Official title: *Cranial Electrical Stimulation (CES) as a First Line Treatment for Insomnia in Patients with Subacute Stroke*

NCT number: *NCT03344562*

Document date: *October 30, 2018*

The University of Texas Southwestern Medical Center at Dallas
Institutional Review Board

Cranial Electrical Stimulation (CES) as a First Line Treatment for Insomnia in Patients with Subacute Stroke

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Funding Sponsor: UT Southwestern Department of Physical Medicine and Rehabilitation

Version number: 3

Date: September 2018

1. Introduction and purpose

Sleep is crucial for the successful recovery from illness, disease or injury. Sleep is often viewed as a neurologic pause giving our bodies a chance to rest, yet in actuality it is a neurologically dynamic environment wherein the brain is continually progressing through alternating cycles of light and deep sleep, collectively known as sleep architecture. During deep sleep, or restorative sleep, our brains clear debris, consolidate memory, and form new connections through a process called neuroplasticity. Restorative sleep is particularly important for patients to achieve in the days and weeks following a stroke. Recently, researchers discovered a network of lymphatic vessels in the brain that run alongside glial cells [1; 2]. This network is referred to as the glymphatic system and has shown to be utilized in the removal of neuronal debris, such as beta amyloid plaques, that build up during waking hours leading to fatigue and mental clouding [2].The glymphatic system is most active during deep sleep, reinforcing the necessity of quality sleep in individuals recovering from neuronal insults such as stroke.

Currently, patients being treated in rehabilitation settings after acute stroke who experience difficulties in achieving sufficient or restful sleep are treated with environmental adaptations (such as minimizing nighttime interruptions in room) and frequently, with pharmacological agents. One commonly used agent, trazodone, is a hypnotic antidepressant with sedative qualities. Trazodone is frequently used because it is viewed as being effective and relatively safe; however, this class of medications is known to alter sleep architecture resulting in more time in light sleep and reduced amounts in deep restorative sleep. Additionally, trazodone has well documented carryover effects that are detrimental to stroke recovery. These carryover effects include deficits in short-term memory, verbal learning, equilibrium, and arm muscle endurance[3]. Most importantly, trazodone has been shown to significantly interfere with sleep-dependent consolidation of cortical plasticity [3]. These effects are in stark contrast to the goals of rehabilitation patient who requires neuronal plasticity for his or her recovery.

Conversely, cranial electrical stimulation (CES) is a safe method tested in a number of pilot studies to promote deep, restorative sleep that is seldom used. There are many potential advantages to using CES in place of medications, including safety. CES has few notable side effects and has none of the drug-drug interactions that are commonplace in pharmaceuticals. CES is FDA approved to treat insomnia, depression, anxiety and pain. Additionally, CES has been shown to increase learning, consolidation of memory, creativity and mood. Patients who use CES report feeling calm, focused, and relaxed. Side effects of CES are extremely rare and the known risks of CES are minimal and mild in nature [4]. Skin irritation may occur at the site of sponge electrode placement when sponges deteriorate or if the sponges are not thoroughly wet before use. The device manufacturer also cites a mild headache or dizziness that may occur during use and ceases when the device is turned off. Such reactions are very rare.

Despite the potential benefits of CES over medications such as trazodone, this technology is seldom used. One reason for this is the paucity of rigorous research proving its benefit. There have been many studies since the technology was first introduced in the 1950's, but there are very few modern well-controlled and powered studies with conclusive evidence for or against CES as a treatment for sleep. Nearly all studies examined cite deficits in power or adequate blinding. Furthermore, there are no studies using CES as a treatment for insomnia in stroke patients. The purpose of this study is to determine if CES is a reasonable first line alternative to the current standard of care (SOC) which relies on the use of trazodone for patients with subacute stroke. This objective will be answered by addressing the following:

- Specific Aim 1: To determine if stroke patients with insomnia who receive CES treatment sleep more hours than stroke patients treated with sham CES.
  Hypothesis: Stroke patients with insomnia who are treated with CES will accumulate more sleeping hours than patients who are treated with sham CES.
- Specific Aim 2: To determine if stroke patients with insomnia who receive CES treatment have better sleep efficiency than stroke patients treated with sham CES.
  Hypothesis: Stroke patients with insomnia who are treated with CES will demonstrate significantly better sleep efficiency than stroke patients treated with shame CES.

