

**Self Cranial Electrical Stimulation for Pain in Older Adults with Knee Osteoarthritis (Self CES
for Knee Pain)**

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Protocol Title: Self Cranial Electrical Stimulation for Pain in Older Adults with Knee Osteoarthritis (Self CES for Knee Pain)

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Population: A maximum of 30 community-dwelling older adults with knee osteoarthritis who are 50–85 years old in Southeast Texas will be enrolled. Participants who meet eligibility criteria will be randomly assigned to either (1) active-CES (n=15) or (2) sham-CES group (n=15) (1:1 for two groups) using the order of entrance in the study.

Number of Sites: UTHealth School of Nursing is the only site for this study.

Study Duration: One year

Subject Duration: Three weeks

General Information

- Clinical studies of Cranial Electrical Stimulation (CES), which modulates central nervous system pain processing in a noninvasive and painless manner, have shown promising results for other types of chronic pain, but no studies to date have determined the efficacy of self CES in older adults with knee osteoarthritis (OA). The purpose of this study is to determine the feasibility and preliminary efficacy of a two-week self CES on pain using randomized controlled trial design. In this randomized controlled study, clinical pain intensity, experimental pain sensitivity using quantitative sensory testing, pain-related cortical response using functional near-infrared spectroscopy, and psychosocial symptoms will be compared between these two groups. This research has the potential to improve treatment of osteoarthritis-related symptoms in older adults.

Background Information

- Arthritis is one of the leading causes of pain, impairments of activities in daily life, and disability in people aged 45 and above.^{1,2} Of the 53 million adults diagnosed with arthritis, more than 22 million (42%) reported trouble with their activities of daily living due to arthritis.³ Osteoarthritis (OA) is the most common of the arthritic conditions, with the knee being the most commonly affected joint.^{2,4,5} Patients with chronic pain, such as knee OA pain, do not have sufficient pain relief,⁶ and this leads to decreased physical functioning and mobility disability. OA pain is characterized by altered pain and sensory processing in the central nervous system similar to other chronic pain syndromes.^{7,8} Because pharmacologic treatments can increase adverse events among older adults,⁹⁻¹¹ there is a growing interest in non-pharmacological interventions targeting central nervous system pain processing for this population. Specifically, noninvasive brain stimulation, such as CES, has received significant attention for the treatment of pain in chronic since CES stimulates adaptive changes in

the brain.^{12,13} Therefore, we will evaluate the feasibility and preliminary efficacy of a self CES in older adults with knee OA pain. Our hypothesis is that 10 daily sessions of self CES over 2 weeks will reduce clinical pain intensity, experimental pain sensitivity, and pain-related cortical response (e.g., reduced heat pain-evoked response in pain-related cortical regions) more than sham CES group.

Objectives

- The purpose of this project is to determine the feasibility and preliminary efficacy of a two-week self CES on pain in older adults with knee OA. The specific aims are the following: (1) To evaluate feasibility and safety of self CES in older adults with knee osteoarthritis pain, and (2) To estimate preliminary efficacy of self CES on clinical pain, experimental pain sensitivity using quantitative sensory testing measures, fNIRS imaging, and psychosocial symptoms in older adults with knee OA. Outcome measures include clinical pain intensity, experimental pain sensitivity using quantitative sensory testing, pain-related cortical response using functional near-infrared spectroscopy (hemodynamic activity in pain-related cortical regions), and psychosocial symptoms.

Study Design

- We will conduct a randomized, sham-controlled, parallel-group study in 30 older adults with knee OA at UTHealth School of Nursing with two groups: (1) two-week self CES (n=15) and (2) sham-CES (n=15).
- Expected duration of study is one year after the IRB approval from CPHS.
- CES will be applied for 60 minutes per session daily for 2 weeks (Monday to Friday) via the Alpha-Stim M (Electromedical Products International, Inc., Mineral Wells, TX). The CES devices will be preset at the same low subsensory level microcurrent of 0.1 mA (one on the dial) at the frequency of 0.5 Hz by the manufacturer. CES intervention protocol will be as follows: 1) the electrode pad of ear clips was moisturized using a conduction solution supplied to the patients; 2) ear clips were applied comfortably to the earlobes; 3) to initiate the intervention, the CES device button was turned on; 4) only one button was operable, and device starts to count down 60 minutes; and 5) at the completion of 60 minutes, device would automatically shut down. For sham CES, the electrodes will be identical look and be placed in the same positions as for active stimulation, but the stimulator will not deliver electrical current. This sham stimulation method has been shown to be reliable and indistinguishable from active treatment.¹⁴

