High Intensity Training for Neurological Injury Using Overground Exoskeletons in Inpatient Rehabilitation

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Protocol Title:	High Intensity Training for Neurological Injury Using Overground Exoskeletons in Inpatient Rehabilitation
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Population:	Human subjects (male and female), age 18 years or older, who have a confirmed diagnosis of spinal cord injury or cerebrovascular accident.
Number of Sites:	1. TIRR Memorial Hermann
Study Duration:	1 year
Subject Duration:	2 weeks

GENERAL INFORMATION

Recovery of walking ability remains one of the most important predictors of quality of life in patients with neurological conditions such as spinal cord injury (SCI) and cerebrovascular accident (CVA). Not only is gait an essential activity of daily living, but it can also help minimize many of the secondary complications seen as a result of sedentary lifestyles due to neurological injuries, such as cardiovascular deconditioning and bone mass loss. With advanced robotic technology, robotic exoskeletons in neurological rehabilitation have gained attention and have become more popular for mobility and gait training. One of the most important advantages of robotic exoskeleton-assisted gait training is that the robot is powered and operated by motors and actuators that promote repetitive movement, such as bipedal movement in walking for a sustained period, and enable the achievement of maximal practice effects during retraining. Therefore, this type of gait training has the potential to induce neuroplasticity by modulating neuronal excitability and connectivity at the spinal and supraspinal level, thereby improving walking and the quality of life of individuals with mobility impairments.

Based on the concept of neuroplasticity, it is important to consider intensity and variability in the recovery of walking after neurological injury. It is unclear whether using exoskeleton technology following task-specific gait training combined with high aerobic intensity practice can achieve neuromotor behavior changes or gains in functional recovery improvement such as walking. Therefore, the purpose of this study is to determine whether high-intensity locomotor training can safely be achieved while utilizing overground robotic exoskeletons. We hypothesize that subjects can safely achieve high cardiovascular intensity (70-80% heart rate reserve) gait training utilizing the overground exoskeleton. We also hypothesize subjects will demonstrate improvement in overground walking ability after receiving high-intensity gait training sessions in the exoskeleton.

BACKGROUND INFORMATION

The impaired ability to walk independently is a significant consequence after neuromuscular injuries resulting in substantial limitation in mobility and performance of daily activities, thus restricting full participation and home and community re-integration.[1, 2, 3] This contributes to an extremely limited number of steps taken per day, and often leads to a sedentary lifestyle.[4] Further, a sedentary lifestyle contributes to secondary medical problems such as diabetes, obesity, osteoporosis/osteopenia, urinary, pulmonary, and cardiovascular disease.[5-8] Walking, therefore, is not only an important activity of daily living but also helps to reduce secondary complications and improve the overall quality of life.[9-10]

Historically therapy was limited to teaching compensatory strategies. Evidence is now growing to support the ability of the nervous system to adapt after injury.[12] Emerging research indicates that the intentional massed practice of activity-based training may promote neural plasticity and cortical reorganization and subsequent recovery of walking ability after neurological injury.[13-18] Moreover, studies have shown that placing the body in a load-bearing position and moving the lower limbs in a repetitive stepping pattern leads to improved locomotor recovery.[19-21]

One example of locomotor training is the use of bodyweight supported treadmill training (BWSTT) to drive changes in spinal cord pathways by increasing the excitability of the spinal cord leading to the recovery of movements controlled below the level of injury.[22, 23] In BWSTT, a bodyweight support system allows for unweighting of the body while using a treadmill to provide repetitive stepping. An alternative method for achieving load-bearing, repetitive stepping in an overground environment is the use of lower extremity robotic exoskeletons. This locomotor training technique requires less energy expenditure and physical strain for the clinician while still providing repetitive stepping in a full load-bearing position.

Robotic exoskeletons, such as Ekso® by Eksobionics, have been developed and approved by the FDA for rehabilitation after neurological injury. These devices are worn outside of the body and can move an individual's legs via motors in the hip and knee joints. The users of the exoskeleton must be both physically and cognitively engaged in advancing the limb. The benefits of utilizing robotic exoskeleton for gait include 1) Opportunity for maximizing the effects of massed practice, task-specific training by producing large numbers of repetitions without demanding intensive physical labor of trainers. The anticipated improvements could be maximized by the active engagement in consciousness by the individual [24]; 2) Potential promotion of neural plasticity with subsequent recovery of walking ability after neurological injury [25-30], and 3) Creating an environment that will support ideal gait kinematics and speed, optimize joint loading, and provide accurate sensory cues to promote spinal and cortical neuroplasticity in an overground environment.[25]

