PROTOCOL TITLE:

Impact of Intense Physical Therapy on Functional Mobility Outcomes in the Acute Stroke Population (<24 hours post-stroke)

PRINCIPAL INVESTIGATOR:

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1.0 Objectives/Specific Aims

Objective: To evaluate the impact of increased frequency and intensity of Physical Therapy (PT) services on patient outcomes in the acute stroke population

Aims & Hypotheses:

Aim 1: To determine the impact of increased frequency and intensity of PT services compared to the usual care PT on discharge disposition of patients post-stroke.

Hypothesis 1: We hypothesize that patients receiving an increased frequency of PT services will have higher rate of discharging to home/acute rehabilitation center than to a subacute rehabilitation/skilled nursing facility compared to patients in the usual care PT group.

Aim 2: To determine the impact of increased frequency and intensity of PT services, as opposed to usual care, on functional mobility.

Hypothesis 2: We hypothesize that patients in the treatment physical therapy group will demonstrate higher degree of improvement on the Activity Measure for Post Acute Care (AMPAC) and Postural Assessment Stroke Scale (PASS) from admission to time of discharge from the hospital and at 90-day follow up. We also expect lower overall Modified Rankin Scale (mRS) scores for the increased frequency PT group compared the usual care PT group at three months post stroke.

Aim 3: To ensure that high frequency dosage is safe and feasible to implement the proposed PT regimen in the acute inpatient setting.

Hypothesis 3: We hypothesize that there will be fewer adverse events experienced by patients in the increased frequency compared to the usual care group.

2.0 Background

The Department of Physical Therapy in conjunction with the Comprehensive Stroke Center at the Medical University of South Carolina (MUSC) seeks support for developing an evidence-based approach for the mobilization of patients within the first 24 hours after an acute stroke admission and for increasing the frequency of acute PT services while inpatient. This evidence will prepare physical therapists and guide the practice in the delivery of acute stroke mobilization in the hospital setting to optimize length of stay, disposition planning, and enhance long term recovery outcomes.

Very little is known about the optimal approach for mobilizing patients after an acute stroke, however, prior studies demonstrate the significance of early postural control and balance to be a prognostic indicator of a return to independent walking.1,2 Patients who do not regain sitting balance or motor recruitment strategies demonstrate an increased correlation with dependent gait at 6 weeks post stroke.3,4 Acute stroke patients may not be able to tolerate an extensive early mobility program, but may benefit from shorter more frequent sessions of

therapy early in their recovery. Therapy would focus on specific functional treatments such as seated postural control, motor recruitment strategies, and transfer training siloed into separate sessions[5]. Throughout the literature, there is guidance for the approach to post stroke recovery in both the inpatient rehabilitation and outpatient therapy sectors. Little is known regarding the importance of frequency within the first 24 hours after an acute stroke and the contribution of therapy services in the acute hospital setting. The goal of this project is to determine the appropriate dosage of post stroke mobility in the acute care hospital setting.

The dosage of an overall treatment session is defined by the frequency, intensity and duration of physical therapy services. The objective is to determine if changing one component of the overall mobility dosage, adjusting frequency, will improve patient outcomes. As a comprehensive stroke center, MUSC strives to provide the best of patient care by committing to a higher standard of clinical service, providing a framework to improve patient outcomes, and organizing teams within the continuum of care- therapy included. A cohesive approach to mobilization in the hyper acute phase of stroke may impact patient outcomes across the continuum of care

3.0 Intervention to be studied

Early mobilization is a widely accepted pillar of acute hospital therapy services. In most populations, early mobility is regarded as safe, feasible, and yields positive results.6 A considerable amount of clinical and scientific literature has evaluated and upheld the positive effect of early mobility on patient safety, ICU delirium, duration of mechanical ventilation, hospital length of stay, functional mobility, ambulation ability, and mortality. However, most of the research in the field of early mobilization has focused on intensive care patients with multiple medical comorbidities.[7]