Our study will take place at Zale Lipshy Hospital and Parkland Hospital in Dallas, TX. The study will enroll 85 stroke patients who score 7 or higher on the Insomnia Severity Scale. Patients will be randomized to a control group or CES treatment group. Patients will receive CES or sham CES for 7 days after a 24-hour washout period. Objective and subjective sleep assessments will be conducted daily during the 7-day study period. Endpoints will be total time spent sleeping, sleep efficiency and daytime drowsiness.

The known risks of CES are minimal and mild in nature. They include potential for headache, irritation at the site of electrode placement and dizziness. These adverse reactions are rare and in most cases there are no immediate or delayed side effects.

Compared to the known adverse reactions of the current standard of care, trazodone, the known adverse events of CES are considerable less severe. Known adverse reactions of trazodone include black box warnings for risk of suicidal thinking and behavior in patients less than 24 years of age. In addition, trazodone has a long list of potential adverse events, most involving anticholinergic effects (sedation, dry mouth, blurred vision) and must be used with caution with platelet inhibitors, MAO inhibitors, and other drugs causing prolonged QT intervals.

2. Background

Cranial Electrical Stimulation (CES) is safe and potentially effective way to promote restorative sleep without the carryover effects of pharmaceuticals. CES introduces miniscule electric currents, often no more than 1-2 mA to the head of individuals suffering from depression, anxiety and insomnia[5; 6]. While the exact mechanism is unknown, it is generally accepted that CES acts through direct action on the brain at the limbic system, thalamus, hypothalamus, and reticular activating system[7]. In these areas, the penetrating micro-currents stimulate the release of neurotransmitters such as serotonin, beta-endorphin, and GABA (FW manual). The overall effect of this is increased alpha brain wave activity and decreased delta wave activity which translates to feelings of serenity, relaxation and reduced agitation[7]. In addition to insomnia, CES is FDA approved to treat anxiety and depression, much like trazodone which is the most commonly used hypnotic at this time.

Trazodone is widely used, but its mechanism of action is not fully understood either. What is known is that it exerts its antidepressant effect as a serotonin (5-HT2) antagonist and reuptake inhibitor[8].

Serotonin is an important chemical neurotransmitter which has functions in both the central nervous system and the peripheral nervous system. Alterations in levels of serotonin by trazodone therefore cause widespread effects as detailed previously.

Low intensity current has the potential to modulate the release of neurotransmitters but since the reuptake mechanisms are not affected there is little risk in overstimulation. The CES device we will be using is an alternating current (AC) stimulator. This means that each electrode rapidly switches between being the cathode and the anode. The electronic waveform generated from the device is a 15,000Hz square wave carrier which is rectified, varying from zero to a maximum of 4 milliamperes. This device is a bipolar version of a TENS device, where there is a brief burst (50 milliseconds) of positive energy [above the zero axis], followed by a 16.7 millisecond "OFF" time, followed by a 50 millisecond burst of negative energy [below the zero axis], followed by a 16.7 millisecond "OFF" time. In this manner consecutive positive burst and off time is followed by an equal and opposite negative burst and off time, thereby generating alternating current[4].

The output amplitude is 0-4 milliamperes at a cycling rate of 15/500/15,000 Hz with a pulse width of 33 microseconds. The maximum charge per pulse is 0.13 microcoulombs. The output voltage is variable from zero to 40 volts and then the voltage limited, first positive and then negative. This allows for load impedances of up to 10,000 ohms to be able to have a constant current of up to 4 milliamperes[4].