New evidence is developing that demonstrates, along with repetition, it is important to consider intensity and variability in recovery of walking after neurological injury.[31-37] Intensity can be evaluated as power, time, frequency, or repetitions. The growing body of literature describes the high intensity, measured as power, to increase neuromuscular, cardiovascular, and metabolic demands on the body to promote neurological recovery. Specifically looking at recovery of gait, locomotor training modalities that maximize stepping at high intensities with a variability of the task have led to significant improvements in walking compared to conventional therapy. [32, 36, 38, 40] Individuals post SCI and CVA have been

able to successfully achieve high aerobic intensities (70-80% heart rate reserve) during gait training sessions without adverse reactions.[35, 39] For this proposed study, we will set variables of time and frequency as those that can be reasonably achieved during standard of care in an acute rehabilitation setting. Repetitions of steps will be logged; however, the primary measure for power will be aerobic intensity.

Typically, high-intensity training protocols involved the use of bodyweight supported treadmill systems, unweighting machines, and stepping overground. Overground exoskeletons offer the opportunity for individuals to receive full weight-bearing while working on stepping. However, it is unknown if an individual utilizing an exoskeleton can work hard enough to reach high aerobic intensity levels. Therefore, we propose the investigation of performing task-specific gait training at high-intensity levels in an exoskeleton to achieve greater gains in the neurological recovery of walking.

OBJECTIVES

The purpose of this study is to determine the feasibility and potential efficacy to implement high cardiovascular intensity training parameters (70-80% heart rate reserve) with the use of overground wearable robotic exoskeletons in an inpatient rehabilitation setting for locomotor recovery.

Specific Aim 1: To determine whether it is feasible to achieve high-intensity locomotor training sessions at 70-80% of subjects' heart rate reserve using an overground wearable robotic exoskeleton. We hypothesize that all subjects will successfully achieve targeted heart rate for at least 50% of the treatment session (>25 min of 45 min of activity in the exoskeleton) in 3 out of 5 sessions, without adverse reactions.

Specific Aim 2: To investigate the potential functional improvements in gait after receiving high-intensity locomotor training with an overground exoskeleton. We hypothesize subjects will demonstrate improvement in overground walking ability, measured on the 10-meter walk test and six-minute walk test, after participation in high-intensity locomotor training with an overground exoskeleton.

STUDY DESIGN

A pre-post design with outcomes monitored before and after participation in high-intensity gait training intervention with an overground robotic exoskeleton will be used.

Study Population

We plan to enroll up to 20 human subjects (male and female), age 18 years or older, admitted to inpatient rehabilitation with a confirmed diagnosis of cerebrovascular accident (CVA) or motor incomplete spinal cord injury (SCI), classified by the American Spinal Injury Association Impairment Scale (AIS) grades C or D.

Potential subjects will be recruited from the TIRR Memorial Hermann inpatient rehabilitation facility. Subjects will be excluded if they lack sufficient range of motion at lower extremity preventing the achievement of normal stepping kinematics, are unable to physically fit within the exoskeleton, have evidence of an unstable spine, presence of lower extremity or pelvic fractures, or other conditions limiting weight-bearing into legs, history of severe neurological disorder other than CVA or SCI, difficulty completing forms written in English

or following verbal instructions provided in English, use of mechanical ventilation for respiratory support. See the chart for all inclusion and exclusion criteria.

Inclusion Criteria	Exclusion Criteria
• Male or female â‰¥18 years of age • Able to achieve adequate fit within the exoskeleton • Diagnosis of CVA or motor incomplete SCI (AIS C or D) • Sufficient range of motion to attain normal, reciprocal gait pattern, and transition from normal sit to stand or stand to sit • Intact skin on all surfaces in contact with device and load-bearing surfaces • Weight <220 pounds	• Pregnancy • Spinal instability • Unhealed limb or pelvic fractures or any condition restricting weight-bearing in limbs • Diagnosis of other neurological injuries other than CVA or SCI • Uncontrolled spasticity (3 on Modified Ashworth Scale) • Colostomy • Decreased range of motion or contractures in legs (>10° at hips, knees, or ankles) • Uncontrolled autonomic dysreflexia • Unresolved deep vein thrombosis • Inability to tolerate standing due to cardiovascular issues or orthostatic hypotension • Inability to follow 3 step commands • Severe comorbidities: active infections, heart, lung, or circulatory conditions • Pressure sores, impaired skin integrity • Use of mechanical ventilation for respiratory support

Procedures

The study will require subjects to participate in 7 visits. The initial visit will be a screening visit and baseline assessment (2 hours), followed by five intervention visits (1.5 hours each) and a post-assessment (1 hour). These sessions are additional to the subjects regular inpatient rehabilitation plan of care.