The consideration of an acute stroke diagnosis in relation to the approach of acute care PT and “early mobility” is limited. The AVERT trial was novel in opening the doors to considering physical therapy’s approach to acute stroke care on these dedicated stroke units, critical since earlier research surmised that complications of immobility could be estimated to account for as many as 51% of death in the first 30 days post stroke.8 The results of the AVERT trial, however, raised concern that very early mobilization may cause changes in cerebral blood flow and blood pressure leading to worsened stroke outcomes, increased mortality and increased rate of falls during early mobility.[9]

From the publication of the AVERT trial, there has been a rise in clinical interest regarding the correlation of early mobility and improved functional outcomes post stroke. The majority of physical therapy studies in the acute stroke population have only examined the optimal time to begin mobilization post admission to the hospital.[9] This project proposes the idea that patients with acute stroke may not be able to tolerate an extensive early mobility program.

Instead, patients may benefit from shorter more frequent sessions of therapy early in their recovery to focus on specific areas such as seated postural control, motor recruitment strategies, and transfer training delivered in separate sessions. We hypothesize that the approach of shorter, more frequent sessions of intense quality therapy services will negate the post stroke fatigue factor. Thus, allowing patients to progress functional mobility with improved tolerance to therapy sessions, frequent repetition, as well as implementation of motor learning principles to ensure carryover by providing distributed over massed practice.

The research in the field of neuroplasticity and neuro rehabilitation illustrates the importance of high intensity, repetitive and aggressive approaches for motor recovery, however, most of this research has been performed in the subacute stroke population. Error augmentation training is one way to increase the difficulty of a task to enhance motor learning.[10] In the current research, Error amplification training was found to induced more robust aftereffects after locomotion training as compared to assistive training.[10] Thus, error augmentation/ amplification may be one approach to increasing the intensity and complexity of the task without changing the task itself. For acute stroke patients in the hospital setting- error augmentation can be implemented by targeting the patients post stroke deficits by emphasizing them. If a patient has a hemiparetic limb- error augmentation would include resisting and challenging the movement of that limb rather than facilitating and assisting with the movement of that limb. For patients whose stroke did not cause hemiparesis but rather balance impairments, narrowing the base of support or dynamically resisting balance in the direction of a patient's lateral lean can also amplify and augment their error. The celebrated motor learning theory, "The Challenge Point Theory" states that learning is maximized when the task difficulty is appropriate for the individual skill level of the performer[11]; this theory leaves us with hope that increasing the challenge of mobility tasks in the acute hospital setting may be beneficial to increasing the success and progress of functional mobility.

Rather than decreasing the time to upright mobility, it may be beneficial to examine the effect of short sessions of more frequent challenging mobilization in these patients, within the early stages of their hospitalization. If, as assumed, a prolonged duration of upright sitting posture has a negative effect on cerebral blood flow12 it may be possible to gain the positive effects of early mobility by continuing to provide PT services while combating the negative effects of cerebral perfusion by returning all patients to a supine position in bed following therapy services within the first 24 hours of acute stroke. This study aims to examine the approach of increased frequency and intensity of physical therapy services as a way to gain the benefits of the publicized early mobility approach, while weighing the concerns raised by previous trials and decreasing amount of time left upright to combat negative effects of cerebral perfusion on the ischemic penumbra. As part of this study, there will be an experimental group of participants who will receive PT sessions twice a day for the first three out of five days of admission, followed by daily treatment sessions at an intensity of at least 20-50-minute sessions. The intensity of the treatment provided to the

treatment group will be increased by incorporating error augmentation training. Error augmentation/amplification is an approach to increasing the intensity and complexity of the task without changing the task itself- thus, allowing the treatment group to participate in the same protocol of bed mobility, transfers and gait training as the control group- except with amplification of their errors rather than correction of these errors. This group will be compared to a group of control participants who will receive standard PT services 3-5x/wk (on average 20-50 minutes/session) while in the acute hospital setting.
Outcomes of interest include average length of stay, discharge disposition, Postural Assessment Stroke Scale & Modified Rankin Scale scores, and rate of readmission at 30 days. There is a critical need to evaluate how the mobilization approach of patients with acute stroke during their hospitalization impacts their discharge disposition, length of stay, and future functional outcomes

4.0 Study Endpoints

Physical Performance and Functional Measures: PASS scores & AMPAC scores on evaluation, day three, discharge, and 90 day follow up. Discharge disposition recommended vs ultimate discharge disposition, hospital length of stay, and 30-day readmission.

