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Study Title: Sensory Stimulation during Constraint-Induced Movement Therapy

NCT03558230

Version Date: 07/24/2018

IRB Approval Date: 7/30/2018

PROTOCOL TITLE: Sensory Stimulation during Constraint-Induced Movement Therapy

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1.0 Objectives / Specific Aims

The *objective* of this pilot project is to assess the impact of the novel sensory vibration stimulation technique we have developed, named TheraBracelet, in enhancing outcomes of constraint-induced movement therapy (CIMT) in children with cerebral palsy (CP). TheraBracelet is peripheral sensory stimulation involving application of low-level (imperceptible), random-frequency vibration to the wrist skin. The *hypothesis* is that improvement in upper extremity function will be greater for the experimental group receiving the TheraBracelet stimulation during CIMT compared with the control group who will wear the device with no vibration (placebo).

2.0 Background

Pediatric CIMT is one of the most effective treatment approaches for children with unilateral motor weakness or hemiparesis, regardless of the neuromotor impairment's etiology (Ramey et al. 2013). CIMT involves applying a hand splint and mitt on the stronger, unaffected upper extremity a hand splint and mitt on the stronger upper extremity to encourage use of the affected upper limb in intensive therapy. Research evidence supports the use of intensive therapy models, such as CIMT, to improve overall function in adults and children with one-sided motor weakness or a hemiparesis (Taub et al. 2007 & 2004, Eliasson et al. 2005, Brady and Garcia 2009, Case-Smith et al. 2012, Huang et al. 2009, Coker et al. 2009, DeLuca et al. 2003, 2007, 2012a,b, Nelles 2004, Sakzewski et al. 2009, Al-Oraibi and Eliasson 2011, Barry 2001, Bower and McClellan 2004).

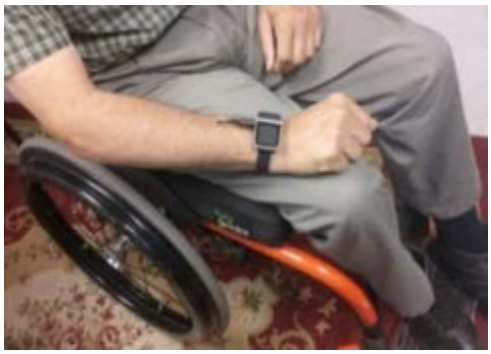
Patty Coker-Bolt, PhD, OTR, FAOTA co-developed and currently hold a yearly one-week modified pediatric CIMT camp at MUSC which has provided an intensive CIMT therapy program for over 200 children (approximately 3 to 9 years of age) with hemiplegic CP since 2001 and is an ongoing annual effort. The camp provides a hands-on on learning opportunity for occupational and physical therapy students who serve as camp counselors under the mentorship of licensed therapists. The intensive group-based day camp program is now embedded into the occupational and physical therapy course curriculum and a systematic course with training modules has been developed to teach students how to provide the essential components of pediatric CIMT. The children that have participated in this intensive 30 hour CIMT program have demonstrated significant improvements in overall self-care, upper extremity function and mobility skills (Coker et al 2010, Ramey et al 2013).

3.0 Intervention to be studied

TheraBracelet stimulation entails application of low-level, random-frequency vibration to the wrist skin, to affect the cortical sensorimotor activity during concurrent upper extremity activities, with an intent to increase outcomes of therapy. Unlike existing methods including transcutaneous electrical nerve stimulation, muscle/tendon vibration, and repetitive transcranial

magnetic stimulation that require prior exposure to the sensory stimulation as long as 2 hours before each therapy session, TheraBracelet can immediately and continuously prime the central sensorimotor system based on preliminary data using neuroimaging (in preparation), and enhance hand motor scores (as measured by the Box and Block and Nine Hole Peg Tests) (Seo et al. 2014) and finger sensory scores (as measured by the Semmes-Weinstein Monofilament Test) (Enders et al. 2013) in adult stroke survivors while TheraBracelet was on. TheraBracelet stimulation is given to the wrist so that the entire hand is exposed to receive relevant sensory information and appropriately manipulate objects. Wearable wrist devices with a vibrating function are low cost and can be easily adopted for rehabilitation purposes to impact a wide range of patients with sensorimotor impairment. TheraBracelet has been used concurrently during 2-week therapy in adults with stroke and resulted in significantly greater improvement in the hand dexterity score compared to dose-matched therapy with no TheraBracelet, in the PI's previous study (in review).

