

Contralaterally Controlled Functional Electrical Stimulation for Hand Opening in Hemiplegic Cerebral Palsy: Pilot RCT

NCT02925455

Study Protocol and Statistical Analysis Plan

Note: The text below was extracted from the IRB protocol for this study, which was first approved on April 21, 2016. The most recent amendment to the protocol was approved on March 27, 2017

STUDY PROTOCOL

1. Brief Summary of the Proposed Research

This is a pilot randomized controlled trial of an intervention to improve arm function in children ages 6 to 17 with cerebral palsy and upper limb hemiparesis. Twenty participants will be randomized to either a group treated with neuromuscular electrical stimulation and video games or video games alone. Both groups will receive 6 wks of treatment. Changes in upper extremity motor impairment and function will be assessed for each participant at baseline, mid treatment, end of treatment and at 3 mo follow-up.

Rationale

Cerebral palsy is the leading cause of disability in children, one third of whom suffer from hemiparesis. Video games and functional electrical stimulation are complimentary approaches that have independently improved outcomes in hemiplegic cerebral palsy children [1], [2]. We propose a unique intervention that combines custom hand therapy video games with contralaterally controlled functional electrical stimulation (CCFES). CCFES assists hemiparetic children to open their paretic hand in direct proportion to the degree of voluntary unimpaired hand opening, as detected by a sensor glove worn on the child's unimpaired hand. This is designed to facilitate motor control learning by linking movement intent to motor execution and returning somatosensory and proprioceptive sensations back to the brain.

In order to facilitate exercise with CCFES at home, we developed finger-motion controlled video games that are played with the assistance of CCFES. The video games are played by opening and closing the paretic hand, and facilitate motor practice based on learning principles (goal-oriented movement, intense repetition, task variation, engagement and motivation, and appropriate task difficulty). The finger motions are captured by a sensor that is attached to a fingerless glove worn on the paretic hand.

Because hand therapy video games without CCFES assistance may also be an efficacious therapy in this population, we propose a randomized clinical study comparing CCFES + video games to video games without CCFES.

This will be the first controlled trial of the CCFES + Video Game treatment in cerebral palsy. The purpose of the study is to estimate its efficacy in improving arm/hand movement and function.

References

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Specific Aims

The primary aim of this study is to collect pilot data to estimate the efficacy of CCFES videogame therapy in improving outcomes of upper extremity impairment and function. CCFES + videogame therapy is new, so estimating its effect is a first step to test our hypothesis that it leads to greater outcomes than video game therapy alone. We will assess clinical measures of upper extremity impairment, function, and community use to test this hypothesis.

Methods and Procedures

Both the experiment group and control group interventions last 6 weeks and consists of therapist-guided sessions in the rehabilitation clinic and self-administered or caregiver-assisted sessions at home. While both groups will receive the same task practice and video game training, only the experiment group will receive an electrical stimulation device to assist with hand opening during practice. An adaptive randomization algorithm will be used to balance the two groups with respect to age, gender, and baseline severity (not severe if the child is Manual Activity Classification System level I-II, severe if level III-V).⁵² The treatment dose will be the same for both groups: 10 sessions per wk of self-administered video game training at home plus 2 lab sessions per wk for the first 3 wks and 1 lab session per wk for the final 3 wks – 58 hrs total. Blinded assessment of upper limb impairment and function will be done at baseline, mid-treatment, end-of-treatment, and 3-mos post-treatment.

- Note: Contralaterally controlled electrical stimulation (CCFES) – Enables patients with upper extremity hemiplegia to open their paretic hand by stimulating finger and thumb extensors with surface electrodes. Stimulation is proportional to degree of unimpaired hand opening as detected by an instrumented glove worn on the unaffected hand. Thus, volitional opening of the non-paretic hand produces stimulated opening of the paretic hand. CCFES is used during functional task practice and hand therapy video games to link motor intent with execution.
- Note: Hand Therapy Video Games – Four intuitive and engaging games were developed specifically for play with CCFES to provide goal-oriented motor skill training, impairment-appropriate difficulty, and performance feedback that motivates iterative play and skill improvement. Paddle Ball (i.e., Pong) is a simplified tennis simulation that uses hand movement to control a vertically moving paddle. Skee Ball uses hand-opening speed to launch balls at targets. Sound Tracker requires the

hand to precisely follow a moving track generated by different songs. Marble Maze uses hand opening to rotate mazes and guide marbles out into a bucket.

