CLINICAL TRIAL PROTOCOL

Therapeutic Effects of Constraint-Induced Movement Therapy on Young Children With Cerebral Palsy

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Background

Cerebral palsy (CP) occurs when the immature brain develops non-progressive lesions due to multiple causative factors, resulting in impaired motor and postural function.[1] Unilateral CP, which accounts for nearly 30% of all cases,[2] is characterized by sensory and motor impairment on the unilateral side. Children with unilateral CP tend to only use the non-paretic side after discovering that it is more effective and efficient in performing tasks, even though impairment of the paretic hand is mild, which does not prevent them from performing daily tasks.[3] This so-called "developmental disregard"[4] can be reduced by constraint-induced movement therapy (CIMT). CIMT is a therapy that forces the use of the paretic upper limb by restraining the non-paretic limb. To demonstrate the effect of CIMT on developmental disregard, evaluating the amount of paretic arm use in real-life situation is important. For this reason, Pediatric Motor Activity Log (PMAL),[5] a questionnaire-based test that assesses the real-world use of the paretic upper limb, has been frequently used in CIMT studies.[5-7] However, PMAL is a parental-rating scale; thus, it may not be completely objective. In addition, several standardized assessments that evaluate the motor function of upper extremities are available, but those tools only focus on measuring a child's capacity to use the paretic upper extremity. Actual use of the paretic upper limb in the real world differs from its motor capacity.[8]

Accelerometer is an objective instrument used to assess physical activity in structured and unstructured settings in the general pediatric population.[9] This tool has become the preferred method for objectively examining real-world physical activity owing to its affordability and portability. Recent study has suggested that ActiGraph accelerometer is a valid and reliable tool for children with CP[10] including toddlers.[11] Coker-Bolt et al. applied accelerometers to determine the effects of CIMT on paretic arm use in real-life situations, but 7/12 participants showed no increase in the amount of paretic arm use after CIMT.[12] A plausible explanation

for this unexpected result was the age of participants (mean: 4.9 years). An animal study confirmed that early CIMT during the corticospinal tract (CST) refinement period is effective for motor performance, and no longer effective once the CST refinement period has passed.[13] Considering that the myelination of the CST is complete by 3 years of age in humans,[14] application of CIMT in infants and toddlers is expected to yield different results.

Study Objective

The main purpose of this study is to determine whether modified CIMT (mCIMT) with continuous restraint is feasible for infants and toddlers with unilateral CP and is effective in enhancing the amount of paretic arm use in the real world. The study is based on the hypothesis that mCIMT would be feasible and facilitate better use of the paretic hand in the real world.

Methods

Participants

Informed consent forms were obtained from the children's parents or legal guardians before enrollment. From November 2015 to October 2018, we prospectively enrolled consecutive children with unilateral CP who were admitted to a territory hospital in Seoul, Republic of Korea. The inclusion criteria were (1) age 7 to 36 months and (2) diagnosed with unilateral CP due to central nervous system lesions. The exclusion criteria were (1) severe cognitive dysfunction that rendered them unable to perform simple tasks (e.g., reaching, grasping), (2) untreated seizures, (3) visual or auditory problems interfering with treatment, and (4) prior history of musculoskeletal disorders. We asked parents to report if their child presented any adverse events such as sleep disorder or skin rashes. This study excluded

participants whose potential risks exceeded the efficacy, and those with absence rates >20% (>3/15 sessions).

Study design

Thirty-two potential participants received a face-to-face screening assessment. A sample of 32 eligible participants were randomized into the mCIMT or control group by permuted block randomization with block length 4 (N=16 per group). The evaluations were performed on two occasions: at baseline and immediately after the intervention. Only children in the control group who participated in the accelerometer study (N=4) underwent an additional evaluation to determine whether changes in the values of accelerometers were due to mCIMT or whether they changed as they grew older. The measures were conducted by occupational and physical therapists with more than 10 years of experience who were blinded to the intervention.

Modified constraint-induced movement therapy (mCIMT)

Each child in the mCIMT group wore an individually tailored plastic forearm resting splint that is detachable on his or her non-paretic side for 3 weeks. The therapist removed the splint for 15 minutes before each mCIMT session to allow for active range of motion of the non-paretic upper limb and to assess non-paretic hand function by the grasping domains of PDMS-2. The participants could take off the splints during washes and while in sleep. In addition, parents were asked to take off the splints and report if adverse events such as increase of stress/crying, sleep disorders, or skin rashes occurred. A standardized pediatric CIMT protocol, which is a technique to shape motor behavior with repetitive and concentrated training of the paretic upper limb according to Taub's and Deluca's protocol,[15,16] was applied by an occupational therapist. The 15 treatment sessions occurred over a 3-week

period (excluding weekends) in the mCIMT group, for 2 hours each (30-hour dosage in total). The control group received no mCIMT protocol except for children who wore accelerometers; they received mCIMT protocol post-test. All subjects who participated in this study retained the occupational or physical therapy they received.

Statistical analyses plan

Baseline characteristics between the mCIMT and control groups will be compared using independent t-test, chi-square test, and Fisher's exact test. Differences between groups in standardized assessments at post-treatment will be compared with analysis of covariance using pre-treatment measures as covariates to determine the effect of mCIMT treatment. In addition, pre- and post-treatment outcomes of standard assessments will be compared using paired t-test in each group, and Wilcoxon signed-rank test was performed to compare pre- and post-treatment accelerometer outcomes (VMA, %MVPA, UR) of the eight children. Effect sizes will be expressed as partial eta-squared, which was calculated and reported as recommended by Cohen.[17] The ranges for effect sizes are small ($.01 < \eta p2 < .06$), moderate ($.06 < \eta p2 < .14$), and large ($\eta p2 > .14$). Data analyses will be conducted using IBM SPSS Statistics for Windows, version 21.0 (IBM Corp., Armonk, NY).

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