After informed consent is provided, the subject will participate in a screening evaluation and baseline assessment, which will include assessment of skin integrity, hip, knee, and ankle range of motion, and spasticity, functional mobility, measurements to ensure the individual will safely fit inside the robotic exoskeletons and cardiopulmonary measurements (blood pressure, heart rate).

Subjects will then participate in 5 high-intensity gait training sessions utilizing Ekso® exoskeleton. Intervention sessions will be performed at TIRR Memorial Hermann and will occur in addition to the subject's daily scheduled 3 hours of therapy. Each training session will last up to 60 minutes in the Exoskeleton and will be completed within 14 days. Training will focus on walking in the Ekso®. The goal of each session is to achieve high-intensity stepping, maintaining heart rate (HR) within 70-80% of heart rate reserve (HRR), or a Rating of Perceived Exertion (RPE) of 15-17. Target HR ranges will be calculated using age-predicted maximum heart rate (HR_{max} = 208 - [0.7 * age]) and the Karvonen formula (target HRR = 0.7 * [HR_{max} - HR_{rest}) + HR_{rest}). Heart rate and RPE will be monitored continuously and recorded every 5 minutes throughout the session. There will always be at least one trainer present during the

training sessions to provide assistance as needed for safety. After completing five intervention sessions, subjects will participate in a post-assessment evaluation for functional mobility measurements.

We will also measure subjects' heart rate during standard of care physical therapy sessions. Subjects will be asked to wear a heart rate monitor for up to 5 therapy sessions.

Outcome Measures

- Seated dynamic reach: We will assess a subject's stability with the Modified Functional Reach, measuring the maximum distance an individual can reach forward from a seated position. We will average three trials.
- Gait Speed: The 10 Meter Walk Test (10MWT) will assess the subject's self-selected and fast gait speeds. Four marks will be placed on the ground at 0, 2, 12, and 14 meters. Subjects will walk a total of 14 meters, where the middle 10 meters (between marks at 2 and 12 meters) will be timed and recorded as their gait speed. Subjects will complete two attempts at their self-selected pace and two at their fastest pace.
- Spatial-temporal gait parameters: The GAITRite pressure map will be used during the 10MWT. This pressure map will digitally record the subject's footprints' placement and pressure as they walk over it during the 10MWT. This data will calculate temporospatial gait parameters, such as swing and stance times, lengths, widths, etc.
- Walking endurance: The 6 Minute Walk Test (6MWT) will measure the distance subjects can walk over six minutes. Subjects will walk along a 100-foot hallway as many times as they can in 6 minutes. Subjects are allowed to rest as needed; however, the timer continues to run for 6 minutes consecutively, whether they are standing or walking.
- Metabolic expenditure during walking: Oxygen consumption will be calculated on a breath-by-breath basis measured by a portable metabolic system (Cosmed K4b2). During the testing, the subject will wear a face mask at all times and will be asked to breathe normally. Subjects will also wear a heart rate monitor. This task will be performed during the 10MWT and 6MWT.
- Heart rate: We will measure heart rate using a wearable heart rate sensor (Polar® H10) that captures continuous heart rate data via Bluetooth technology. Data collected during pre and post assessments, during exoskeleton sessions and overground physical therapy sessions.

PHOTOGRAPHY and VIDEOTAPING

We would like to obtain photographs and video during the exoskeleton training sessions. The goal of the photography and videotaping will be used for educational purposes when presenting results of this study. The photographs will be used to demonstrate what exoskeleton training looks like. The identity of subjects will not be revealed in the photograph. If a photograph or video is used, a black box will be placed in front of subjects face to protect their identity. Any photographs and videos taken during the study will be saved on a locked computer in a file labeled with the subjects research number and no other identifying information.

DATA and SAFETY MONITORING

We will use following strategies to prevent some expected events for this study:

1) Loss of confidentiality or privacy

Information obtained for this study will be kept private to the extent allowed by law. However, research information may be shared with the University of Texas Health Science Center at Houston Institutional Review Board (IRB), the research physician investigator, the research staff and others who are responsible for ensuring compliance with laws and regulations related to research. The study will be performed at TIRR Memorial Hermann. Data will be collected on paper forms which will be kept in a locked room in a locked filing cabinet in the research office in UT Health Motor Recovery Laboratory at the TIRR NeuroRecovery Research Center. To allow for data analysis, data will be de-identified and entered into an excel spreadsheet. All computers are password protected and therefore, only authorized persons have the access to the electronic files saved in computers and will adhere to TIRR Memorial Hermann standards.

