Title: Spinal Cord Stimulation to Augment Activity Based Therapy
NCT #: NCT03240601
Date: 12/28/2021

Protocol

This study was carried out with the ethics approval from the Shepherd Center Research Review Committee (Project #696). All participants provided written informed consent prior to study enrollment in accordance with the Declaration of Helsinki, and the study was conducted in accordance with HIPAA guidelines. This study was registered with clinicaltrials.gov (NCT03240601).

Subjects

We captured data related to both feasibility of applying TSS as part of a program of usual care LT, as well as data related to the impact of LT+TSS on walking and spasticity measures. Participants were recruited from the inpatient clinical services of a specialty rehabilitation hospital. Recruitment was via advertisements, information provided in a monthly research education class, and information conveyed to potential participants by clinical staff. To be eligible for the study, participants had to be in the subacute rehabilitation phase of the SCI (2-6 months post injury) and had to qualify for participation in a clinical LT program as determined by their physical therapist. Individuals were eligible for participation if they met the following inclusion criteria: 16-65 years of age with SCI, ability to take at least one step with or without an assistive device, and presence of at least mild spasticity affecting the lower extremity muscles (as determined by participant self-report). Individuals with the following exclusion criteria were not considered for participation: neurological level of injury at or below T12, progressive or potentially progressive spinal lesions, (including degenerative or progressive vascular disorders of the spine and/or spinal cord), history of cardiovascular irregularities, difficulty following instructions, orthopedic problems that would prevent participation in study interventions (i.e. knee or hip flexion contractures >10 degrees), women who were pregnant, or had reason to believe may become pregnant, persons who have implanted stimulators/electronic devices of any type, and persons with an active infection of any type.

Study Design

We used a wash-in, randomized, control study design consisting of four consecutive weeks of LT directed by physical therapists. For the first two weeks, participants received 6 bouts of LT. For the last 2 weeks, participants were randomized to receive 6 bouts of either 30 minutes of TSS coupled with LT or a sham-control stimulation coupled with LT. Primary outcome assessments for walking function and spasticity were conducted at the beginning and end of each 2-week intervention block (first 2-weeks [wash-in phase] and second 2-weeks [intervention phase]). The assessments at the end of each 2-week block were performed prior to the training on that day. Pre-post training assessments of spasticity and assessments of tolerability (see below) were performed on each training day.

Intervention

Intervention. LT approaches used in the study included treadmill-based training with or without body weight support and with or without manual or robotic assistance (Lokomat, Hocoma, Volketswil, Switzerland) as well as overground locomotor training with or without body weight support and with or without manual assistance. LT approaches for each participant were chosen by the treating therapist in accordance with standard clinical practice. LT duration was approximately 1 hour and included both setup and take down time of all equipment.

Transcutaneous Spinal Cord Stimulation (TSS). Electrical stimulation (50Hz, biphasic pulses) was applied using a portable electrotherapy device (Empi Continuum, DJO Global, Vista, CA, USA), as previously described (Estes, Iddings et al. 2017). Briefly, with the participant seated, the stimulating electrode (5 cm round electrode) was placed over vertebral levels T11/T12, identified via manual palpation and the reference electrode (10 cm x 15 cm butterfly electrode) was placed over the umbilicus. With the participant standing, the stimulator was turned on and

adjusted to a level at which the participant reported sensations of tingling in the legs and feet or to the highest level the participant could tolerate. participants were standing. For those with impaired sensation as well as those with sensation, target stimulation was subthreshold for lower extremity muscle activation and verified by the absence of visible muscle contraction. Stimulation was delivered for 30 minutes at the target stimulation intensity and occurred concomitantly with LT. Following 30 minutes of stimulation, the intensity was ramped down and the stimulation unit was turned off and disconnected. If LT finished prior to the 30 minutes of stimulation, then participants completed their 30 minutes of stimulation while seated on a high-lo mat where training day assessments would occur. Conversely, if the 30 minutes of stimulation finished prior to the end of LT, then the LT session was completed prior to the assessments.