Device: TheraBracelet stimulation is provided by a vibrator connected to an MP3-playing watch via an audio jack (see the pictures below; total weight 40g, watch=3.7cm×5.3cm). No external power source is needed, since the MP3 player drives the vibrator with its internal battery. Both the vibrator and watch are off-the-shelf products (i.e. available to purchase for anyone). The MP3 player/watch is charged using a conventional phone charger. The MP3 player can play any file including the treatment vibration file with white noise vibratory signal and control file with zero amplitude (i.e. no vibration). The treatment vibration will be scaled to a level that is 40% below the sensory threshold for healthy adults without neurologic disorders, neuropathy, or compromised skin (i.e., the treatment vibration is imperceptible to healthy adults). The rationale for the subthreshold intensity is that our previous studies with TheraBracelet showed that this level of imperceptible vibration intensity improved finger sensation more than suprathreshold (i.e., perceptible) vibration in healthy adults as well as adult stroke survivors. Adults' sensory threshold will be used, as children could not reliably respond regarding their perception of barely noticeable or unnoticeable vibration.



FDA: The use of the vibrator for this proposed purpose of affecting the cortical sensorimotor activity during therapy with an intent to increase therapy outcomes has not been approved by the FDA. The vibrator is a general-purpose vibrator, not specifically designed for any particular purpose.

Safety: Currently there is no vibration exposure guideline for this small level of vibration (at 40% below the sensory threshold). People are exposed to higher-intensity, suprathreshold

vibration daily (e.g. from a phone, riding a car). Truck drivers who get exposed to whole-body vibration are limited to driving 11 hours after 10 consecutive hours off duty, according to Federal Motor Carrier Safety Administration. TheraBracelet has been used during 2-week therapy (2 hours/session, 3 sessions/week for 2 weeks) in adults with stroke and resulted in significantly greater improvement in the hand dexterity score compared to dose-matched therapy with no TheraBracelet, without adverse events (i.e., no skin irritation, no numbness) in the PI's previous study (in review). In the PI's current study, TheraBracelet is being used all day (during waking hours), everyday, for a month, in adult stroke survivors, without a safety concern thus far. TheraBracelet has not been used in children, although high-level (i.e. perceivable) vibration has been used in children with CP to treat spasticity and motor function (Katusic et al. 2013).

Control/placebo: No vibration will be the control condition. The MP3 player will play a zero-amplitude file, producing no vibration.

4.0 Inclusion and Exclusion Criteria / Study Population

Children will be between the ages of 3 and 9 year of age and have a unilateral upper limb motor weakness. The child must use the affected extremity as a gross assist during play and self-care activities. The children demonstrate no significant developmental delays that would limit spontaneous use of the more affected extremity. The children will be ambulatory for their age and demonstrate intact balance and protective reactions throughout the less involved upper extremity. The children will have no other health impairment other than hemiparesis. No inclusion or exclusion criteria will be based on race or gender.

5.0 Number of Subjects

Total Planned Enrollment: 20

6.0 Setting

Site: Laboratories of the College of Health Professions, 151A Rutledge Ave., Charleston SC
The camp will be directed by Dr. Coker-Bolt who is a licensed occupational therapist and will be staffed with a physical therapist and camp counselors. The camp counselors will be occupational and physical therapy students enrolled in programs at the Medical University of South Carolina. This will allow each camper to have 2-to-1 ratio of staff to child ratio with personnel that have experience working with children.

7.0 Recruitment Methods

Participants for this study will be recruited children who attend the yearly camp CIMT program. Parents/guardians of all children who will attend the CIMT program will be informed of the study. The CIMT is an ongoing yearly camp.