It is well described how depolarizations of neuronal membranes lead to release of chemical neurotransmitters; therefore, one could potentially modulate the cerebral chemical environment by electrical intervention. Research from the University of Texas at Austin indicated that indeed external electrical stimulation can readily alter the deep brain electrical environment. In their 1996 publication, Ferdjallah et all reported that 1 mA of current from CES reaches the thalamic area at a radius of 13.30 mm and may facilitate the release of neurotransmitters[9].

The structures that CES is believed to affect are centrally located in the brain and are known to be involved in regulation of emotions. These subcortical brain structures are the reticular activating system, thalamus, and hypothalamus, and the limbic system. As the low intensity external charge supplied by CES reaches these deep brain structures there is a measurable physiologic result. Researchers from the University of North Texas used electroencephalogram (EEG) to show that CES is able to increase alpha brain waves (8–12 Hz) and decrease delta (0–3.5 Hz) and beta (12.5–30 Hz) brain waves. Increased alpha correlates with improved relaxation and increased mental alertness or clarity. Decreased delta waves indicate a reduction in fatigue. Beta-wave reductions between 20 and 30 Hz correlate with decreases in anxiety, ruminative thoughts, and obsessive/compulsive-like behaviors[10].

While CES has been shown to be clinically effective in multiple studies, there are equal numbers of studies showing no effect or an indeterminate effect[11]. In nearly all these studies the researchers call for further study with higher patient numbers and rigorous blinding. This study will be an extension of previous work showing potential efficacy in sleep, while introducing a new population in subacute stroke patients. We anticipate our findings will benefit future patients by providing an alternative to hypnotics which may have negative effects that are detrimental to the recovery of the stroke patient.

3. Concise Summary of Project

This will be a double blinded randomized clinical trial carried out at Zale-Lipshy and Parkland Hospital Inpatient Rehabilitation Facilities. Acute stroke patients with insomnia, identified by the Insomnia Severity Index (ISI), and who choose to participate in this study will be randomized to CES or sham CES. Patients who do not feel they are getting adequate sleep but want to continue in the study will be given the option to receive the standard of care medication as a rescue starting on the 3rd night.

Patients will receive treatment with a Fisher-Wallace CES device or Sham CES. Treatment with CES will be for 20 minutes once a day, and the treatment period will be for 7 days. Patients will be allowed to increase the intensity of the device from the suggested starting point of level 2 if they feel no improvement in sleep on night 1. Groups will be monitored with a wrist worn actigraph that records the patient's activity for the duration of the period of study and provides data on sleep latency, time spent asleep, and sleep efficiency. The outcome measures will be total minutes/hours of sleep, sleep efficiency and subjective reports of drowsiness using the Karolinska Sleepiness Scale. Actigraphic data will be collected 24 hours a day for 7 days. The total length of study will be 4-12 months with a target N of 100 consented individuals and 85 participants. Patients will be allowed to exit the study at any time on their own choosing. To minimize loss of subjects, patients will have the option to choose SOC rescue starting on the third night. Patients who choose the SOC rescue will continue to be monitored with an actigraph for data collection purposes.

The investigator should discontinue study participation for a given subject or withdraw the subject from study if he/she believes that continuation would be detrimental to the subject's well-being. A subject can decide to withdraw from the study at any time and for any reason.

4. Study procedures

This randomized controlled trial is designed to meet two study objectives related to quality of sleep and daytime drowsiness.

Demographic data will be collected from the hospital record and will include age, gender, type of stroke, self-reported history of insomnia or other sleep disorder, prior use of sleep medications, in-hospital use of sleep medications, co-morbid medical conditions.

