Official Title: Effects of physical therapy and Dalfampridine on functional mobility and lower extremity strength in non ambulatory subjects with MS

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Background: Multiple Sclerosis presents in individual patients with a variety of clinical manifestations which can impact functional mobility. Epidemiologic studies have shown that within 15 years after the onset of MS, 50% of individuals will require the use of an aid for walking and 10% will require a wheelchair (Courtney, 2009). Twenty-five years after disease onset, approximately 90% of those with MS will have significant functional limitation and disability(Simon, 2005) with 50% of those individuals requiring a wheelchair for mobility.

Impairments related to functional mobility are integral to disability in patients with MS. The International Classification of Functioning, Disability, and Health (ICF) defines mobility as "… moving by changing body position or location or by transferring from one place to another, by carrying, moving or manipulating objects, by walking, running or climbing, and by using various forms of transportation." (WHO, 2008)

In a study conducted in 2008 in which patients prioritized the importance of 13 bodily functions, lower limb function was ranked the highest regardless of actual level of disability and disease duration (Heesen C, 2008). Similarly, among factors affecting quality of life, mobility was given the highest priority by 65% of patients with MS(Datamonitor, 1999).

Cognitive changes may also occur in MS and in some patients may be an early symptom of the disease(Morgen, et al., 2006) (Kushwaha, Suri, Gupta, & Bala, 2009) A recent study suggests that exercise in a healthy older population may enhance executive functioning(Angevaren, Aufdemkampe, Verhaar, Aleman, & Vanhees, 2008) and similar findings have been reported in patients with chronic stroke(Rand D, 2010). A study just completed in MS suggests that physically fit individuals with MS have less gray matter atrophy and as a result better cognitive function than their counterparts with MS who are less physically fit (Hilton, 2010).

Rationale and Specific Aims: This double blind study will examine the effectiveness of Dalfampridine (Bever, et al., 1996) (Bever & Judge, 2009) when administered in conjunction with physical therapy between the effects of a 12 week physical therapy program and placebo on standing tolerance, transfers, repeated sit to stand, arm and leg strength for non-ambulatory individuals living with MS. Previous studies have examined changes in subjects who are

ambulatory, specifically gait speed and in leg strength assessed with manual muscle test (Goodman, et al., 2008). Changes in basic mobility such as transfers and sit to stand should be examined in non-ambulatory subjects as maintaining safety in performance of these tasks could enable an individual to continue living independently. Muscle strength will be assessed with the use of a hand held dynamometer which is a more sensitive measure of muscle power (Schwartz, Cohen, Herbison, & Shah, 1992) and will demonstrate if Dalfampradine and physical therapy, or physical therapy alone can impact muscle strength in individuals with MS who are non-ambulatory. Improving arm and leg strength could result in safer and more efficient transfers as well as the ability to perform standing activities. Another benefit of increasing standing tolerance is the effects on bone density as well as pulmonary hygiene. In studies of spinal cord injured patients with quadriplegia, it was found that weight bearing through the lower extremities in a standing posture impacts bone density as well as promoting pulmonary hygiene and gastric motility (Claus-Walker J, 1975; Eng JJ, 2001). In addition, this study will assess change in cognitive processing for subjects who exercise regularly and take Dalfampradine 10mg bid.

Specific Aim 1: To assess the change in standing tolerance, transfers, repeated sit to stand, arm and leg strength for non-ambulatory individuals with MS between subjects on Dalfampridine who receive physical therapy and those who participate in physical therapy and receive a placebo. Enhancing the propagation of action potentials along axons in addition to regularly contracting the muscles through exercise may have a greater effect on strength and functional mobility. A hand held dynamometer will be used to assess strength in the iliopsoas, gluteus maximus, quadriceps and gastrocsoleus in the lower extremities and triceps and serratus anterior [shoulder depression] muscles in the upper extremities bilaterally.

Specific Aim 2: To determine within the combined group receiving physical therapy the change in standing tolerance, transfers, repeated sit to stand, arm and leg strength. Evidence supporting the effectiveness of physical therapy in this population is non-existent.

Specific Aim 3: To assess the change in cognitive processing between subjects who participate in physical therapy and take Dalfampradine 10mg bid and those subjects that receive physical therapy alone. Preliminary research suggests a change in cognitive processing in ambulatory

individuals with MS who exercise on a consistent basis (Hilton, 2010). The action of Dalfampradine on neuronal transmission for cognitive tasks has not yet been investigated.