5.0 Inclusion Criteria

Inclusion/exclusion criteria will be determined based on patient chart review in EPIC, once PT consults are received. Thorough chart review and discussion with patient's medical team will serve as a means of determining patient eligibility. Both treatments as usual and experimental group patients will meet the same eligibility criteria and will be randomized to their treatment after consent is obtained.

Inclusion Criteria:
Acute stroke
NIH Stroke Scale score of 2-18 with motor involvement
Age </=80yo
Medical stability for increased therapy services, determined by Stroke Service NP
Ability to give informed consent

Exclusion Criteria:
Medical instability or cerebral perfusion dependence, requiring bed rest
Pregnancy (noted in chart)
Inmates (noted in chart or visible by guards present at bedside)
Known & Current COVID-19 infection (PCR positive labs)
Dialysis (noted in chart & performed while inpatient)
External Carotid Stenting Procedure

6.0 Number of Participants

Goal enrollment is 150 participants. Based on the past literature, in similar populations the standard deviation of PASS measurements is at the most 7.[20] Using this, with a sample of 75 patients in each group, with 95% confidence at the end of the study we can estimate this difference within a margin of error of 2.3.

7.0 Setting

This research will be conducted on the inpatient stroke service at MUSC (ED, 9E, 9W, 8W, ICU) within 24 hours of the patient's admission to the vascular neurology service for an acute stroke. Follow up values will be collected at post discharge neurology clinic (either in person or through password protected zoom call) by a member of the study team. Adverse events will be documented in the patient's medical chart and research record and the primary investigator will direct and oversee services provided. No additional safety risks are anticipated, other than those noted below (section 13.0)

8.0 Recruitment methods:

Potential subjects will be identified via chart review on admissions to the stroke service and appropriateness of enrollment will be decided by PI based on discussion with the patient's clinical care team. Consent will be obtained by PT on initial evaluation. The PI/study team will already be part of these patients' clinical care and the PT or nurse practitioner obtaining consent will be an approved member of the study team on the eIRB application.

This study will also recruit from the Registry for Stroke Recovery (RESTORE-Pro#00037803, IRB approved 9/6/14) which is a research tool sponsored by the National Institutes of Health (NIH) Center of Biomedical Research Excellence (COBRE) in Stroke Recovery with subjects consented for future contact to support stroke recovery research conducted at MUSC. RESTORE staff will query the registry for potential subjects and provide the Principal Investigator (PI) with the contact information of subjects who meet their criteria. The PI or research staff will contact subjects to further screen for potential enrollment.

9.0 Consent process:

To conduct this research, we will require a signed informed consent from all patients. The signed informed consent is necessary to be randomized to either arm of the study. A written copy of the consent form will be provided to the patient in the hospital prior to PT evaluation. The participant will be given the opportunity to read the consent, their questions will be answered and they will be provided with a copy of the consent document. Capacity to consent will be determined by the patient's primary medical team. For patients who are unable to physically sign their name, they may use make a mark on the consent and there will be a witness to the consent process.

10.0 Study Design:

This study will be designed as a randomized control trial with a 1:1 randomization. This study will utilize a permuted block design to randomly allocate a participate to a treatment group, while maintaining a balance across treatment groups. All patients will be identified and consented within 24 hours of admission.