Sham-control stimulation -- TSSsham. The sham-control was designed to control for placebo effects associated with the perception of intervention. For the TSSsham, a 2-inch round electrode was placed over T11/T12 and a reference electrode was placed over the umbilicus, as performed with TSS. The intensity of electrical stimulation was briefly ramped up to a level at which the participants reported perceiving the stimulation, then ramped down and turned off for the remainder of the intervention. The stimulator and electrodes remained attached to the participant for 30 minutes of the LT session, similar to the active TSS intervention. After 30 minutes, the stimulator unit was disconnected from the electrode leads.

Outcome Measures

Walking Assessments:

All walking-related data were captured during overground walking; participants were given the standardized instruction “walk as quickly and safely as possible”. Participants wore a gait belt during walking assessments and were guarded by a physical therapist for safety. During testing, participants used the walking assistive and orthotic devices they typically used during therapy, however no body weight support was provided during testing.

10-Meter Walk Test (10MWT). We utilized the 10MWT, which was our primary outcome measure for walking speed to assess changes in walking speed at the beginning and end of each 2-week LT block. A stopwatch was used to capture walking speed. Participants completed 3 walks in each assessment session with a 2 min rest between trials.

Additionally, spatiotemporal gait characteristics were recorded during the 10MWT using a 6-meter instrumented walkway (GAITRite, CIR Systems, Franklin, NJ, USA) positioned in the middle of the 10-meter walking path. Each walk consisted of at least 4 consecutive footfalls over the mat. Footfall data generated by the GAITRite software were used to compute step asymmetry between the stronger and weaker leg as follows: Step Length Asymmetry: larger step length / (larger step length + smaller step length). Step length asymmetry was averaged across trials and used for analysis.

2-Minute Walk Test (2MWT) was used to assess changes in walking distance at the beginning and end of each 2-week LT block. Distance was measured with a measuring wheel.

Spasticity Assessments:

Pendulum test. The pendulum test, our primary measure of spasticity, was used to assess stretch-induced quadriceps reflex excitability based on first swing excursion (FSE) angle (recorded using motion capture software) wherein a larger angle indicates a greater excursion of the limb before the onset of reflex muscle contraction, and therefore less spasticity (Stillman and McMeeken 1995). Briefly, participants were positioned reclined at the edge of an adjustable height mat with both legs flexed at the knee, and with the lower leg hanging over the mat with shoes removed. Wireless sensors were strapped to both lower extremities to capture knee joint angles using inertial motion capture software (XSENS MVN, Xsens Technologies BV, Enschede, The Netherlands). Calibrated angles were verified with the leg in full extension prior

to starting the test; each leg was extended, and dropped separately. Pendulum responses in each leg were tested 3 times. For each leg, the average FSE in the 3 trials of each test session was used for analysis. To confirm stretch-induced quadriceps activation during the pendulum test, electromyographic (EMG) was concurrently monitored via electrodes (Motion Lab Systems, Baton Rogue, LA) placed over the rectus femoris muscle. EMG data were monitored using Spike software (Cambridge Electronic Design Limited, Cambridge, England). Knee angle data were analyzed off-line using customized MATLAB software (MATLAB, Mathworks).

Ankle clonus drop test (drop test). The drop test, the plantar flexor analog of the pendulum test, was used to assess stretch-induced reflex excitability in the ankle plantar flexors. The number of clonic oscillations captured using the drop test correlates with both electrophysiologic and clinical measures of spasticity (Manella, Roach et al. 2017). Participants sat upright with back support on the edge of a mat table, with shoes removed and socks left on. Wireless sensors were strapped to both lower extremities to capture ankle joint angles using inertial motion capture software (XSENS MVN, Xsens Technologies BV, Enschede, The Netherlands). The ball (metatarsal heads) of one foot was positioned on the edge of a platform (10cm height). The mat height was adjusted to ensure that the hip, knee, and ankle joints were at 90-degree angles. The participants' leg was lifted from beneath the knee until it came into contact with a T-bar positioned 10cm above the resting position of the knee. The examiner quickly released the leg allowing the forefoot to impact the edge of the platform, eliciting a quick stretch of the plantar flexors. Responses in each ankle were tested 3 times. For each leg, the number of clonic oscillations in each trial was counted off-line, and the average number of oscillations for the 3 trials of each test session was used for analysis. Soleus EMG data were concurrently monitored using Spike software (Cambridge Electronic Design Limited, Cambridge, England), and testing resumed only when the muscle had been quiet for 30s. Ankle joint oscillations were analyzed off-line using customized MATLAB software (MATLAB, Mathworks).