8.0 Consent Process

Study personnel will obtain the informed consent of the parent, parent/guardian, or guardian of each child participating in the study. In a private setting, the content of the consent will be verbally explained and the parent/guardian will be asked to raise any questions and concerns. If the person requests a waiting period, then one will be given. If the person desires to consent immediately, then the person will provide consent immediately.

9.0 Study Design / Methods

Study design: The study will be a double-blinded stratified randomized controlled trial. Consented children will be stratified in terms of their functional levels (based on MACS). Within each functional level, children will be randomly assigned to either the experimental or control group, in a balanced manner (half the children assigned to one group, and the other half assigned to the other group). All consented children will receive CIMT 6 hours/day, 5 consecutive days for 1 week. This duration of CIMT resulted in significant improvement in capacity and quality of affected upper limb functioning (Coker et al 2010, Ramey et al 2013, Coker-Bolt et al 2017). All consented children will wear the TheraBracelet device during CIMT. The device will provide treatment vibration to the experimental group and no vibration to the control group.

Blinding: A custom MATLAB program will perform group assignment and produce a treatment vibration or zero vibration file depending on the group assignment for each child. The produced vibration file will be uploaded to the TheraBracelet device for each child, and used throughout CIMT. The treatment vibration is imperceptible to healthy adults. Therefore, all personnel involved in CIMT will be blinded to the group assignment. It is anticipated that children who receive treatment vibration would not perceive the vibration from the TheraBracelet device. In an unanticipated case where a child indicates that s/he perceives vibration any time during CIMT, the vibration intensity will be lowered immediately.

Pediatric CIMT protocol: 1) The soft mitt will be worn on the child's stronger, less affected upper extremity during CIMT. 2) The child will be engaged fun, playful camp-based activities to encourage repetitive practice with the weaker limb and shaping of more mature motor responses while the mitt is being worn. These play activities will be implemented by MUSC occupational and physical therapy students who are supervised by licensed therapists. 3) Tasks such as reaching, grasping, and manipulation of objects, weight-bearing, and making hand gestures with the weaker limb will be encouraged during play activities. 4) When the children demonstrate new motor movements, students and therapists will shape and guide the quality of these movements through participation in age appropriate activities.

Outcome Measures: Experimental and control groups will be compared for post-therapy changes in the upper limb functioning. The upper limb functioning in daily living will be measured by standard pediatric therapy parent's questionnaire assessments before and after therapy. The quality and quantity of upper limb movements will be measured by the Quality of Upper Extremity Skills Test, and the Box and Block and Nine-Hole Peg Tests, respectively. Additionally, goal attainment scaling will be used to measure achievements of goals after CIMT. Lastly, we will measure the wear time of the device and the child pain level at each CIMT day.

10.0 Data Management

Confidentiality protection: The data from test results will be de-identified once it has been collected and before it is stored. This means individual results would not be able to be linked to the participant by others who review the results of this research. The linkage between participant codes and identities as well as all other identifiable information including consent forms will be stored in a locked room and be accessible only to the study personnel.

Analysis: Repeated measures ANOVA with post hoc comparisons will be used to determine if each clinical hand function score improves more for the experimental compared with the control group. A significant interaction between time (pre/post) and group (experimental/control) will support the hypothesis that improvement of upper limb function will be greater with the low-level vibration stimulation.

Sample size determination: This is a pilot study using a convenience sample of children who will attend the summer CIMT camp program at MUSC.

Data sharing: Only de-identified coded data will be reported and/or shared with the public in publications, in ClinicalTrials.gov, or upon written request.

11.0 Provisions to Monitor the Data to Ensure the Safety of Subjects

Data and Safety Monitoring Board (DSMB): The primary purpose of the DSMB is to ensure the safety of participants and the validity and integrity of data collected during the study. By having the DSMB, safety concerns will be assessed and addressed objectively. If the intervention definitively has safety concerns, the DSMB may make recommendations to address the safety concerns.