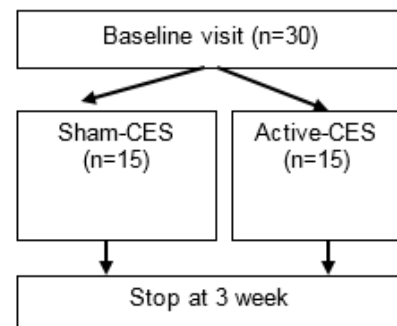


Figure 1. Study flow diagram

Study Population

- A maximum of 30 community-dwelling older adults with knee osteoarthritis (OA) will be enrolled. Participants who are 50–85 years old will be considered eligible if they (1) have self-reported unilateral or bilateral knee OA pain, according to American College of Rheumatology criteria,¹⁵ (2) have had knee OA pain in the past 3 months with an average of at least 30 on a 100 Numeric Rating Scale (NRS) for pain, (3) can speak and read English, (4) have a device with internet access that can be used for secure video conferencing for real-time remote supervision, (5) have no plan to change medication regimens for pain throughout the trial, (6) are able to travel to the coordinating center, and (7) are willing and able to provide written informed consent prior to enrollment. According to American College of Rheumatology criteria,¹⁵ participants should meet at least 3 of 6 criteria, including age > 50 years, stiffness < 30 minutes, crepitus, bony tenderness, bony enlargement, and

no palpable warmth. Participants will be excluded if they have concurrent medical conditions that hinder the completion of the protocol, including: (1) history of brain surgery, brain tumor, seizure, stroke, or intracranial metal implantation, (2) serious medical illness, such as uncontrolled hypertension (i.e., systolic blood pressure/ diastolic blood pressure \geq 150/95 mm Hg), heart failure, or history of acute myocardial infarction, (3) alcohol/substance abuse, (4) cognitive impairment, (5) pregnancy or lactation, and (6) hospitalization within the preceding year for psychiatric illness.

- Participants will be recruited in Southeast Texas under the direction of the PI. We will advertise around local institutions (e.g., UTHealth) and communities by advertisement study flyers. PI will oversee participant screening and recruitment. Obtaining written informed consent will take place in-person at a scheduled baseline visit.

Study Procedures

- Participants will do self CES at their home or private room for two weeks (Mondays-Fridays) under real-time supervision by the research staff. Data will be collected by study staff across several points using equipment and resources available at Dr. Ahn’s (PI’s) laboratory at UTHealth School of Nursing (see Table below). Participants will visit UTHealth School of Nursing two times, and each visit will take 2-3 hours.

Stimulation Session	Baseline	Treatment Session									
		1	2	3	4	5	...	8	9	10	
Informed Consent	X										
Medical History Questionnaire	X										
Pregnancy Test (female)	X										
Clinical Pain Intensity											
NRS	X	X	X	X	X	X	X	X	X	X	X
WOMAC	X										X
Psychosocial Symptoms											
PROMIS Anxiety	X										X
PROMIS Depression	X										X
PROMIS Sleep Disturbance	X										X
PCS	X										X
Feasibility and Tolerability											
Participants’ CES experience											X
Side Effects Questionnaire		X	X	X	X	X	X	X	X	X	X
CSQ											
Experimental Pain Sensitivity											
QST measures	X										X
Pain-related Cortical response											
fNIRS imaging	X										X

Note: B, Baseline; NRS, numeric rating scale for pain; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index; PROMIS, Patient-Reported Outcomes Measurement Information System; PCS, Pain Catastrophizing Scale; CSQ, Client Satisfaction Questionnaire; QST, quantitative sensory testing; fNIRS, functional near-infrared spectroscopy;

- Pregnancy Test. If participants are a woman of childbearing potential, there may be unknown risks to the fetus. Therefore, pregnancy test by a sample of urine will be obtained in all woman of childbearing potential once at baseline visit.
- Medical History Questionnaire. All patients will complete a thorough medical history that include height and weight, self-reported duration of OA, current and past treatments for OA, comorbid conditions, and current medication use.