Research Plan: Forty-five non ambulatory subjects, meeting an Expanded Disability Status Scale 7.0 to 8.0 (Kurtzke JF, 1983), will be referred to this study by their neurologist at the Jacobs Neurologic Institute (JNI) and by physical therapists supervising the MS Wellness program offered at DeGraff Memorial Hospital. The referral of subjects to the study will be a rolling admission with subjects screened and tested as identified by the neurologist or physical therapists. It is anticipated that the study will last one year to achieve 40 subjects completing the study. As subjects are identified they will be randomized into 2 groups; Group 1 will receive physical therapy for 12 weeks while taking Dalfampradine 10 mg 2x/day and Group 2 will receive physical therapy while taking a placebo pill 2x/day. Two baseline measures will be completed prior to the initiation of the interventions. Both groups will receive physical therapy treatment two times per week and perform a home exercise program three times per week which will be monitored weekly by the physical therapist. At the conclusion of the study the control subjects will be offered Dalfampradine for 12 weeks.

As potential subjects are identified they will meet with the primary investigator at the Jacobs Neurologic Institute or DeGraff Hospital to discuss the study, and be screened for participation in the study. Subjects who meet the inclusion/exclusion criteria will read and sign the consent form indicating their willingness to participate (see Informed Consent Process at end of this document). Within a week of identification all subjects will complete a physical therapy evaluation and perform the standardized measures for this study. Subjects who do not meet the screening criteria will be thanked for their participation and excused.

Inclusion Criteria: Patients 20 years of age or older with a confirmed MS diagnosis based on Mc Donald Criteria (Polman CH, 2005), and who have an Expanded Disability Status Scale (EDSS) of 7.0 to 8.0 (Kurtzke JF, 1983). The EDSS will be confirmed through review of the most recent documentation in the medical chart. In addition, subjects should not have any evidence or indication of active disease or relapse within the past 30 days.

Exclusion Criteria: Any subject with a history of seizures or renal function disease will be excluded from the study. In addition, subjects presenting with limited active range of motion in the upper and/or lower extremities due to soft tissue or joint contractures, presence of neuropathic pain in the extremities, and extremity manual muscle test of extensor muscles less than 2/5 will be excluded from the study. Patients with cognitive limitations that prevent their ability to provide consent will be excluded from participation.

Methods: Once it has been determined that the subject meets the inclusion criteria, he/she will be randomly assigned to dalfampridine or placebo, in a 1:1 fashion. Random order assignment will be established through computer generated program 1 to 40 and investigators will be blind as to subject group assignment. All subjects in Groups 1 and 2 will be scheduled for an appointment at The Wellness Center at DeGraff Memorial Hospital to complete the following:
1) Respond to a questionnaire describing their health history, symptoms associated with MS, and current medications. Subjects will then complete the MS Quality of Life 54 (MSQOL 54) (Vickrey BG, 1995), Spasm Frequency Scale (SFS) (Ordia IJ, 2010), Symbol Digit Modalities Test (SDMT) (Smith A, 1982).
2) Undergo a baseline physical therapy (PT) evaluation which will include manual muscle test, passive range of motion, Modified Ashworth Scale (Alibiglou, Rymer, Harvey, & Mirbagheri, 2008) (Anwar & Barnes, 2009), proprioception, and dynamic visual acuity. The EDSS will be obtained by the principal investigator from the neurologist's most recent documentation in the chart (within 30 days ±10 days to the baseline PT evaluation).

At the conclusion of the physical therapy examination subjects will be seated in the waiting room to rest for 15 minutes. Following the rest period subjects will complete the standardized tests as outlined:
1. Dynamometer test of strength in the upper and lower extremities, 3 trials for each muscle [measured in kilograms] (Schwartz, et al., 1992) (Noreau L, 1998). Muscles to be assessed: iliopsoas, gluteus maximus, quadriceps, gastrocsoleus, triceps, serratus anterior
[2 minute rest]
2. Standing tolerance (in seconds) two trials
[5 minute rest]

2. Transfer onto a low mat table, maintain sitting posture 2 minutes, and transfer back into wheelchair (Granger, Cotter, Hamilton, Fiedler, & Hens, 1990)
[5 minute rest]
3. Repeated sit to stand test five repetitions measured in seconds, two trials (Takai Y, 2009)

The subjects and the examiner participating in the study will be blinded to subject's group assignment. The examiner will test all subjects throughout the duration of the study.

After the initial baseline measurements all subjects will be scheduled for their physical therapy appointments. The physical therapy program will be 45 minute sessions 2 times a week for 12 weeks (Dalgas 2009) at the Wellness Center at DeGraff Memorial Hospital. The physical therapy intervention will consist of manual stretching, cycling, tall kneel and quadruped core activities, seated balance activities, bridging, sit to stand, and standing squats in parallel bars (Dalgas, Stenager, & Ingemann-Hansen, 2008) (Dalgas, et al., 2009; Dodd, Taylor, Denisenko, & Prasad, 2006) (Donze, 2007) (Patti, et al., 2003). The prescribed home exercise program will be performed 3x/week and will consist of self stretching, wheelchair pushups, bridging, short arc quads and resistive band exercise for trunk and upper extremity strengthening.