- i. Rehabilitation clinic sessions – These will occur up to twice per week for the first 3 weeks and once per week for the second 3 weeks of the 6 week treatment. They are therapist-guided and last up to 90 min consisting of 45 minutes of CCFES-mediated video games and up to 45 minutes of CCFES-mediated functional task practice. Early sessions will focus on training the patient and caregiver to self-administer play of a CCFES-mediated video game at home. As proficiency with one game develops, more games will be introduced. The functional task practice part of the session will engage the participant in using the CCFES system to assist them in practicing using their hand in activities such as lacing beads, throwing balls, eating finger foods, and other play and activities of daily living.
- ii. Home sessions – These consist of CCFES-mediated hand opening and video game exercises with caregiver assistance and supervision as needed. As proficiency develops and more games are added, each home session will increase in duration up to 90 minutes per day, as determined by the treating therapist based on the adherence of each participant. Self report of game difficulty and engagement will be made at the completion of each game (see below)

Outcome Measures

We will collect the following data during this study.

At eligibility, medical records will be used to provide demographics and baseline information regarding the participant's cerebral palsy, its effects, comorbidities, impairments, and medications taken that might affect the results of this study.

Additionally, we will administer an End of Treatment Questionnaire (15 min) and collect usage and performance logs from the computer and stimulator device in an effort to determine the feasibility of cerebral palsy children using the treatment at home.

At enrollment, we will categorize the participant's general ability to handle objects in daily life using the Manual Ability Classification System (5 min). Using a flowchart, we ask the caregiver to identify which of five levels best describe the child's ability to handle age-appropriate objects. For example, level 1 is "Handles objects easily and successfully", level 2 is "Handles most objects but with somewhat reduced quality and/or speed of achievement", level 3 is "Handles objects with difficulty, needs help to prepare and/or modify activities", level 4 is "Handles a limited selection of easily manage objects in adapted situations, requires continuous support", and level 5 is "Does not handle objects and has severely limited ability to perform even simple actions. Requires total assistance."

At the end of each video game practice session (in lab and at home), we will assess game difficulty and engagement via self-report. A screen will appear at the end of each video game session (180 sessions) that asks the child to rate the difficulty and how engaged they were in the preceding session. The screen will show two visual analog scales (one for difficulty and another for engagement) for the child to report using the computer's touch screen.[6], [7] For difficulty, the choices are: very easy (face with a wide smile), easy (face with a narrow smile), neither easy or hard (neutral face), hard (face with a narrow frown), and very hard (face with a wide frown). For engagement, the choices are: very fun (face with a wide smile), fun (face with a

narrow smile), neither fun or boring (neutral face), boring (face with a narrow frown), and very boring (face with a wide frown). The de-identified data will be saved to the USB drive along with game usage and performance data. This takes 30 seconds during a treatment session.

Additionally, we will assess the following hand muscle co-activation measures during lab visits prior to treatment:

Intervention outcomes that are assessed at baselines, end of treatment, and follow up will include the following.

- **Melbourne Assessment 2:** This is an assessment of unilateral upper extremity function for children ages 2.5 to 15. Participants will perform 14 tasks using their weaker arm and hand, each of which is scored on a 3, 4 or 5 point scale. The tasks involve using the hand to reach different positions (reaching, pronation, supination) and manipulate pellets and crayons. This assessment takes 15 minutes to perform.[9]
- **Finger movement tracking accuracy:** Finger movement tracking is a method of measuring motor control. Using the same bend sensor used for controlling the video games, the relative degree of finger extension will be displayed as a cursor on a computer screen, its vertical position corresponding to the degree of finger extension. A sinusoidal trace having a frequency of 0.1 Hz (1 cycle in 10 seconds) will scroll across the screen. The amplitude of the sine-wave track will be scaled so that it oscillates between 15% and 85% of the participant's full active finger extension. The participant will be seated with the wrist and forearm stabilized in a neutral posture. The participant's task is to keep the cursor on or as close to the scrolling trace as possible by extending and flexing their index finger. The vertical distance between the cursor and the target trace will be calculated for every time point of data collected. The final error for each 30-sec trial will be the average vertical distance (percentage of the participant's range of motion) from the cursor to the target trace. Three trials will be administered after a practice trial, resting 1 minute between trials. This test takes approximately 5 minutes.
- **Box and Block Test:** The Box and Block test is a measure of gross manual dexterity, which requires the participant to pick up 1 block at a time, move it over a partition, and release it in a target area as many times as possible in a 1-minute period. The Box and Block test measures changes in functional grasp and release but not during activities of daily living (ADL), and therefore cannot be strictly categorized as either an impairment or activity limitation measure. This test takes approximately 5 minutes.
- **Assisting Hand Assessment** examines the ability of a child to use both hands during play tasks (such as wearing a hat, bang cymbals together, hold a bottle with one arm and manipulate marbles with the other, etc.) This test has two components, a score and a description of hand function. The score reflects how well the impaired hand assists the other and ranges from 22 points (if the impaired hand is not used at all) to 88 points (if the affected hand is used like a normal non-dominant hand). The descriptions detail whether the child grasps an object from the table or from the other hand, how stable objects are in the hand, and how quickly use of the affected hand is initiated relative to the other hand. This test takes 15-20 minutes to administer.
- **Number of Hand Opening Repetitions** will be counted during task practice and during video game play. During video game play, repetitions are detected by a change in the sign of the first difference (analogous to finger velocity) of the bend sensor signal. We will use the total number of repetitions for correlations.