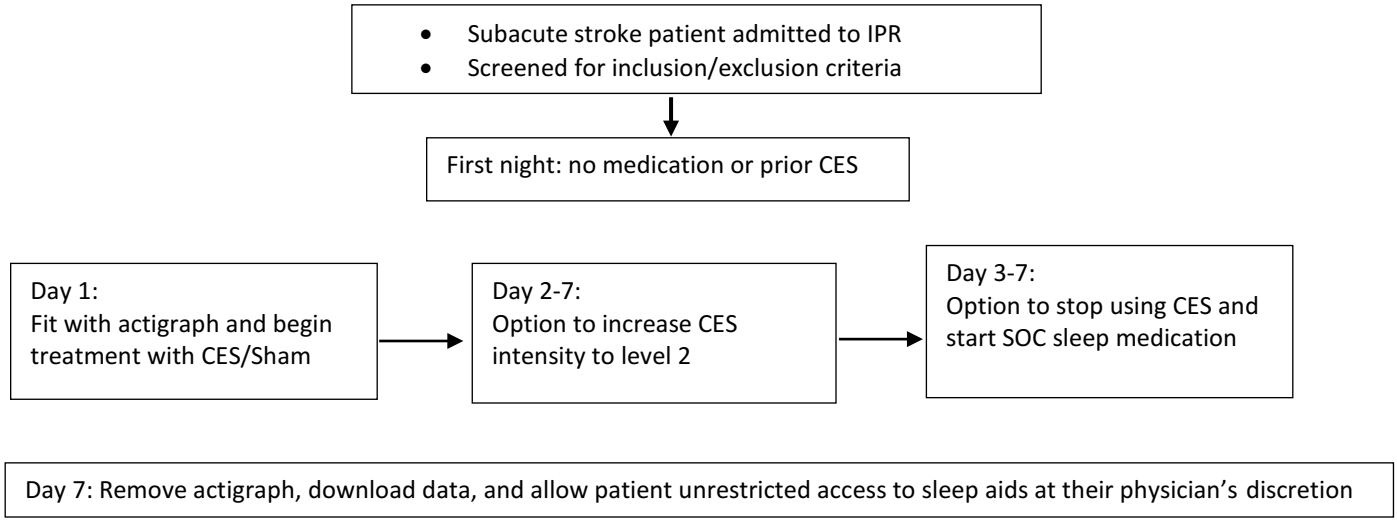
Patients admitted to inpatient rehabilitation (IPR) who consent to the study will undergo an overnight washout period before initiation of CES or sham treatment. This allows for any sleep medication they might have received while in acute care to be metabolized and leave their system. On their admission day, day 0 (d0) patients will be asked if they want to participate in our study. If they choose to participate and meet medical inclusion criteria, they will be tested with ISI. Patients who meet the full criteria will not receive sleep medication or CES on their first night.

The study will begin on day 1 (d1) with the patient receiving 20 minutes of CES/sCES in the morning. This time will be distraction free without the entrance of laboratory technicians, nurses, housekeeping or other staff members. When this period is complete, they will participate in usual care. At midday they will be asked to complete the Karolinska Sleepiness Scale (KSS). The patient will wear the actigraph throughout the study. This procedure will be repeated for 7 treatment days. All procedures will be carried out by research team members or a trained nurse.

The intensity of the CES will begin on setting 2, standard setting recommended by the device manufacturer, and the patient will have the option to increase the intensity to setting 3 on the second treatment day if they feel they did not receive any benefit from the device.

If the patient does not feel they are getting adequate sleep the patient may choose to opt out of CES/sCES treatment and receive the standard of care medication for the remainder of the study. Patients who choose the SOC rescue will continue to be monitored with the actigraph. A patient may choose to leave the study at any time.

We will collect information on side effects for the CES treatment during the 7 days of the study.



Methods of assigning patients to treatment groups and blinding
Patients will be randomized to the active or sham treatment group using an online randomizer, Research randomizer (www.randomizer.org). A list of random numbers will be generated prior to the study. Patients will be assigned a random number in the order that the generator produces. All even patients will be assigned to the control group; odd numbered patients will be assigned to the treatment group.

Procedural responsibilities and oversight
Nursing staff at UTSW will be educated how to administer the CES and asked to help distribute and collect the Karolinska Sleepiness Scale questionnaire. Photos of proper placement and instructions will be posted in subjects' rooms for reference. Researchers affiliated with this project will apply and remove the actigraph watches and be responsible for data acquisition, cleaning and charging of the devices. Researchers affiliated with the study will be responsible for ensuring CES is delivered to the appropriate patients on the days required per protocol. Research personnel will be responsible for all study-related activities at Parkland.

