Identifiers: NCT03547687 Unique Protocol ID: STUDY00018079

Brief Title: Neurosciences-Intensive Care Unit Electrical Stimulation

Revision Date 7/22/2019

1. Protocol Title

Electrical stimulation to reduce length of stay and duration of intubation in the neurosciences-intensive care unit (Neuro ICU)

2. Objectives

The purpose of this pilot trial is to estimate the effect of electrical stimulation (e-stim) to the bilateral quadriceps on duration of intubation, intensive care unit (ICU) and hospital length of stay, and functional recovery in the Neuro ICU in comparison to historical matched controls. The objective of this initial pilot and feasibility study to estimate the effect size to power a future full scale randomized controlled trial of this intervention and to optimize study logistics for a future full scale trial. We propose the following specific aims:

Specific Aim 1 - Feasibility: Determine whether at least 80% of planned treatments can be performed as described, and that there is adequate patient population meeting inclusion criteria available for study

Specific Aim 2 - Efficacy: Evaluate efficacy of e-stim by comparing length of ICU stay (days from admission to "intermediate level of care" ordered in Epic) and duration of intubation (days) of subjects (for those who were intubated) to that of historical controls.

Specific Aim 3 - Exploratory: Evaluate functional recovery (measured by modified Rankin Scale [mRS] and Extended Glasgow Outcome Scale [GOSE] at Neuro ICU discharge) of subjects compared to that of historical controls.

Hypothesis: We hypothesize that e-stim treatment will be feasible in the Neuro ICU and will reduce the length of hospital stay and intubation and improve functional recovery.

3. Background

Neurosciences Intensive Care Unit (Neuro ICU) patients have a unique risk factor profile for developing ICU-associated weakness, leading to prolonged periods of intubation and prolonged lengths of stay. Neurologic impairment from the patient's underlying condition interacts synergistically with loss of strength and deconditioning from immobility in the Neuro ICU to create severe impairment. Multiple mechanisms drive muscle atrophy in Neuro ICU patients: mitochondrial dysfunction, changes in microcirculation, the release of pro-inflammatory cytokines, inactivation of sodium channels of skeletal muscles, and increases in calpain, a protein involved in skeletal muscle protein breakdown (Koukourikos 2014). This atrophy may contribute to "intensive care unit acquired weakness," along with axonal neuropathy from immobilization. The main risk factors for ICU-associated weakness include high severity of illness upon admission, sepsis, multiple organ failure, prolonged immobilization, hyperglycemia, and advanced age (Hermans 2015). Weakness is present in up to 2/3 of patients who are mechanically ventilated for a week (Ali 2008, Sharshar 2009), and 25% of these remain weak for at least another 7 days after awakening (De Jonghe 2002).

Reducing the duration of immobilization is an important target for preventing ICU-associated weakness. While early mobilization has been shown to improve functional outcomes in Neuro ICU patients and decrease length of stay (LOS), there are risks to early mobilization. Risks associated with early mobilization unique to neurologically critically ill patients include increased intracranial pressure, hemodynamic instability, vasospasm and decreased cerebral blood flow with resultant cerebral ischemia (Olkowski 2017). Further compounding these difficulties is the high incidence of neurologic dysfunction such as aphasia and delirium, rendering many patients unable to reliably follow commands. Thus, many patients cannot participate in traditional physical therapy facilitating early mobilization. Interventions that could provide some of the benefits of early mobilization without these risks would be of great utility in the Neuro ICU.

A number of studies have demonstrated that electrical stimulation of the lower extremity muscles, generally the quadriceps, can retard disuse atrophy and loss of strength associated with medical ICU stays, and one study has

shown reduced length of intubation and accelerated functional recovery. In most studies, stimulation was applied to the lower extremity muscles bilaterally, generally to the quadriceps, and occasionally also to the hamstrings and/or calves, and in one study to the biceps brachii of the upper extremities. Stimulation was applied for 30 to 60 minutes/day, between 3x/week to twice/day for up to 14 days or until ICU discharge, whichever came first, with sufficient current amplitude to produce a muscle contraction.

