TOPSS: TOlerability of transcranial direct current stimulation in Pediatric Stroke Survivors

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Protocol Title:	TOPSS: TOlerability of transcranial direct current stimulation in Pediatric Stroke Survivors
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Co-Investigators:	Nuray Yozbatiran, PhD, PT.
Study Coordinator:	Melika Abrahams, RN, BSN. Research Nurse
Population:	Patients who have arm weakness from a childhood stroke Sample size – 5 Gender – male and female Age – 5 to 19 years of age Geographic location – near UTHealth Houston
Number of Sites:	Single site – UT Health Houston
Study Duration:	Expected Duration 1 year
Subject Duration:	3 months

General Information

- Stroke is defined as an abnormal blockage of a blood vessel or bleeding in the brain that leads to death of brain cells. Childhood stroke affects about 1 in 25,000 children every year and is a top 10 cause of disability in pediatrics. The purpose of this study will be to assess the tolerability of a rehabilitation technique referred to as Transcranial Direct Current Stimulation (tDCS) in childhood stroke survivors.

Background Information

- Hypothesis: tDCS will be well tolerated in childhood stroke survivors.
- **Background and Epidemiology:** Pediatric Stroke is a major neurologic problem that is among the top ten causes of death in pediatrics.[1] Up to 75% of children suffer long-term neurologic impairment after stroke, with greater than one third suffering moderate to severe deficits years after their stroke.[2–10] The 5 year direct medical costs of a single childhood stroke are over $130,000 per patient.[11] Given the large number of disability-years caused by a single childhood stroke, development of adjunctive treatments to traditional rehabilitation therapy for children with stroke is imperative. Transcranial direct current stimulation is an important neuromodulatory technique that holds promise in improving the outcome of patients with childhood stroke.
- Notably, pediatric stroke, defined as stroke occurring before the 18th birthday, is divided into two types; perinatal stroke and childhood stroke. Perinatal stroke includes intracerebral hemorrhage or arterial ischemic stroke occurring between 28 weeks gestation and 28 postnatal days of life, and 'childhood stroke' includes spontaneous intracranial hemorrhage and arterial ischemic stroke occurring between 28 days of life and 18 years of age.[3] Childhood stroke occurs in approximately 1 in 25,000 children per year.[3,6] This study will be of childhood stroke survivors with arm impairment.

- **Summary of prior safety data:** Transcranial direct current stimulation (tDCS) is a non-invasive neuromodulatory technique that has been studied extensively in adult stroke and has been subject of early efficacy trials in childhood cerebral palsy. [12,13] This technique involves application of a small electrical current to the scalp during therapy sessions targeted at a specific impairment.[14] The application of this small amount of current is thought to enhance neuroplasticity temporarily, and has shown benefit in motor learning in children and adults.[15,16] A review safety paper in 2016 found that tDCS has been safe in adult and pediatric trials in the past. Modeling data from that paper suggested that the current used in human studies of tDCS was likely 2 orders of magnitude lower than the amount needed to induce damage to brain tissue.[12] In cerebral palsy, a study analyzing adverse events in 119 children over 12 years found no serious adverse events. 58% had prior brain injury and/or epilepsy and 43 of the patients were perinatal stroke survivors. There were no seizures or major adverse events. Mild tingling/itching was reported in 37% of patients.[17] Another study enrolled 13 patients with perinatal stroke, and also found no major adverse events, with similar rates of mild side effects.[18]
- **Summary of prior efficacy data:** Importantly, 2 separate 2016 meta-analyses found treatment benefit in upper arm function for adult stroke patients receiving repeated sessions of tDCS vs sham.[19,20] Due to these promising results in adult stroke, treatment-effect is currently under investigation in the NINDS-funded TRANSPORT 2 trial; a multicenter, Phase II, randomized, sham-controlled trial evaluating the effect of bihemispheric tDCS in adults with arm impairment after stroke. Efficacy in perinatal stroke is being investigated in the SPORT trial, with results likely to be published in the next 2 years.[21]

Objectives

- Primary objective: To evaluate the tolerability of tDCS in childhood stroke survivors.
    - Tolerability will be evaluated by
        - The percent of patients who are able to complete the study
        - The percent of patients that endorse mild side effects as documented on the 'Stimulation Monitoring Sheet' (included separately)
        - Monitoring of Peg-Board test results pre stimulation, post stimulation, and at the end therapy session
        - Monitoring of Vital Signs (pulse and blood pressure) pre stimulation, post stimulation, and at the end of the therapy session.
- Secondary Objectives: To assess for improvement in arm function in patients receiving tDCS and occupational therapy, 3 functional assessment visits will take place.
    - At each visit, the patient will complete the following:
        - Fugl-Meyer Upper Extremity Assessment
        - Canadian Occupational Performance Measure
        - Box and Blocks Test
        - Pediatric Stroke Outcome Measure
        - Melbourne Assessment of the Upper Extremity

Outcome Measures:

- Tolerability Primary outcome measure:
    - Percent of patients who complete the study, as defined by patients who complete the 1-week post therapy assessment visit. Patients who voluntarily withdraw for any

reason or who stop due to an adverse event will be defined as not completing the study.