5. Inclusion criteria

To be eligible for inclusion in this study, subjects must fulfill all of the following criteria at screening.

1. Written informed consent must be obtained.
2. Patients must be admitted to inpatient rehab.
3. Patients must have a documented acute stroke (ischemic, hemorrhagic or embolic).
4. Patients must have at least one fully functional arm which can be used to record actigraph data via a wrist worn actigraph device.
5. Subjects must Score a 7 or higher on the ISI.
6. Patients must be able to communicate consent and/or desire to discontinue the study.

6. Exclusion criteria

Subjects fulfilling any of the following criteria at screening will not be eligible for inclusion in this study.

1. Demand or sensing type cardiac pacemaker.
2. Known uncontrolled seizure disorder.
3. Current history of vertigo.
4. Need for continuous O2.

5. Inability to communicate or provide consent.
6. Restricted use or absence of both arms.

7. Sources of research material

All data will be collected prospectively through a wrist-worn actigraph and a sleep questionnaire. This data will be used specifically for research purposes. Demographic data will be collected from the hospital chart.

8. Recruitment methods and consenting process:

We will use verbal recruitment process for the study. The attending and resident physicians will be educated about the study and asked to identity patients who may be appropriate. A member of the research team will explain the risks, benefits and rationale for the study to patients who meet inclusion criteria. Patients will be enrolled when they arrive on the rehabilitation floor if they choose to participate. Consent will be attained via a written document in the subject's primary language (English or Spanish).

The research team will protect subjects' privacy by conducting all study related verbal interactions with the subject in a closed room, such as the patient's room. For confidentiality, each subject screened will be assigned a unique identification number (ID#). Subjects will only be identified by the unique ID # in the data. No demographic data or personal information will be used to identify subjects. This unique ID# will be linked to subject name and will be kept in a locked file cabinet, accessible only to the research team. Only the research team will have access to the data. All data for presentations and publications will be reported as mean ± standard error of means. Investigators will educate faculty and residents on each floor about the study to maintain privacy and compliance.

9. Potential Risks

The Fisher Wallace Cranial Electrical Stimulator is known to have the potential for very rare and mild adverse reactions. These include, skin irritation at the site of sponge electrode placement, especially if the sponges deteriorate. Per Fisher Wallace recommendations, the sponges will be replaced every two weeks to prevent contact between the skin and the metal part of the sponge receptacle. This risk will also be mitigated by ensuring the sponges are thoroughly wet before each use. In rare cases a mild headache or dizziness may occur, and should cease after stopping use of the device. Such reactions represent minimal risk.

11. Subject Safety and Data Monitoring

Study data will be accessible only to study personnel. All paper study records will be kept in a secured locked location. All electronic study data will be stored on password protected, encrypted computers; flash drives used for data storage will be encrypted. Each subject will be assigned a study number in consecutive order. The key linking the subject identifier (name and MRN) to the subject study number will be kept secure and separate from the research data. The key will be destroyed at the time that data entry and analysis is completed.

All patient information will be de-identified prior to statistical analysis. This spreadsheet will be destroyed after the data has been analyzed and PHI will not be re-used or disclosed. A link will be needed to ensure accurate collection of data on subsequent visits.

For participants who are screened and included in the study the essential documents will be filed with the individual's research file and kept for seven years.

12. Procedures to Maintain Confidentiality

The research team will protect subjects' privacy by conducting all study related verbal interactions with the subject in a closed room, such as private space in the patient's room. For confidentiality, each subject screened will be assigned a unique identification number (ID#). Subjects will only be identified by the unique ID # in the data. No demographic data or personal information will be used to identify subjects. This unique ID# will be linked to subject name and will be kept in a locked file cabinet, accessible only to the research team. Only the research team will have access to the data. All data for presentations and publications will be reported as mean ± standard error of means.