Recent meta-analyses support that electrical stimulation results in positive outcomes in critically ill patients. These positive outcomes include accelerated recovery of, or better preservation of, muscle strength after cardiothoracic surgery (Fischer et al. 2016) and, in one study, the weaning period was statistically significantly shorter in patients undergoing electrical stimulations as compared to the control group [1 (0 to 10) days vs. 3 (0 to 44) days, respectively, median (range), P = 0.003], and activity limitations were reduced reflected by increased 6 minute walk test distance, and the average days to achieve transfer from the bed to the chair was reduced from 14.33 days to 10.75 days (Routsi 2010, Burke et al. 2016). Similar outcomes, including increased strength, VO2 max, and 6-minute walk test distance, as well as improved mood and quality of life, have been demonstrated in response to lower extremity electrical stimulation in patients with heart failure or other advanced diseases (Gomes Neto et al. 2016, Jones et al. 2016). Sepsis, edema, and receipt of vasopressors is associated with lower likelihood of response to this intervention (Segers 2014). Overall, these studies support that electrical stimulation can improve outcomes, including reducing duration of ventilation and accelerating recovery of functional mobility, in appropriately selected critically ill patients and in those with advanced systemic disease

To date, no published trials have evaluated the impact of electrical stimulation on patients in the Neuro ICU and none have evaluated the impact specifically on length of ICU and hospital stay. We therefore propose a trial to estimate the effect of electrical stimulation (e-stim) to the bilateral quadriceps on duration of intubation, ICU and hospital length of stay, in 22 patients in the OHSU Neuro ICU and compare these outcomes with historical pooled de-identified data from the Neuro ICU quality/safety database with regards to age, sex, illness severity, comorbidities and other predictors of LOS.

4. Study Design

The study will be a prospective, feasibility pilot study to estimate the effect size to power a future, full scale randomized controlled trial of electrical stimulation. The information learned in the pilot will help the team optimize study logistics for a future full-scale trial. The historical controls used for comparison will be from pooled, de-identified data pulled from quality improvement databases maintained by the Neurosciences ICU group. The research team will not have access to identifiable data for the historical controls--only means from the historical controls on data such as length of stay and hospital costs.

5. Study Population

a. Number of Subjects

There will be 22 subjects enrolled from the Neuro ICU. We will end enrollment at the end of the 2019 calendar year, whether or not the enrollment target has been met. We will compare the hospital course of the prospectively enrolled e-stim patients with pooled, de-identified historical patients identified from quality improvement databases maintained by the Neurosciences ICU group.

b. Inclusion and Exclusion Criteria

Patients admitted to the Neuro ICU will be screened for eligibility through a review of medical records in Epic by study co-investigators who are also clinicians in the Neuro ICU. Screening data will be destroyed at the end of the study.

Inclusion criteria

- Age ≥18 and ≤100
- Admission to the Neuro ICU for care for a neurologic illness requiring critical care
- Prognosis for prolonged ICU stay and/or prolonged intubation as evidenced by at least one pre- morbid risk factor: age ≥ 65 years, major medical co-morbidity (ex: heart failure, chronic obstructive pulmonary disease, chronic renal insufficiency, diabetes, poorly controlled hypertension, etc.), or severe acute critical illness (APACHE II >12)

Exclusion criteria

- Contraindications to electrical stimulation – demand cardiac pacemaker, implanted cardiac defibrillator, deep brain stimulator, adhesive allergy, pregnancy
- Agitation such that the individual is at risk for pulling off the self-adhesive electrodes
- Moribund prognosis (not expected to survive >48 hours, initiation of comfort measures only)
- Severe peripheral edema
- Hemodynamically unstable
- Elevated intracranial pressures
- Any condition likely to be aggravated by repeated muscle contractions (e.g. myasthenia gravis) or where electrical stimulation cannot produce a muscle contraction (e.g. peripheral neuropathy affecting innervation of the quadriceps muscles)

c. Vulnerable Populations

We will not be enrolling any vulnerable populations, such as minors, pregnant women, or prisoners, other than decisionally impaired adults. Inclusion of decisionally impaired adults is discussed in greater detail in the Consent Process and Adults Unable to Consent sections of the protocol.