2) Loss of saved electronic data after a computer crash

All original data will be maintained on paper data collection forms. De-identified data may be entered into computer for data analysis. A standard procedure of electronic file backup is established and enforced by the PI. All file backups are routinely performed in the local hard drive. However, if there are other unanticipated problems which occur during and after data collection: the original paper version of the data will be maintained in the locked file cabinet.

3) Loss of balance or fall from testing

One research team member will remain next to the subject as long as the subject is donned in the exoskeleton robot to prevent loss of balance or fall whether sitting or standing. If a fall or significant loss of balance occurs, one staff physician will be notified immediately. All adverse events will be reported per CPHS protocol.

4) Possible skin irritation

Local skin irritation, bruising, swelling, or temporary discomfort following wearing of the exoskeleton may occur. Prior to donning the exoskeleton subjects skin will be inspected by a licensed Physical Therapist for baseline, and compared after doffing exoskeleton. Any differences will be recorded and followed up with the study physician accordingly. All adverse events will be reported per CPHS protocol.

5) Muscular soreness or fatigue

Borg Rating of Perceived Exertion Scale (Borg) will be administrated periodically throughout the intervention sessions. Subject will be provided with rest period as needed, in particular if BORG rating 17.

6) Bone Fracture

The risk of fracture to the subject is no greater with the use of exoskeleton than conventional weight bearing and walking therapy.

STATISTICS

The proposed study is a single-arm, pilot study; therefore, no data is available to calculate the sample size. This study's data will allow for performing power analysis to determine the effect size and sample size for future studies.

Descriptive analysis will be used to analyze the heart rate variables, such as the number of minutes the target heart rate is met during the training and the heart rate- time relationship

during a typical session. Paired t-tests will be used to compare dependent variables (i.e., functional assessment) between baseline and post-training. The significant level is set at 0.05.

ETHICS

The study will be performed under the prevue and in accordance with the rules set by the Committee for the Protection of Human Subjects (UT IRB). Potential subjects will be identified by physiatrists and physical therapists working on the inpatient wards at The Institute for Rehabilitation and Research (TIRR) Memorial Hermann. Once identified, the potential subjects will be approached and asked if they wish to discuss a study utilizing exoskeletons (Robotic suits worn on the outside of the body) for individuals with CVA or SCI. It will also be explained that choosing not to inquire further about the study will in no way jeopardize the relationship with anyone at TIRR or in the Memorial Hermann system. Once the potential subject agrees he/she will be introduced to either the Principal Investigator or the study coordinator. Once the potential subject agrees to discuss the study, the individual and anyone that the potential subject wishes to accompany him/her will go into a private room to discuss the contents of the consent form with either the Principal Investigator or study coordinator. After the consent is reviewed in its entirety, and after allowing ample time for questions, either the Principal Investigator or the study coordinator will give the potential subject time to discuss the study with whomever the potential subject cares to discuss the study with. If the subject agrees to enroll in the study, the Principal Investigator or study coordinator will review the informed consent form with the subject in its entirety.

DATA HANDLING and RECORD KEEPING

The subjects name and demographic information will be collected prior to testing. Each subject will be assigned an identification number which will be used from this point forward. All measurements will be stored according to the identification number. All research materials will be kept in a locked file cabinet in the research office. All computers are password protected and only authorized persons have the access to the electronic files saved in computers. Paper data will be stored in the UT Health Motor Recovery Laboratory research office at TIRR NeuroRecovery Research Center in a locked file cabinet. Access to the file cabinet will be given to the Primary Investigator and authorized team members. All electronic data stored on the hard drive of the desktop machine will be password protected and available only to the authorized research team members. Identifiable data will be stored for 5 years after the study is completed. Stored files will be deleted from the portable hard drive after 5 years as well. Identifiable data will be shredded at the end of 5 years after the completion of the study.

QUALITY CONTROL and ASSURANCE

To ensure research integrity, standard written procedures for all tests will be established by the Principle Investigator and the Study Coordinator who will then assess each team members competence for research conduction on a regular basis. Therefore, the testing protocol will be consistent throughout the entire data collection for this study.

COSTS, REIMBURSEMENTS and COMPENSATION

Subjects will receive $100 for participation in this study. Subjects will receive $20 at the completion of each exoskeleton intervention.

FUTURE STUDIES

Subject will be asked to answer a question regarding their interest in being contacted in the future to participate in other studies. Subjects will be given the choice to say yes or no if they agree to be contacted in the future regarding other projects.

PUBLICATION PLAN

The results of this study will be used for presentation at national conferences and publications in peer-reviewed journals.

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