal tDCS at 2mA for 20 minutes. Electrode sizes are 5x7cm, saline-soaked. Active (anodal) electrode) will be placed over the primary motor cortex and reference electrode will be placed over contralateral supraorbital area. This single-position headgear include clearly labeled sponge markers to eliminate room for user error (see attached brochure for tDCS with head gear and sponge electrodes). Participants in the sham stimulation (control) group will use same stimulation location, however the duration of stimulation will be set to 30 seconds at the beginning and end of 20 minutes. This is a reliable method of sham stimulation as sensations arising from tDCS treatment occur only at the beginning of application (Gandiga, Hummel et al. 2006). Subjects often feel during current ramp up; however the same procedure will be adopted for sham stimulation (that will receive active current for 30 seconds only (insufficient time to produce meaningful changes) and therefore mimic the initial sensation associated with active stimulation. It should be noted that less than 3 minutes of tDCS induces no effects on cortical excitability (Nitsche and Paulus 2000) and also using 30 seconds of sham is a reliable method of blinding as shown by a randomized controlled study (Gandiga, Hummel et al. 2006).

Immediately after stimulation ceases, participants will continue with unilateral repetitive arm and finger exercises for 60 minutes. Exercise difficulty will gradually increase and adjusted as needed per participants tolerance. All treatment sessions will be supervised in real-time via videoconferencing by Dr.Yozbatiran in her office at the NeuroRecovery Research Center at TIRR/Memorial Hermann.
The tDCS device in this study (Soterix 1x1 tdCS mini-CT stimulator, see attachment), is specifically designed and developed for home-use. The intensity and duration of stimulation will be pre-programmed by Dr.Yozbatiran. After pre-programming device, it won't allow patient/caregiver to make changes. All session will be monitored remotely by Dr.Yozbatiran. After home-therapy ends, study participant will bring the FitMi and Music Glove devices, and the laptop back to the research lab.

Schedule of activities

Event	Baseline (Day -6 to 0)	Treatment Sessions (1-10)	Post-treatment (Day 5±3)	Follow-up 1 (Day 35±5)
Informed Consent	X			
Inclusion/Exclusion Criteria	X			
Demographics	X			
Medical and Social History	X			
Medication Checklist	X		X	X
ASIA-Impairment Scale	X		X	X
GRASSP	X		X	X
Grip Strength				
NHPT	X		X	X
SCIM-II	X		X	X
tDCS	X			
Music Glove and FitMi arm training		1-10		
tDCS-Side Effects Questionnaire		1-10		
Pain and Fatigue		1-10		
Participant-tDCS &Arm Exercise Survey		1,6,10		
Participant- Usefulness of Intervention Survey			X	X
Caregiver tDCS&Arm Exercise Survey		1,6,10		
Caregiver-Usefulness of Intervention Survey			X	X

Post-treatment and Follow-Up Assessment (Duration: two-hours): During this period subjects will be asked to come within a-week after they have completed the study and at week 4 for follow-up. GRASSP, Grip Strength, SCIM-II and fNIRS measurements will be repeated at post-treatment visit and at 4-week follow-up visit.

7. Potential Risks/Discomforts

tDCS: Transcranial direct current stimulation (tDCS) is a technique that poses a non-significant risk to subjects. The safety of this technique has been addressed and tested by multiple researchers (e.g., Hummel, et al., (Hummel and Cohen, 2005); Fregni, et. al., (Fregni et al., 2006a, Iyer et al., 2005); Nitsche, et al., (Nitsche et al., 2003c, Nitsche et al., 2003b, Nitsche et al., 2003a), (Nitsche et al., 2004); Priori, et al., (Priori, 2003)). Researchers have concluded that tDCS, as applied in a manner similar to our proposed protocol, induces only temporary mood, cognitive / motor effects, and no negative side effects. No undesirable or long-lasting effects have been reported, nor have any subjects reportedly abandoned a study due to discomfort. The most common side effects according to a recent consensus are: headache, dizziness, nausea, itchy sensation as well as irritation under the area of the electrodes (Nitsche et al., 2008). Researchers at the National Institute of Neurological Disorders and Stroke (NINDS), Iyer et al., (2005) (Iyer et al., 2005) conducted a safety study on tDCS, investigating 20-minute sessions of 1 mA and 2 mA current stimulation with healthy controls (n=103). No negative effects were identified. Nitsche and colleagues (2004) found no measurable structural changes in brain tissue due to tDCS (Nitsche et al., 2004). Finally, two recent studies showed that

several sessions of tDCS are safe to be used in chronic pain syndromes such as fibromyalgia and spinal cord injury (Fregni et al., 2006c), (Fregni et al., 2006a). Thus, a growing body of research from different laboratories has shown that tDCS is a safe, noninvasive and painless technique for modulating neural excitability, with measurable but only transient effects.
The current protocol uses stimulation level of 2mA and a duration of 20minutes which fells within safety limits published by numerous clinical studies applying tDCS with human subjects. In our lab at NeuroreRecovery Research Center at TIRR, we completed several tDCS studies (HSC-MS-12-0868, HSC-MS-15-0269, HSC-MS-14-0354) and did not observe any serious side effects that required termination of subject's treatment program. As expected, tingling was the most common transient symptom followed by skin redness. Both are physiological responses to direct current stimulation and require no medical action.

The safety of tDCS in the pediatric and pregnant population has not been assessed. Therefore female subjects will be questioned for pregnancy at the screening, and pregnant women will be excluded. If a subject becomes pregnant during the course of the study, they will be withdrawn from the study.