d. Setting

Neurosciences ICU (Neuro ICU).

e. Recruitment Methods

Patients admitted to the Neuro ICU will be screened for eligibility through a review of medical records in Epic by study staff, and approached for consent. Patients with prognosticated prolonged stay will be approached on day 2 to 5 of their ICU stay for enrollment. If patients have reversible exclusion criteria, such as hemodynamic instability or elevated intracranial pressures, they will be rescreened daily for potential enrollment until day 7.

f. Consent Process

If a patient meets inclusion criteria, the study team will approach the patient or the legally authorized representative (LAR) for consent. In instances where the patient is unable to give informed consent (brain injury, sedation, etc.), the LAR will be approached for consent. Initial consent discussion will take place in a quiet private place in the Neuro ICU. The written consent form will be presented and reviewed with the patient or the LAR. At this time, the patient or LAR can ask any questions prior to enrollment. Understanding of the study will be assessed after the consent discussion and prior to enrollment by asking pertinent study related questions. When the study staff is satisfied that the patient or LAR understands, the study consent form will be signed. One copy will be given to the patient or patient's LAR, and one copy will be retained by the study team.

In the event that the patient's LAR lives at a distance, the consenting discussion may be conducted by telephone. Prior to this discussion, the LAR will be sent a copy of the consent form by mail, email, or fax. Once the LAR has received the ICF, a member of the study team will contact them by phone and go through the ICF with them, answering any questions that may arise. The LAR will sign their copy of the ICF, and may send it back to the study team by mail, email, or fax.

If a patient regains the ability to consent during the study period, the coordinator will return and re-consent the patient him or herself. If the participant during the research study does not wish to continue e-stim treatments, the decision must immediately be respected. Subjects will be asked if they are willing to allow the study staff to perform a brief assessment of their recovery. If so, the subject will be considered to still be enrolled in the study, and it will be noted that the intervention was stopped early. If not, the subject will be considered to be completely withdrawn from the study, and no more data will be collected from the subject. The study team will no longer access the patient's medical record or other confidential records requiring the subject's consent.

Non-English Speaking Subjects

In regards to non-English speaking subjects, a translator and/or the interpreter services provided by OHSU will be utilized for the initial consent process and any subsequent study visits to ensure the consent capacity of the subject and/or LAR and that the informed consent is being properly obtained. Short-form consent forms will be used.

Adults Unable to Consent/Decisionally Impaired

The electrical stimulation process itself does not pose any more of a risk and/or harm on a decisional impaired patient vs. a competent patient. Subjects will have varying degrees of decisional impairment related to the indication for admission for the majority of our patients, including: fluctuating decisional impairment, progressive decisional impairment, limited decisional impairment, or complete decisional impairment. In order to assess for decision-making capacity and prior to the consent process, the study team member will assess the subject's ability to understand information about the treatment, to appreciate how that information applies to their situation, to reason with the information provided, and to make a choice and express it. If there is any doubt, the LAR will be consented.