The treatment group will receive increased frequency of PT services within the first 3-5 days of admission, followed by daily PT services for the duration of their inpatient stay. As part of the increased intensity of the treatment provided- this group will receive error augmentation training where the treating therapist will induce errors throughout mobility to challenge the patients rather than facilitating error-free movement. The deficits identified on evaluation will be targeted and emphasized throughout all therapy sessions. For patients with hemiparesis, the hemiparetic limb will be resisted during mobility. For patients with balance impairments- balance will be challenged by narrowing the base of support and resisting midline positioning

toward the side of the balance impairment. The treatment as usual group will receive standard care of PT services 3-5 times per week during their hospitalization which focuses on performing bed mobility, transfers and ambulation vs wheelchair mobility as able. Safety will be ensured throughout therapy sessions. Fall risk will be avoided with the use of a gait belt and non-skid socks and cerebral perfusion concerns will be mitigated by checking a resting blood pressure prior to upright mobility. The Postural Assessment Stroke Scale will be obtained as part of the initial PT clinical evaluation, on day three of hospital admission and at 90 day follow up. Follow up will be conducted (at 90 days +/- 15 days) via neurology clinic- either in person, through virtual clinic or, patient will be contacted via password protected Zoom. NIHSS and MRS scores will also be obtained from patient's chart on admission and at 90 day follow up. All of this data will be collected prospectively for both groups for this research study.

Precaution will be taken to lessen the probability of risks; despite increased frequency of treatments, duration of upright will still be approached cautiously within the first 24 hours s/p stroke for cerebral perfusion. ALL stroke patients will be returned to supine within 24 hours post stroke and maintain head of bed <30 degrees except for medication, meals, and therapy. Therapy will be stopped if patient deemed medically unstable for increased frequency of treatments by the Stroke NP, Attendings, Fellow, or PI; this decision will be documented via "bed rest" orders in the patient's electronic medical chart, so that the study team is aware to avoid progressive frequent upright mobilization.

Data collection: Patient data will be collected from their medical record. Data collected from EPIC/patient's MUSC EMR will be coded in the research database. Data collected include:

1) Demographics: sex, age, race

2) Stroke risk factors: history of HTN, HLD, A-fib, or DM

3) Stroke specifics: type of stroke (hemorrhagic vs ischemic), location of stroke, stroke severity (measured by NIHSS & MRS), time of symptoms to presentation, intervention (tPA or thrombectomy) and complications

3) Physical Performance and Functional Measures: Postural assessment stroke scale scores on evaluation, day three and 90 day follow up. Discharge disposition recommended vs ultimate discharge disposition, hospital length of stay.

11.0 Data Management:

Paper consent will be stored in a locked cabinet in the PT department. All data management will be conducted using the Redcap platform developed and housed at MUSC. All other collected data will be stored electronically in the MUSC OCIO approved secure SharePoint system. Access to this database will be restricted based on netID permissions to a secured server and will only be accessible to IRB study personnel. Identifying information will be removed from the primary database. Identifying information will be stored in a separate file with a unique identifier assigned to the patient to link the two datasets.

Since this study includes only the addition of one physical therapy session a day at an

increased intensity to patients post stroke for 150 patients, it is a rather low risk study. Therefore, our data and safety monitoring plan will be continuous, close monitoring by the study investigator/co-investigators of all participants. The PI and Co-I's will meet every 25 patients to discuss data and safety monitoring. During these meetings we will look for any negative trends in the data we have collected (vitals, NIH stroke scale- ie stroke severity, and functional mobility scores) that could indicate adverse events and provide a timely summary report of adverse events to the IRB/NIH.

Any reportable safety events that are unexpected, serious or may be related to the subjects' participation in this research will be reported to the MUSC IRB in accordance with their policies.

Once the Principal Investigator (PI) determines that an adverse event meets the IRBs' reporting requirements, she will report the SAE, and related safety information, to the IRB. Supporting documents, including a copy of the Informed Consent (IC), will also be attached. For reasons of confidentiality, subjects' names will not be included in the report. If the adverse event results in the need to revise the informed consent, or other study documents, the PI will submit a study amendment to the IRB. Any trend in a type of adverse event will be relayed to the IRB as soon as the trend is noted. All events that do not meet the criteria of significant or trending, will be recorded in a summary form and included at the close of the study. Per consistency with the NIH guidelines- all serious and significant adverse events involving risks to a participant or suspension/termination of IRB approval for this study will be immediately reported to the sponsor.