Selection Criteria

Inclusion:

- Upper Extremity hemiparesis from Cerebral Palsy
- Age 6-17
- Caregiver can transport participant to weekly sessions and assist with home treatment
- Medically stable; stable medications
- Recall 2 of 3 items after 30 min
- Finger extension strength $\leq 4/5$ on paretic side
- Able to follow 3-stage commands
- Adequate active movement of paretic arm to position the hand for table-top task practice
- Skin intact on hemiparetic arm
- Surface NMES trial opens hand without pain
- Full volitional hand opening and closing of contralateral hand
- Box & Blocks Score of weaker side < 90% of stronger side score
- Able to hear and respond to auditory cues
- English proficiency of both caregiver and child

Exclusion:

- Uncontrolled seizure disorder
- Co-existing neurological conditions other than CP affecting the hemiparetic upper limb (e.g., peripheral nerve injury, PD, SCI, TBI, MS, stroke, hemispherectomy)
- Severely impaired cognition and communication
- History of cardiac arrhythmias with hemodynamic instability
- Insensate arm, forearm, or hand
- Uncompensated hemi-neglect
- Cardiac pacemaker or any other implanted electronic systems
- Pregnant
- IM Botox injections in any UE muscle in the last 3 months
- Severe visual impairment

Informed Consent

The participants will be under the age of 18, so proper assent will be completed along with permission from their parent(s).

The consent/assent interview will be completed in a private room at the Cleveland Clinic Children's Hospital for Rehabilitation or satellites at Westlake, Beachwood, Cuyahoga Falls, Brunswick, and Middleburg Heights. The consenting/assenting interview will be completed at least 24 hours following receipt of the consent document to allow for the participant and family to read over and ask any questions they may have. The consenting/assenting process will be documented in the participant's medical record. All participants will be current patients at Cleveland Clinic.

Potential Risks

Device Risks

These risks are described as common (which means it might happen greater than 10% of the time), uncommon (which means it might happen about 2-10% of the time), or rare (which means it might happen about less than 1% of the time).

Fatigue or Pain (Common): There is a possibility that the concentration and repetition associated with activities during lab sessions may cause "mental fatigue" from the intensity of concentration required during these tasks, or physical fatigue or pain (joint soreness, muscle

ache, or shoulder pain) due to the repetitive tasks. This will vary from person to person. This is similar to what might be experienced after working hard in a traditional occupational therapy session. If the participant experiences such pain or discomfort, we will stop treatments until the pain subsides and adjust the intensity of the treatments to prevent recurring discomfort.

Motion Sickness (Common): There is a possibility that the video games can cause motion sickness. Some of the video games feature objects that rotate or move in a way that may cause temporary dizziness or light headedness. We minimized the possibility for motion sickness by making the video animations smooth and by closely matching participant's hand movements with what they control in the video game. We have also designed several games, some of which feature less video movement and lower risk for causing motion sickness. However, if the participant experiences these sensations while playing a video game, we instruct them to stop playing and close their eyes or look away from the video screen. The nausea may go away with rest. If the nausea does not go away after resting or returns after playing the game again, we instruct them to discontinue playing and notify research staff. If a particular game is causing the motion sickness, we will avoid prescribing it to the participant and have them use only the games that do not cause them motion sickness.

Uncomfortable Sensation (Common): Electrical stimulation of a muscle may be perceived as a twitching or vibrating sensation, and may be uncomfortable. Electrical stimulation of a nerve may be perceived as a strong but short shock, and may be uncomfortable. Electrical stimulation of the skin may be perceived as a "pins and needles" sensation and may be uncomfortable. Discomfort associated with electrical stimulation is common, occurring in approximately 40% of subjects if the stimulus parameters are not well-adjusted. Stimulus parameters will be adjusted to your comfort.

Surface Electrode/Adhesive Skin Irritation (Uncommon): There is a chance participants may experience a temporary redness of the skin from the electrodes, the conductive gel used with them, or the adhesive used to secure them. Irritation from the electrodes occurs in approximately 10% of subjects. The irritation and redness will go away when the electrodes are removed. Skin irritation from electrical stimulation is rare, but possible. The type of stimulation that will be used minimizes the possibility.