6. Procedures Involved

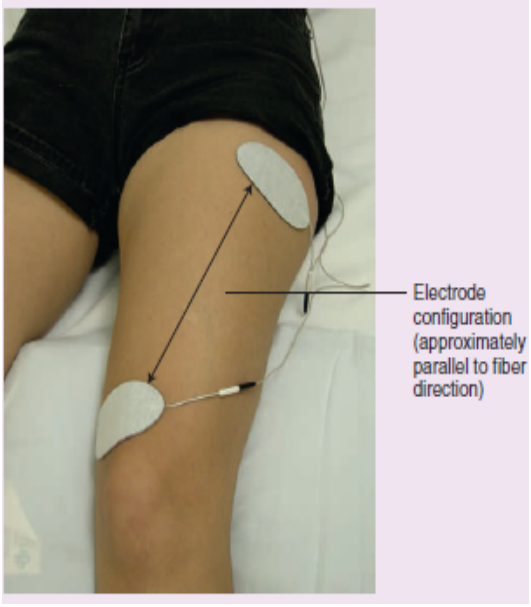

Figure 1. Application of E-Stim Device

Electrical stimulation will be applied to the quadriceps muscle groups on both lower extremities simultaneously for 30 minutes at a time (Figure 1). The patient will be positioned either supine or sitting.

A Vectra Neo Clinical Therapy System (Chattanooga Group) will be used to provide the stimulation. The stimulator will be set up and taken off the patients by a member of the study team or a trained ICU staff member. The stimulation parameters will be as follows:

Electrode location: Proximal and distal quadriceps
Waveform: pulsed biphasic
Pulse duration: 300-450 µseconds
Pulse frequency: 35 pulses per second
Amplitude: palpable, visible quadriceps muscle contraction
On/off time: 10 seconds on, 30 seconds off
Ramp up and down time: 2 seconds each
Total treatment time: 45 ± 15 minutes/day, for a total of at least 5 treatments each week (Mon-Sun), until ICU discharge or at the discretion of the research team.

At Neuro ICU discharge, a member of the study team will assess functional recovery using the modified Rankin Scale (mRS) and the Extended Glasgow Outcome Scale (GOSE). (uploaded in eIRB) Subjects who withdraw from e-stim treatment may still be assessed with these instruments at discharge, unless they request to withdraw from data collection as well. Subjects may be withdrawn from e-stim treatment without their consent if their physician or the study team decides that it is in their best interest (e.g. due to skin irritation or burns).

All procedures will be performed as part of the research study, and not as standard of care.

Historical Controls

The Neuro ICU administration maintains databases for the purpose of safety and quality improvement. We propose to query this existing database to identify patients cared for in the Neuro ICU during the year 2016 that possess similar demographics and illness characteristics as our inclusion criteria. The ICU quality group will abstract data for us. The research team will not have access to identifiable data for the historical controls--only means from the historical controls on data such as length of stay and hospital costs. The information will be extracted using automated means from this database and Epic to capture average length of stay and length of ventilator support for the purposes of comparison as "historical controls". We will not be performing individual chart review.

7. Data

a. Handling of Data

Data will be collected from the subjects' medical record in Epic, and from the mRS and GOSE instruments (completed by study staff). All data will be stored in REDCap. Data collected from the medical record will include demographics (sex, age, race), illness information (primary admission diagnosis, severity of critical illness as determined by the Sequential Organ Failure Score (SOFA) and/or APACHE II score), critical illness associated complications (e.g. deep vein thrombosis, hospital acquired infection, etc.), and medications associated with neuromuscular weakness (e.g. steroids, neuromuscular blockers, etc.). Data will be stored indefinitely.

b. Sharing of Results with Subjects

No data will be shared with participants.

c. Data Banking

Repository Guardian: Holly Hinson, M.D. M.C.R.

Collection Information: At this time, no contributions to the Repository from outside investigators are planned. If this changes, a modification will be created with submittal requirements as needed.

Consent and Authorization: All subjects will have provided consent and authorization to participate in the research, including the storage and future analysis of their data (i.e., the consent and authorization documents will include appropriate repository language). The repository guardian or designee will ensure documentation of signed consents and authorizations, and maintain a tracking record for all data placed into this repository. Consent is required for participation in study and repository together. No biospecimen or genetic material will be collected—only clinical data. **The historical data will not be included in the repository. This repository will collect data from this study only, for the purpose of using in future analyses pertaining to e-stim treatment and intubation. The repository will collect identifiable information, but identifiable information will not be released to other investigators.**

Maintenance Information: All data will be assigned a unique, subject code as described in the Privacy, Confidentiality and Data Security section in this protocol. The key to the code will be limited only to the

repository guardian or designee, and it will be stored separately from signed consent forms. Any email correspondence will be encrypted.