For the primary outcome, PASS, to test the null hypothesis of no difference between the group versus a MCID of 2.7, at 5% significance level, using a repeated measure designs at 4 time points and an autoregressive correlation of .6, and a standard deviation of 720 with more than 80% power. Although there is power to detect a moderately small difference (2.7 as mentioned), the purpose here is also to estimate the difference between the two randomized groups. Based on the past literature[12], in similar populations the standard deviation of PASS measurements is at the most 7.20 Using this, with a sample of 75 patients in each group, with 95% confidence at the end of the study we can estimate this difference within a margin of error of 2.3.

We are planning to conduct the analysis using intention to treat paradigm. In a preliminary analysis we will compute all summary statistics. Initial plots, such as spaghetti plots, will be used to guide our analyses. A general linear mixed model approach will be used to analyze all the outcomes. This model will account for the correlations between time points using either a compound symmetric or spatial structure for the covariance matrix. Post-hoc analyses using Tukey type adjustments will be performed to obtain least squares estimates of the differences between the two randomized groups. Although the study is powered based on only the primary outcome (PASS), we will apply multiple comparisons adjustments for the rest of the outcomes, using Bonferroni corrections. We will test for the assumptions using diagnostic procedures and take appropriate actions if needed. Also, we will define an outcome to be 'favorable' or 'unfavorable' based on a threshold and apply generalized linear mixed models with logistic link and repeat the analyses. We will attempt to minimize drop- outs but in case of missing data, we will assume Missing at Random or Missing Completely at Random. If necessary we will perform multiple imputations. For all analyses, we will use SAS, (MIXED, GLIMMIX, MI and MIANALYZE).

The RESTORE registry (Pro#00037803), from which this study will recruit subjects, also serves as a data analysis tool by which interdisciplinary teams may share data across projects and provide MUSC's stroke recovery research community with a more complete registry with key stroke elements. Some subjects may have participated or will participate in other stroke related research studies at MUSC. Sharing data from this and other stroke research studies with RESTORE will allow for more targeted recruitment efforts in the future and could reduce the burden placed on subjects by reducing the duplicative efforts of collecting common data and physical function assessments requested by multiple studies and storing them in one centralized and secure location. The third Aim of this study leverages this ability, as other studies will be better able to target their recruitment based on the information collected in these assessments.

Subjects are informed in the consent process if they enroll into the RESTORE registry, their data from this study will be shared. Subjects will be asked to sign a HIPAA authorization stating their health information may be disclosed to MUSC investigators requiring their data for their research projects upon approval by an Institutional Review Board.

12.0 Withdrawal of Subjects:

Subjects will be withdrawn from the research without their consent with the occurrence of worsening medical status, medical instability that limits ability to progress mobility or transfer to the ICU. For subjects who request to withdraw from the research trial, investigators may retain and analyze already collected data relating to that subject.

13.0 Risks to Subjects:

Early mobilization in the acute stroke population may pose risks including but not limited to falls, decreased cerebral perfusion, worsening weakness and/or worsening stroke. The research team will monitor blood pressures before each PT session to make sure it is safe for the individual to participate. A confidentiality breach is also a risk associated with this research. However, no paper records will be stored or reviewed other than consent forms and only coded data will be used for the analysis. Identifying information will be removed from the primary database. Identifying information will be stored in a separate file with a unique identifier assigned to the patient to link the two datasets.

The treatment you receive may prove to be less effective or to have more side effects than the other study treatment(s) or other available treatments. The experimental treatments may have unknown side effects. The researchers will let you know if they learn anything during the course of the study that might make you change your mind about participating in the study.

14.0 Potential benefits to subjects or others:

The potential benefit to patient's is that the treatment they receive may prove to be more effective than the other study treatment or than other available treatments, although this cannot be guaranteed. This treatment may increase a patient's independence and may lead to a shorter hospital length of stay and improved functional mobility outcomes (ie: regaining the ability to stand and walk).

It is hoped that the information gained from the study will help in the treatment of future patients with similar conditions and that it will help the researcher learn more about physical therapy approach to mobility post stroke

15.0 Sharing of results with subjects:

Results of the study will not be shared with the individual subjects.

References

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