Modified Spinal Cord Injury – Spasticity Evaluation Tool (mSCI-SET). The mSCI-SET is a self-report measure of the effect of spasticity on 33 aspects of life. Scores range from -2 to +1; negative scores indicate problematic effects of spasticity, while positive scores indicate helpful effects of spasticity (Sweatman, Heinemann et al. 2020).

Pre/Post training Assessments

Spinal Cord Assessment Tool for Spastic Reflexes (SCATS). The SCATS was used as a clinical measure of spasticity that has been shown to be reliable and valid in persons with SCI (Benz, Hornby et al. 2005). The SCATS was performed on each leg immediately before and after every intervention session by masked clinical assessors. Assessors rated clonus, flexor spasms, and extensor spasms, on a 4-point scale for each lower extremity. For clonus and extensor spasms the scale was as follows: 0-no reaction, 1-mild lasting <3 seconds, 2- moderate lasting 3-10 seconds, and 3- severe lasting >10 seconds. The scale for flexor spasms was determined by measuring degrees of flexion at the knee and hip on the following scale: 0- no reaction, 1- mild <10 degrees, 2- moderate 10-30 degrees, 3- severe >30 degrees.

Tolerability of stimulation. During the 2-week intervention period, participants were asked to rate the tolerability of their stimulation (LT+TSS and LT+TSSsham). Using a numeric rating scale (NRS) from 0 to 10, participants were asked how tolerable the stimulation was in regard to pain, with 0 being no pain and 10 being the worst pain imaginable. Responses were taken prior to the start of the stimulation to determine baseline tolerability, and then 1 minute and 30 minutes during stimulation.

Data analysis

Data were analyzed using SPSS (version 26; SPSS Inc., Chicago, IL, USA). Numerical and ordinal data were presented as the mean(SD) and median(IQR), respectively. For spasticity measures, data in the more- and less-impaired legs (as determined by lower extremity motor score [LEMS]), were analyzed separately. Due to our small sample size, nonparametric tests were performed (Portney and Watkins 2009). Mann-Whitney U tests were conducted to examine differences between the LT+TSS and

LT+TSSsham groups in change in walking ability (speed, distance, step length asymmetry) and spasticity (pendulum test, clonus drop test, mSCI-SET) during the wash-in (LT only) period, and during the intervention (LT+TSS, LT+TSSsham) period. The Wilcoxon signed-ranks test was used to examine changes within each group during the 2 study periods. Significance was set at $\alpha = 0.05$ for all analyses. We did not adjust the significance level for multiple comparisons as our measures cannot be assumed to be independent (Hart and Bagiella 2012), and because such adjustments are known to increase the likelihood of false negatives (Type II errors) (KJ 1990, Perneger 1998, Nakagawa 2004, Hart and Bagiella 2012) which is problematic in preliminary studies.For within-group comparisons, we computed the effect sizes as these are considered more meaningful than p-values for clinical interpretation of results (Borenstein 1997, Nakagawa 2004, Lakens 2013). We computed the effect size using Hedges' g, as this approach is recommended for small samples (Lakens 2013). Effect sizes were interpreted per recommendations for rehabilitation studies as small effects, 0.08 to 0.15; medium effects, 0.19 to 0.36; and large effects, 0.41 to 0.67 (Kinney, Eakman et al. 2020).