Electronic security: Associated data will be held securely in compliance with OHSU's Information and Security Guide. Specifically, data will be held on OHSU networked drives, behind the OHSU firewall. Files will be password-protected. We plan to utilize REDCap as the database.

If a subject withdraws consent, the repository guardian or designee will destroy (delete) their data to ensure no future use.

Repository guardian: The repository guardian is Dr. Holly Hinson. She will be responsible for ensuring that data are received and released according to OHSU policy and the IRB approved repository protocol. The repository guardian is responsible for:

- Ensuring that the data are received and released according to OHSU policy and the IRB approved protocol.
- Executing a repository sharing agreement each time data are released for research purposes.
- Ensuring the security and confidentiality of stored data.
- Ensuring the security and confidentiality of data during transfer.
- Tracking acquisitions and releases of data.
- Maintaining methods for identifying data for which consent has been withdrawn and ensuring no future use.
- Identifying data that have limitations on future uses and ensuring that future uses are not contrary to those limits.

Release Information: Requests for data will first be discussed with the repository guardian or designee to ensure that the nature, quality, and number of data available will meet the scientific needs of their research. Prior to any release, the repository guardian or designee will verify that there were no restrictions placed on the use of the data by the IRB, or by the participant. The repository guardian or designee will verify current IRB approval for each recipient research protocols, and ensure a Repository Sharing Agreement is executed each time data are released for research purposes. All data released from this repository will be tracked, including date of release, IRB approved documents, description of data, and Repository Sharing Agreement signed. Only de-identified data will be released to other investigators. If materials are transferred outside of OHSU, the repository guardian or designee will verify that a materials transfer agreement is in place prior to release. Any email correspondence will be encrypted.

8. Data Analysis

Analysis plan

Covariates The following factors may impact outcome, and thus will be collected to assure the groups are comparable:

i. Demographics (sex, age, race)

ii. Illness information: primary admission diagnosis, severity of critical illness (Sequential Organ Failure Score (SOFA), APACHE II score)
iii. Critical Illness Associated Complications - Complications such as deep vein thrombosis, Hospital Acquired Infection, etc. will be recorded as these conditions may impact outcome.
iv. Medications associated with Neuromuscular weakness: including but not limited to steroids, neuromuscular blockers

Group Comparisons

The study team statistician will analyze the data, and will be blinded to treatment assignment ("Group A" and "Group B", instead of "E-Stim Group" "Historical Controls"). Descriptive statistics will be used to quantify feasibility. Mean length of stay and mean duration of intubation will be compared between the e-stim group and the historical controls using a t-test. If necessary, a linear regression model for length of stay and/or intubation duration will be used to compare between groups while controlling for the potential confounding of covariates. A Wilcoxon rank-sum test will be used to compare the exploratory functional outcome measures between groups, as the mRS and GOSE are both ordinal scales.

Power Calculation

We plan a future trial to determine the efficacy of electrical stimulation to reduce days of mechanical ventilation by 30% (from 10 days to 7 days, observed in the Routsi study). Estimated sample sizes for a two-sample means test (Satterthwaite's t test) assuming unequal variances, with an 80% power to detect a 30% difference in days of mechanical ventilation with a significance level of p=0.05, would require 113 patients in each group (for a total of 226 subjects). In order to prepare for this future RCT, we propose a pilot trial of 45 subjects (20% of the full sample size), with 22 patients in the intervention group (e-stim) and 23 historical controls.