All functional tests and questionnaires to be completed at each measurement are listed below:

Multiple Sclerosis Quality of Life 54: The MSQOL-54 (Vickrey BG, 1995) is a structured, self-report questionnaire that the patient will complete seated at a table in a quiet area. For subjects with visual or upper extremity impairments the MSQOL-54 will be administered as an interview by the examiner. Two summary scores will be calculated for the MSQOL-54; physical health and mental health which will be derived from a weighted combination of scale scores. In addition, the12 subscales: physical function, role limitations-physical, role limitations-emotional, pain, emotional well-being, energy, health perceptions, social function, cognitive function, health distress, overall quality of life**,** and sexual function will be calculated. One of the two single-item measures change in health, will also be recorded**.** (Accessed 9/23/10 http://www.nationalmssociety.org/for-professionals/researchers/clinical-study-measures/msqol-54/index.aspx)

Spasm Frequency Scale: This scale is a self report by the subjects of the number of spontaneous muscle spasms that occur over a one hour period. The subjects will be given the Spasm Frequency Scale (Ordia IJ, 2010) listed below and the examiner will ask how often they experience spontaneous spasms in the leg muscles. The subject's response will be circled by the examiner on the scale.

Spasm Frequency Scale:

0. None.
1. No spontaneous spasms; but vigorous sensory or motor stimulation results in spasms.
2. Occasional spontaneous spasms or easily induced spasms.
3. Greater than one but less than ten spontaneous spasms per hour.
4. Greater than ten spontaneous spasms per hour.

(accessed 9/23/10 http://www.ordia.com/spasm_frequency_scale.htm)

Symbol Digit Modalities Test (SDMT) will be used to measure visual processing speed. This test presents a stimulus key of numbers paired with abstract symbols at the top of a page. Participants scan the page below the key which has rows of symbols without the paired numbers. The task is to generate the associated numbers orally as fast as possible. We will employ the Rao adaptation (L. G. Rao SM, Bernardin L, Unverzagt F,, 1991; L. G. Rao SM, Ellington L, Nauertz T, Bernardin L, Unveragt F,, 1991) of the SDMT originally published by Smith (Smith A, 1982). Like the PASAT, the SDMT can be applied with the MSFC (Drake AS, 2010).

Brief Visuospatial Memory Test Revised (BVMTR) (Benedict RHB, 1996) (Benedict RHB, 1997) presents a matrix of six visual designs presented on an 8.5 x 11 piece of paper for three consecutive learning trials. During each trial the stimulus is presented for 10 seconds, after which the participant is asked to draw the figures as accurately as possible and in the correct location. The six designs receive a score of 0, 1, or 2 based on accuracy and location. After a 20-25 minute delay, participants are again asked to recall and draw the designs. An optional copy trial is presented after the test to help examiners control for motor coordination defects while judging the accuracy of drawings. Common indices of the BVMTR are the total score over the three learning trials and the total number recalled after the delay.

Standing Tolerance: Standardized performance of static standing has not been published. For this study the subject will be positioned with the wheelchair directly in front of a sink counter. The examiner will ask the patient to stand up facing the sink counter, keeping two hands on the counter [at the sink cutout area]. The examiner will stand next to the subject and guard as needed during this task. Upon standing upright the examiner will start the stopwatch. The time will be stopped when the subject is unable to maintain an upright posture defined as flexing of the hips and knees or bending the trunk forward to lean on the counter. Two trials will be performed (separated by a 2 minute rest) with the longest time in upright standing recorded.

Transfer from Wheelchair to Low Mat Table: Performance of transfer (moving from one surface to another) is an item in the Functional Independence Measure [FIM] which will be used to objectively quantify the subject's ability to move from the wheelchair to the low mat table (Granger, et al., 1990) (Hamilton, Laughlin, Granger, & Kayton, 1991) The wheelchair will be position so the subject's stronger side is closest to the low mat. Assistance will be provided as needed by the blinded examiner who is also a physical therapist. The examiner will score the subject's independence or dependence with the task. Scoring ranges from:

7 - Complete independence: fully independent

6 - Modified independence: requiring the use of a device but no physical help

5 – Supervision: requiring only standby assistance or verbal prompting or help with set-up

4 - Minimal assistance: Requiring incidental hands-on help only (subject performs 75% of the task)

3 - Moderate assistance: Subject still performs 50–75% of the task

2 - Maximal assistance: Subject provides less than half of the effort (25–49%)

1 - Total assistance: Subject contributes < 25% of the effort or is unable to do the task

(Accessed 9/23/10 http://www.dementia-assessment.com.au/symptoms/FIM_manual.pdf)

The subject will also transfer from the low mat table back into the wheelchair with a score of level of independence or dependence recorded by the examiner.