Arm Exercise- Training: Patients with spinal cord injury sometimes develop pain or discomfort in the shoulders and arm. Subjects will be questioned for fatigue or discomfort during training sessions, and frequent breaks will be given to mitigate muscle fatigue. If any discomfort related to prolonged sitting happens, the training will be paused and participant will be encouraged to change his/her sitting position (weight shifting).
If there is evidence that pain or fatigue is worsened by the therapy, the sessions will be reduced or discontinued. All therapy sessions will be supervised and monitored by Dr.Yozbatiran.

Assessment/Questionnaires: All assessments will be performed in a designated room inside NeuroRecovery Research Center at TIRR Memorial Hermann. None of these tests are either painful or uncomfortable to perform. In order to prevent potential embarrassment during the testing the test will be done individually and in private. If subjects feel uncomfortable in answering any of the questions they may stop the study at any time.

fNIRS: Prototypes analogous to the Axem Home prototype to be used in the present study have been utilized in four previous REB-approved studies (Dalhousie REB# 2017-4267, National Research Council REB# 2018-107, Dalhousie REB# 2019-4762, Veritas IRB# 16439-11:51:2730-09-2019), with no reported adverse events. The use of fNIRS is recently approved by UThealth IRB for the study #HSC-MS-16-0237 in patients with stroke.

fNIRS is generally regarded as a non-invasive method of brain activity measurement given that the risks associated with it are minor. fNIRS involves the emission of non-ionizing radiation (light at 740 and 850nm respectively) into the skull. The amount of radiation being emitted from the Axem Home prototype is within the exempt risk category for skin exposure according to IEC 62471 (Photobiological safety of lamps and lamp systems) section 4.3.8, and thus does not impose any risk. However, the participant will be told that they should report any discomfort on their head, whether it is from feelings of warmth, or discomfort with the fit of the prototype on their head. However, given that the light output from the Axem Home prototype is not in the exempt risk category for retinal exposure (IEC 62471 section 4.3.7), in the present study the device will only be powered on once it is secured on the head, with the chin strap in place; and moreover, the device will be powered off prior to its removal by the experimenter.
Moreover, the electrical architecture of the device is such that firmware on the device's microcontroller directly controls the current (and thereby the power output) supplied to the LEDs. Further safeguards are in place on the circuit board itself, as resistors on the board

physically limit the potential maximum current (and thereby power output) supplied to the LEDs. And finally, the system overall is equipped with a resettable fuse that stops it from drawing more current than it is intended to and utilizes a certified battery pack as well as protection circuitry prevent any damage from occurring to the battery. All materials used in this experiment will comply with biocompatibility standards (ISO 10993), and both the surface model and the Axem Home prototype will be wiped with alcohol pads following each use.

8. Data and Safety Monitoring

There is no DSMB assigned for this study.

9. Data analysis.

Data for feasibility and adherence will be analyzed using descriptive statistics. For effectiveness, difference in GRASSP score in active arm and between active vs sham arm (immediately after treatment - baseline) will be analyzed with paired t test (if the normality is satisfactory with Kolmogrov-Smirnov test). If the K-S test suggests skewed distribution, we will conduct Wilcoxon signed rank test and Wilcoxon rank sum test for these two analyses.

In multivariable analysis, we will fit a mixed model for data collected at baseline and ten sessions and at 30-days follow-up in both study arms. Patient will be included as random effect of the mixed model. The fixed effects include treatment arm (active, sham) and time (0 for baseline, 1-10 for ten sessions). First, we will consider time levels as nominal and test interaction between treatment and time. The interaction will be added if it will be significant. Second, we hope to parametrically model time. The mean trajectory plot will guide us on the parametric form of time. Our emphasis will be linear time and 3rd-order polynomial time. We tend to favor the 3rd-order polynomial time as we believe that the GRASSP score will increase greatly for the first few sessions and then become stable.

In mixed model analysis, besides incorporating patient random effect, we will also test if there exists stronger correlation among measurements with shorter time intervals. We will specify a few serial correlation patterns including exponential, Toeplitz and banded Toeplitz. The random effect specification will be extended to incorporate random time slope. We will fit all these models and report AIC values to guide our decision on covariance pattern.

10. Potential Benefits

The results of these studies may benefit subsequent future subjects if remotely supervised, home-based combined tDCS and repetitive arm training proves to be effective when compared to repetitive arm training only.

The benefits of participating in this study may be improved arm and hand movement. However, there may be no benefit from participating in this study.

11. Risk-Benefit Ratio:

The potential improvement of arm and hand movement outweighs the risk of non-invasive brain stimulation, fatigue, pain and discomfort.

12. Consent Procedures:

Informed consent will be obtained from the subject at NeuroRecovery Research Center at The Institute for Rehabilitation and Research (TIRR)/ Memorial Hermann. After the patient is identified as eligible participant, Dr.Yozbatiran or her research team will obtain a written informed consent form.

In addition, a photography/videotaping consent will be obtained from the subject, if he/she agrees to be photographed / videotaped during the assessments or treatment sessions.

13. Confidentiality Procedure:
All data will be coded with identification number, database will be in a password –protected computer and kept in a locked file cabinet. There will be no online data transfer, however, to ensure confidentiality and cybersecurity during remote supervision, Dr.Yozbatiran will work with UThealth IT department.

14. Costs:
The subject will not be expected to pay any costs.

15. Payments:
Subjects who travel to the study appointments will be reimbursed $20 per screening and assessment visit. Subjects who complete all study procedures and assessment visits will be reimbursed with additional $20. Total compensation per subject will not exceed $100.

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