Electrical Hazards (Rare): There is a rare possibility of an electrical shock hazard whenever electrical stimulation is used or whenever computers and electrical equipment are used to make measurements. There is a rare possibility of an electrical burn whenever electrical stimulation with surface electrodes is used. Electrical burns will be assessed and treated by the study physician if necessary. Electrical shocks will be assessed and treated by the study physician if necessary, and the equipment will be tested for faults. The equipment to be used has been designed and tested to minimize these risks. Participants will be trained how to use your stimulator safely and will be asked to follow to a list of safety precautions.

Stimulator Malfunction (Rare): There is a rare possibility that the stimulator may malfunction and produce painful stimulation even after it has been properly programmed in the laboratory. The sensation may be a sudden burning sensation, which can damage the skin if it does not stop. If participants experience pain from the stimulation, they are instructed to turn off the stimulator, discontinue its use, and contact study personnel.

Risk Mitigation

All study participants and their caregivers, if applicable, are taught by a therapist how to use the stimulator at home. Pictures of the electrodes in their proper positions are given to the participants, and a manual on how to use the stimulator is reviewed with each participant and caregiver. Before a participant goes home with a stimulator, they are required to demonstrate that they can put on the device, operate it according to the given instructions, and take off the device. Participants are encouraged to call the therapist if they have any questions about using the device while at home. The following safety precautions are listed in the manual:

- Avoid handling the electrodes while the stimulator is on. Always remember to turn off the stimulator before you remove the electrodes.
- Always wash and dry the skin before applying the electrodes. Generally any mild soap is fine; avoid deodorant or perfumed soaps or lotions, as these affect skin adherence.
- Use new electrodes if the reused ones no longer stick to the skin.
- Place electrodes on the skin only where instructed.
- Never position electrodes on the chest, across the heart, or on the neck.
- Do not place electrodes over broken skin as this may cause pain and skin irritation.
- Do not submerge the stimulator in water, or use around water (spills, bathtub/shower or sink).
- Do not operate dangerous machinery or drive while using the stimulator.
- Do not sleep while using the stimulator. Remain attentive during use to avoid skin burns.
- A slight reddening of the skin under the electrode is normal. This should fade after 1 hour once the electrodes are removed. If you note redness or blistering beyond this, discontinue use and inform study personnel.
- The safety of electrical stimulation in pregnancy has not been determined; therefore, we do not enroll pregnant women.
- Electrical stimulation should not be used by patients with implanted electronic devices (cardiac demand pacemakers etc.) unless under specialized medical supervision.
- Do not participate in this study if you have a history of potentially fatal cardiac arrhythmias.
- Electrical stimulation should not be used by people who have poorly controlled epilepsy.
- The stimulator has been programmed specifically for the intended user only. Do not allow anyone else to use the stimulator.

STATISTICAL ANALYSIS

Sample size determination

This is a pilot randomized control trial that aims to estimate the intervention effect necessary to power a larger trial. The sample size target of 20 participants was limited by the amount of funds provided by the R21 funding mechanism.

Data analysis

We will use a descriptive approach using means and standard errors to assess the effect of hand opening repetitions on the treatment group over time for each outcome. Due to the small sample size in our dataset, we will use a robust estimator to calculate the standard errors.

Upper extremity motor function will be assessed at enrollment, 6 weeks (end of treatment), and at 12 weeks post-treatment by a blinded assessor therapist. All assessments will be performed without any assistance from the stimulator and assessments will take place at least 24 hours after their last treatment session in order to avoid any transient carry-over effect or muscle fatigue. Change scores from the following outcomes will be calculated for each subject. Descriptive statistics will be used to describe the results across patients and paired t-tests will be used to analyze the pre-post changes.

- Finger movement tracking error (squared sum distance from the target).
- Box and Block Test number of blocks successfully moved.
- Melbourne Assessment 2 percent score (0-100%).
- Assisting Hand Assessment score.

Additionally, adherence will be determined by downloading usage data from both the stimulator and the computer (via a portable USB thumb drive) – which will be used to calculate the percentage of prescribed treatment time completed by each participant. Participants will also be asked at every visit to report any difficulties or complications they may have experienced during home treatment sessions. Then, at the end of treatment, every participant will be interviewed regarding their impression of treatment and dosage, how easy or difficulty it was to use the equipment and play the games, and what changes they would suggest to the equipment or treatment dose, and whether or not they thought the treatment made any difference in their hand function. The number of hand opening repetitions will be recorded at each training session.