- Tolerability Secondary outcome measures
  - Percent of patients that endorse mild side effects as documented on the stimulation monitoring sheet. The stimulation monitoring sheet is filled out during each stimulation session pre and post stimulation.
  - Percent of patients with hypotension or hypertension on blood pressure monitoring post stimulation and post therapy session. Time points for data collection will be pre-stimulation, post-stimulation, and post-therapy session.
  - Percent of patients with worsening of the Peg-board test (decreased score by 5 or greater) on the Peg-Board Test post stimulation and at the end of therapy session compared to baseline score. Time point will be the end of each therapy session.
- Improvement in Arm Function Primary outcome measure
  - Increase of 5 points or more on the Fugl-Meyer score of Upper extremity function at the 1 week post therapy assessment.
- Improvement in Arm Function Secondary Outcome Measure
  - Increase of 5 points or more on the Fugl-Meyer score of upper extremity function at the 3 month post therapy assessment.

Study Design

- This study is an unblinded interventional trial.
- Subjects will be childhood stroke survivors with chronic arm impairment, defined below in the inclusion and exclusion criteria. 5 patients total will be enrolled.

The Primary Objective is to assess tolerability of tDCS. Tolerability will be evaluated by

- The percent of patients who are able to complete the study
  - If any patients drop out due to tDCS related side effects, this would be considered poorly tolerated.
- The percent of patients that endorse mild side effects as documented on the 'Stimulation Monitoring Sheet' (included separately)
  - We expect 40% of patients to endorse mild side effects per session that will be non-treatment limiting.
- Monitoring of Peg-Board test results pre stimulation, post stimulation, and at the end therapy session to ensure no decrease (worsening) in score post stimulation.
- Monitoring of Vital Signs (pulse and blood pressure) pre stimulation, post stimulation, and at the end of the therapy session.

- Study description and sample timeline:
  - On enrollment, patients will have a study visit where they will have a Pediatric Stroke Outcome Measure completed by the PI as well as a medical history with the enrollment form. The study therapist will then complete the following assessments – Fugl-Meyer Score, Canadian Occupational Performance Measure, Box and Blocks test, Melbourne.
  - The patient will then come for 5 sequential days of 2 hour long occupational therapy sessions augmented by tDCS for the first 20 minutes of the session. At arrival, the "stimulation safety sheet" will be completed by the occupational therapist (form attached). The saline soaked electrodes will be placed on the study subjects head and connected to the

Soterix 1x1 LTE enabled tDCS device. Prior to beginning stimulation, the "Investigator Screening Form" checklist will be completed for each patient during each stimulation. Current output through the device will be sham stimulation on day 1, followed by steady increases to a maximum of 1mA in patients aged 5-12 years old, and 1.5mA in patients aged 13-19 years old, per the study design flow sheet at the end of this protocol. The child and parents will be blinded to the sham stimulation. The investigators will not be, since all patients receive the same age based current protocol. Consequently, investigators will be aware it is sham stimulation on day 1. We have chosen to have sham stimulation on the first day to acquire baseline data for tolerability and reported side effects without current being passed through the electrodes, which we will report with descriptive statistics. Blood pressure, pulse rate, and peg-board scores will be recorded as indicated on the stimulation safety sheet during each session.

- A repeat assessment will be done by the occupational therapist one week post therapy completion.
- There will be a repeat assessment visit 3 months post intervention.

Study Population

Patients to be enrolled will be childhood stroke survivors aged 5-19 yrs. 'Childhood' stroke is defined by the American Heart Association as stroke occurring from 29 days of life to 18 years of life.

- **Inclusion Criteria:**
  1) Childhood stroke survivor - either arterial ischemic stroke or intracerebral hemorrhage.
  2) Stroke must be childhood onset, defined as occurring day 29 of life to 18 years of age (per the American Heart Association's definition of childhood stroke)
  3) 3 months or greater from stroke onset
  4) Arm impairment, defined as pediatric stroke outcome measure of 1 or greater of affected arm.
  5) Affected arm Fugl-Meyer score of 60 or lower.
  6) Able to participate in occupational therapy sessions.
- **Exclusion Criteria:**
  1) Uncontrolled epilepsy, defined as seizure within the past 6 months.
  2) Craniectomy without replacement of bone flap. Patients who underwent craniectomy will need the bone flap reattached prior to participation.
  3) Presence of cranial metal implants or implant device that could be affected by tDCS: cochlear implant, implanted brain stimulator, or programmable ventriculoperitoneal shunt.

Patients will be identified in the UTHealth Pediatric Stroke clinic by the PI, Dr. Stuart Fraser. Flyers for the study will also be available on the UTHealth website. The flyer is included in the study documents.