9. Privacy, Confidentiality, and Data Security

Standard institutional practices will be followed as described by the OHSU Information Security Directives at the following link (http://www.ohsu.edu/xd/about/services/integrity/policies/ips-policies-info-sec-directiv.cfm#results) to maintain the confidentiality and security of data collected in this study. Study staff will be trained with regard to these policies.

To protect confidentiality, all hard-copy forms and identifying information will be kept in locked cabinets located within the offices of study personnel. These forms will be controlled and secured at all times by study personnel. All electronic data will be stored in a secure, password-protected web-based platform accessible to study team members only (RedCap).

Confidentiality will be assured by assigning patients unique study identification numbers rather than names or medical record numbers on all clinical research forms and other source documents. The identification numbers will not contain any part of the 18 HIPAA identifiers (initials, date of birth, medical record number, etc.) The key associating the codes and subjects' personally identifying information will be restricted to the PI and study staff. The key will be kept on a restricted OHSU network drive in a limited access folder.

All published results will exclude all identifying protected health information including names or initials of subjects, birth dates, medical record numbers, etc.

All adverse events and/or unanticipated problems related to the study evaluations or protocol will be reported in a timely fashion to the IRB. Reportable New Information (RNI) (information that meets the regulatory definition of an unanticipated problem involving risks to subjects or others or serious or continuing noncompliance) will be submitted to the IRB within 5 days of discovering the information.

When follow-up assessments are complete, research staff and biostatistical consultants will complete a comprehensive double entry procedure to verify overall data accuracy. All research personnel have completed updated and verified conflict of interest agreements with their respective institutions.

10. Risks and Benefits

The risks involved in the study are all small and mild:

1. Burns – Electrical stimulation can cause burns, although this is very rare with the pulsed current that will be used in this study because electricity is only flowing for a very small proportion of the time with this type of current. The risk of burns is also increased if the electrodes have poor contact with the patients' skin. This will be avoided by closely inspecting the electrodes for good contact when applied, by cleaning the skin with water before applying the electrodes, clipping hair in the area of electrodes if present, and by using new electrodes at least weekly, or sooner if they start to adhere poorly.

2. Skin irritation or inflammation – the adhesive on electrical stimulation electrodes, which is similar to tape adhesive, can cause skin irritation in some individuals. Therefore, individuals with tape allergy will be excluded from this study. In addition, if a subject develops skin irritation we will switch to hypo-allergenic electrodes. If the skin irritation persists, the subject will be withdrawn from the study.

3. Discomfort during the stimulation – if the intensity is high enough an individual may experience discomfort during electrical stimulation. We will limit the stimulation intensity to that sufficient to produce a visible muscle contraction and will discontinue the intervention if the subject either reports pain or has signs of pain e.g. elevated HR or BP in response to the stimulation.

4. Delayed muscle soreness – there is a risk of delayed onset muscle soreness in the muscles stimulated. This is similar to the soreness experienced after exercise and will resolve without intervention. This is only likely if the exercise is substantially greater than the individual's usual activity. Although 30 minutes of visible quadriceps contraction is not generally likely to cause delayed onset muscle soreness, it is possible this will occur.

5. There is a small risk of breach of confidentiality.

It is hypothesized but unknown whether there are benefits to e-stim treatment. E-stim may result in reduced duration of hospitalization and intubation, and may improve recovery outcomes.

11. Resources Available

Not applicable

12. Devices

The Vectra® Neo Clinical Therapy System is a modular system that can be used with or without an optional Cart, allowing for the inclusion of Channel 1/2 Electrotherapy module with or without sEMG, Channel 3/4 Electrotherapy module, Laser module and Ultrasound module. The device we will use will be used without the cart and will have the 2 channel electrotherapy module, without sEMG, laser or ultrasound. The system is commercially manufactured by Chattanooga, a subsidiary of DJO in Vista, California. The device is FDA approved for the prevention of disuse atrophy. It is also used for muscle re-education, increasing range of motion and increasing circulation. This device is used in commonly in clinical Physical Therapy practice in other patient populations.

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