13. Potential Benefits

There are many potential benefits to this study with both immediate and long term applications in improving sleep and minimizing the use of sedative medications during stroke recovery. Cranial Electrical Stimulation is a favorable alternative to standard of care medications like trazodone because individual participants may experience improved sleep and it is without the many side effects of these medications that increase the risk of complications. Some finding suggests that CES also increases learning, creativity and mood, and decreases anxiety, depression, and pain. It is through these mechanisms that patients will benefit immediately from this study.

In the long term, future patients may benefit from this study by potentially having an alternative first line treatment option for insomnia that does not have the negative carryover effects and plasticity reducing effects of hypnotics and sedatives. Additionally, treatment with CES offers the potential for improved functional recovery efficiency, increased patient satisfaction and increased cost effectiveness.

14. Biostatistics

Sample size was calculated based on several studies that measured the number of hours that subacute rehabilitation patients sleep in an inpatient hospital setting. Alpha levels for error probability were set at .05 for a two-tailed test with 80% power to detect a difference between means of control group compared to CES treatment group.

Descriptive statistics will be used to determine differences between CES and sCES treatment groups. A T-test will be used to determine if sleep time means differ between groups ($p \leq .05$). A chi square analysis will be used to compare data collected from the Karolinska Sleepiness Scale. A non-parametric test will be used if data is not able to demonstrate normal distribution.

Works Cited

1 ILIFF, J. J. et al. Brain-wide pathway for waste clearance captured by contrast-enhanced MRI. **J Clin Invest,** v. 123, n. 3, p. 1299-309, Mar 2013. ISSN 1558-8238. Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/23434588 >.

2 _____. A paravascular pathway facilitates CSF flow through the brain parenchyma and the clearance of interstitial solutes, including amyloid β. **Sci Transl Med,** v. 4, n. 147, p. 147ra111, Aug 2012. ISSN 1946-6242. Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/22896675 >.

3 ATON, S. J. et al. The sedating antidepressant trazodone impairs sleep-dependent cortical plasticity. **PLoS One,** v. 4, n. 7, p. e6078, 2009. ISSN 1932-6203. Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/19568418 >.

4 **Fisher Wallace CES stimulator for depression, anxiety and insomnia instruction Manual**. New York, NY: Fisher Wallace laboratories, LLC 2016.

5 LANDE, R. G.; GRAGNANI, C. Efficacy of cranial electric stimulation for the treatment of insomnia: a randomized pilot study. **Complement Ther Med,** v. 21, n. 1, p. 8-13, Feb 2013. ISSN 1873-6963. Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/23374200 >.

6 EBAJEMITO, J. K. et al. Application of Transcranial Direct Current Stimulation in Neurorehabilitation: The Modulatory Effect of Sleep. **Front Neurol,** v. 7, p. 54, 2016. ISSN 1664-2295. Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/27092103 >.

7 KIRSCH, D. L. et al. Military service member and veteran self reports of efficacy of cranial electrotherapy stimulation for anxiety, posttraumatic stress disorder, insomnia, and depression. **US Army Med Dep J**, p. 46-54, 2014 Oct-Dec 2014. ISSN 1524-0436. Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/25830798 >.

8 FRECSKA, E. [Trazodone--its multifunctional mechanism of action and clinical use]. **Neuropsychopharmacol Hung,** v. 12, n. 4, p. 477-82, Dec 2010. ISSN 1419-8711. Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/21220793 >.

9 FERDJALLAH, M.; BOSTICK, F. X.; BARR, R. E. Potential and current density distributions of cranial electrotherapy stimulation (CES) in a four-concentric-spheres model. **IEEE Trans Biomed Eng,** v. 43, n. 9, p. 939-43, Sep 1996. ISSN 0018-9294. Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/9214809 >.

[10] KENNERLY, R. **QEEG analysis of cranial electrotherapy: a pilot study**: J Neurotherapy 2004. 8**:** 112–3 p. 2004.

[11] KLAWANSKY, S. et al. Meta-analysis of randomized controlled trials of cranial electrostimulation. Efficacy in treating selected psychological and physiological conditions. **J Nerv Ment Dis,** v. 183, n. 7, p. 478-84, Jul 1995. ISSN 0022-3018. Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/7623022 >.