Study Procedures

- There will be 3 assessment visits and 5 therapy visits.
- Baseline assessment visit: This visit will take approximately 2 hours. A study physician will fill out the 'medical history' form and complete the Pediatric Stroke Outcome Measure
  - The Pediatric Stroke Outcome Measure is a standardized neurologic exam used for childhood stroke survivors.

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- The therapist will complete 4 tests:
    - 1) Fugl-Meyer test, a 30 minute therapy evaluation tool to assess arm function
    - 2) The Canadian Occupational Performance Measure, a structured interview to assess activities of daily living
    - 3) The Box and Blocks test – a two minute test of hand dexterity in which the subject moves blocks from one area to another while remaining seated.
    - 4) Melbourne Assessment of the Upper Extremity, a 30 minute unilateral assessment of the affected arm.

- 5 occupational therapy sessions. These will take approximately 2 hours each.
- The 2 follow up assessments are done at 1 week and 3 months post intervention. Each which will take 1-2 hours. A study physician will perform the Pediatric Stroke Outcome Measure, and the study therapist will perform the Fugl-Meyer test, the Canadian Occupational Performance Measure, Melbourne Assessment of the Upper Extremity and the Box and Blocks test.

Data and Safety Monitoring

- No major adverse events are expected. We will monitor for hypotension, tachycardia, and mild side effects like headache. We expect about 40% of patients will endorse the expected mild side effects: headache, numbness or tingling. We expect no patients will develop hypotension or tachycardia.
- If any patient does have a major adverse event, the intervention will be stopped, the event will be logged on the case report form and the patient will be given all usual emergency medical care. The event will be sent to the Data Safety Monitoring Board who will independently review the event and decide whether the event was caused by the intervention. If it is, the study will be discontinued and the protocol revised.
- There is a two person Data Safety Monitoring Board. Case Report Forms for all participants will be sent to the DSMB electronically after completion of the 1st follow up assessment visit (1 week post intervention) for review. The DSMB will need to approve that the study can continue prior to beginning the intervention for the next patient.

Statistics

- As this is a 5 patient tolerability study, only descriptive statistics will be used.
- 5 patients total will be enrolled, and results will be reported with descriptive statistics.
- The trial will be terminated if there is a major safety event deemed to be due to the intervention by the DSMB.
- All subjects will be included in the descriptive analysis.

Ethics

- In-clinic. Potential participants will be informed about the study by the PI. If given permission, the research nurse will approach the patient with the consent form to enroll them in the study. Subjects and parents will be able to voluntarily withdraw consent at any time and will continue to receive all standard of care medical treatment and evaluation as before enrollment in the study.
- A flyer for the study will be available on the UTHealth Stroke Institute Website with information on how to reach the research nurse, Melika Abrahams, for information on the study.

Data handling and record keeping

- Source documents will be kept in a double-locked cabinet in the Center for Treatment of Pediatric Neurodegenerative Disease, UTPB suite 1535.
- CRF data will be entered into a password protected redcaps database after completion by study staff. A linking log with patient identifiers (name, DOB) will be kept in a folder in the redcaps database.
- Only the PI, Co-PI, DSMB, research nurse, OT, and research coordinator will have access to patient information via the redcaps database.
- Human subjects will be not be identifiable through case report forms.
- Special Note: The Canadian Occupational Performance Measure is completed through a web-based application available at https://app.thecopm.ca. Once completed, the COPM printout will be downloaded and stored in the redcaps database.

Quality control and assurance

- The DSMB will monitor data for safety as above
- All investigators will have completed biomedical researcher citi training as required. Data will be reviewed for accuracy by the PI and research nurse.

Publication Plan

- The results are intended to be published in the American Heart Association Stroke Journal after study completion.

ATTACHMENTS

1. Schematic of Study Design
2. Study Schedule
3. Consent Documents
    - Parental, English and spanish
    - Patient, English and spanish
    - 7-17 year old Assent Forms, English and spanish
4. Case Report Form
    - Medical History
    - PSOM
    - Pre-intervention OT assessment forms
        - Fugl Meyer- Upper Extremity
        - Box and Blocks CRF
        - COPM to be performed through web based application – https://app.thecopm.ca
        - Melbourne Assessment of the Upper Extremity CRF
    - Day of tDCS screening sheet
    - Day of tDCS safety sheet
    - Post-intervention OT assessments
        - Fugl Meyer- Upper Extremity
        - Box and Blocks CRF
        - COPM to be performed through web based application – https://app.thecopm.ca
        - Melbourne Assessment of the Upper Extremity CRF

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- 3 month post-intervention OT assessments
  - Fugl Meyer- Upper Extremity
  - Box and Blocks CRF
  - COPM to be performed through web based application – https://app.thecopm.ca
  - Melbourne Assessment of the Upper Extremity CRF

5. Linking Log
6. Flyer

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