Sit to Stand Test: The subjects will be seated in a chair of 43 cm in height with armrests. The chair will be placed facing a kitchen sink counter to enable the subject to use hand support in standing. Subjects will be instructed to push off the armrests and stand up fully and then to sit down, placing their buttocks on the chair in a sitting position between repetitions (Takai Y, 2009). Upon standing subjects may use the kitchen counter as needed for balance. The time will be recorded using a stopwatch to the nearest 10th of a second. The test will start with the examiner's command "Go" and stop when the subject is fully seated on the 5th repetition. Prior to the measurement, 2 practice trials with sub maximal effort will be performed for positioning and learning of the task. The sit to stand measurements will be performed two times with an interval of 2 min between trials. The fastest time will be adopted for the individual data (Takai Y, 2009)

Strength Test: The hand-held dynamometer is a portable device used as a quantitative and objective method of muscle assessment (Swartz et al. 1992) (Arnold CM, 2010). Testing in this study will be performed with the examiner resisting a maximal voluntary contraction by the patient, thereby producing an isometric contraction. The mean force of three administrations for each muscle group tested will be performed (Noreau L, 1998) with a practice trial preceding the testing (Andrews AW, 1996). Ten seconds of rest will occur between each trial. The starting position of the individual and the dynamometer will be consistent for each trial and among all subjects. Assessment of strength will be performed with the muscle at approximately mid range for a concentric contraction. The recommended unit of measurement will be in Kilograms [Kg] (Andrews AW, 1996) and will be rounded to the nearest Kilogram.

Starting test positions for each muscle:
Iliopsoas - seated in a straight back chair, hands in lap
Gluteus maximus – prone with knee in 90° flexion, hip in neutral
Quadriceps – seated knee in 90° flexion, hands in lap
Gastrocsoleus – supine with hips in neutral and knees in extension
Triceps – supine with elbow in full flexion with hand by ear
Serratus anterior – seated in straight back chair with elbow in 90° flexion

Repeated Measures
The subjects in both groups will be asked to return 2 weeks after the initial testing to repeat baseline evaluation of all functional tests and questionnaires. The physical therapy exam will not be repeated. After the second baseline measures are obtained, the two groups will begin physical therapy and start taking Dalfampradine (Group 1) or a placebo pill (Group 2) twice a day as prescribed.

At 6 and 12 weeks of the intervention all subjects will be retested following the same format as the initial testing excluding the physical therapy evaluation. After 12 weeks all interventions will be discontinued. All subjects will complete two post tests, absent of interventions at weeks 18 and 21 to examine short term longitudinal effects.

Statistical Analysis Plan: All data will be reported as means ± SD and analyzed by SPSS software. A t-test will be utilized for demographic differences between groups. A mixed factor repeated measures ANOVA will be used to evaluate within subject factor of Time (Baseline; 6 weeks; 12 weeks) and between subject factors of Group (Drug vs. Placebo). Data will be checked for normal distribution and for equality of multiple variances utilizing the Box's M test. When data is found to be non parametric, a Friedman's test was employed to determine significance. A p value <0.05 will be used to determine statistical significance for all tests.

Data Safety and Monitoring Plan: A neurologist who is not blinded will evaluate all potential subjects to determine any risks that may be associated with participating in the study (i.e. seizure history, history of kidney disease or pregnancy). All subjects will be instructed to contact the PI and Co-PI in the event of a serious adverse event. The neurologist (unblinded) will follow patients during the study and will review any adverse events within a 48 hour period. The neurologist will use their clinical discretion and patient concerns to decide if subjects should be removed from the study. The Health Sciences Institutional Review Board (HSIRB) will be

notified of any serious adverse event within 24 hours and a detailed report will be filed. The PI and Co-PI will continuously examine the data as it is collected and ensure systematic and precise data collection procedures.

Informed Consent Process: The PI and Co-PI will explain the study and obtain the informed consent from the subjects using the HSIRB approved informed consent form. No assent is required since the subjects must be at least 20 years old to participate. English will be the only language used to describe and discuss the study with the patients and for the consent form; no translators will be provided. There will be no waiting period between informing the prospective subjects or his/her legally authorized representative about the study and obtaining consent. Consent will be obtained at either the Jacobs Neurologic Institute (JNI) or DeGraff Hospital when patients come in for their regularly scheduled MS follow-up appointments. If the patient is unable to give consent secondary to cognitive limitations, he/she will be excluded from the study. Patients will be told verbally about the study through their support groups and visits to the JNI or DeGraff Wellness Center. While the health care team that works with these patients may mention the study to the patients, the patients will receive no special services, supports or monetary compensation for participating (or not participating) in the study.

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