The DSMB will be composed of (1) a board certified physician with expertise in neurologic disorders, (2) a registered and licensed occupational therapist with expertise in rehabilitation, and (3) a biostatistician with expertise in design and analysis of clinical trials.

The responsibilities of the DSMB are as follows. Prior to enrollment, the DSMB will review the study design, protocol, recruitment/enrollment plan, statistical analysis plan, and data safety monitoring plan, and document the agreement or recommendation. After enrollment begins and the CIMT camp is provided, the DSMB will convene again to review the safety data, enrollment data including any discontinuation of participation in the study with or without adverse events, and study results. Safety data will include emergence of skin irritation, increase in muscle tone, reduction in the number of functional tasks completed by children, worsening in the quality of motor movements in children, and any other adverse events noted by camp counselors and/or licensed therapists, regardless of whether it is related to the device use or not. The DSMB will review the aggregated summary data as well as the individual participants' data (de-identified). The DSMB will have access to coded (de-identified) data but not identifiable data. The group

assignment information will become available upon completion of the data collection. The DSMB will provide recommendations for adverse events and safety concerns. The DSMB will also provide a report to the IRB to summarize oversight activities, recommendations, and any concerns regarding participant safety.

Reporting: All safety data including adverse events will be reported to the DSMB and IRB. Summative data will be reported in ClinicalTrials.gov and in publications. Following the guidelines, we will register this study in ClinicalTrials.gov as soon as the study commences (at the latest within 21 days after the first participant is enrolled) and report results including all adverse events as soon as the study is completed (at the latest within 12 months of the trial's primary completion date). To protect participants' confidentiality, personally identifiable information will not be used for reporting. Only de-identified or aggregated data will be used for reporting.

Endpoint: Participants will be assured of their right to discontinue their participation in the study at any time. In addition, Dr. Coker-Bolt may recommend discontinuation of participation if his/her adverse event is deemed to warrant discontinuation, without breaking the double-blinding.

12.0Risks to Subjects

- Confidentiality: There is a risk for loss of confidentiality.
- Injury: There is a risk for injury during engagement in play activities involved in therapy interventions. Although therapy interventions used in the pediatric CIMT involve those play activities that a child would normally engage in during a typical day, children are at risk for injury during play and daily activities. There is a risk of physical and mental fatigue from engaging in the CIMT.
- Mitt restraint: There is a risk of skin breakdown or irritation from the soft mitt restraint and stiffness in the less involved limb being constrained. The children could become frustrated or anxious from having their stronger hand restrained for several hours a day.
- Randomization: The treatment a person receives may prove to be less effective or to have more side effects than the other study treatment or other available treatments.
- Watch/Vibration: There is a minor risk of skin irritation from wearing the wristband and/or from vibration. There is a minor risk of discomfort in moving the arm/hand due to the weight of the device on the wrist, although the device weighs only 40g. Potential risks that may be associated with prolonged use of wrist vibration, including irritation, muscle tones, reduction in the number of functional tasks completed by children, and worsening in the quality of motor movements in children will be noted during each day of CIMT, and formally assessed during pre/post assessments.
- There is also a risk of unexpected medical emergencies.

13.0 Potential Benefits to Subjects or Others

There may be no benefit from participating in this study. The potential benefit is that the vibration the person receives may help their upper extremity functional recovery, although this

cannot be guaranteed. The knowledge regarding the potential of using low-level vibration as a therapy adjunct is important to increase functional recovery of children with CP and may benefit those with CP in general. The risks are deemed reasonable in relation to the potential gain of knowledge regarding TheraBracelet's feasibility, safety, and efficacy in potentially enhancing upper extremity function.

14.0 Sharing of Results with Subjects

The results of the standardized tests will be shared with each child's parent/guardian.

15.0 Drugs or Devices

The vibrators and watches will be stored in the laboratory and will be provided to the participants by the study personnel on each day of CIMT. The participants will use the device during CIMT and return the device to the study personnel when they leave CIMT each day. The device does not have an IDE

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