- Clinical Pain. Clinical pain will be measured by (1) numeric rating scale for pain (NRS) for pain (primary outcome),¹⁶ (2) Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC).¹⁷ The NRS assess pain from 0 (no pain) to 100 (most intense pain imaginable), and has been reported to have Cronbach's alpha coefficient of ≥ 0.8 and well-validated measure with good ability to detect pain change in adults with knee OA.¹⁶ The WOMAC ranges from 0 to 96, with higher scores indicating worse OA pain-related symptoms. NRS will be conducted at 15 time points (baseline, and each treatment session during the treatment period), and WOMAC will be obtained two times (baseline and at the end of the treatment week).
- Psychosocial Symptoms. Psychosocial symptoms will be measured by (1) PROMIS anxiety-short form, (2) PROMIS depression-short form, and (3) PROMIS sleep disturbance-short form scale,¹⁸ and (4) Pain Catastrophizing Scale (PCS). The 7-item PROMIS Anxiety Short Form assesses the pure domain of anxiety in individuals age 18 and older, and each item on the measure is rated on a 5-point scale (1=never; 2=rarely; 3=sometimes; 4=often; and 5=always) with a range in score from 7 to 35 with higher scores indicating greater severity of anxiety. The 8-item PROMIS Depression Short Form assesses the pure domain of depression in individuals age 18 and older, and each item on the measure is rated on a 5-point scale (1=never; 2=rarely; 3=sometimes; 4=often; and 5=always) with a range in score from 8 to 40 with higher scores indicating greater severity of depression. The 8-item PROMIS Sleep Disturbance Short Form assesses the pure domain of sleep disturbance in individuals age 18 and older, and each item on the measure is rated on a 5-point scale (1=never; 2=rarely; 3=sometimes; 4=often; and 5=always) with a range in score from 8 to 40 with higher scores indicating greater severity of sleep disturbance. The Pain Catastrophizing Scale (PCS) consists of 13 items assessing three components of catastrophizing: rumination, magnification, and helplessness.¹⁹
- Feasibility. We will calculate the number of participants who a) meet the inclusion criteria, and b) complete the full CES protocol. We will also collect data on participants' CES experience at the conclusion of CES treatment on a 0 (strongly disagree) to 10 (strongly agree) scale: 1) It was easy to prepare the device and accessories, 2) The device was unnecessarily complex, 3) The device was easy to use, 4) I felt the video conferences with a technical person were helpful, 5) I would imagine that most people would learn to use this device quickly, 6) The device was cumbersome to use, 7) I felt confident using the device, 8) I needed to learn a lot of things before I could get going with this device, 9) The effectiveness of the treatment increased over the course of treatment, 10) Overall, I felt that this treatment benefited me. Also, we will measure participant satisfaction with treatment using the Client Satisfaction Questionnaire (CSQ-8).^{20,21} The CSQ-8 comprises eight items that are summed to yield an overall score of 8-32, with higher scores indicating greater satisfaction. The CSQ-8 has a reported Cronbach's alpha coefficient of 0.87-0.93.^{20,21}
- Tolerability. We will evaluate the presence and severity of possible side effects of treatment at the end of each session on a 0 (not at all) to 10 (highest degree) scale. The participants will be asked in an open-ended manner whether they have experienced any side effects, and they will then be asked specifically about tingling, itching sensation, burning sensation, pain at the stimulation site, fatigue, nervousness, headache, difficulty concentrating, mood change, and changes in vision or visual perception. If any side effects are reported, the degree of relatedness to the intervention will be assessed on a 5-point scale. This approach has been used in our previous study and frequently in other studies.²²⁻²⁴
- Experimental Pain Sensitivity. In order to measure experimental pain sensitivity, a multimodal Quantitative Sensory Testing (QST) battery will be completed: heat pain (e.g. threshold, tolerance), pressure pain threshold, punctate mechanical pain (e.g. suprathreshold ratings and temporal summation), and Conditioned Pain Modulation (CPM). These measures will be assessed using equipment and methods available at the Dr. Ahn's laboratory, including a Medoc TSA-II

Neurosensory Analyzer and Wagner pressure algometer. These QST battery will be obtained two times: at baseline and at the end of the intervention.

- Pain-related cortical response. We will measure pain-related cortical response using a continuous-wave, multichannel fNIRS imaging system (LIGHTNIRS, Shimadzu, Kyoto, Japan) with three semiconductor lasers at 780, 805, and 830 nm. This instrument encompasses 8 light sources and 8 detectors connected to comfortable headgear using optical fibers. The illumination and detection optodes will be arranged in a geometrical layout that will cover the prefrontal and somatosensory cortex regions bilaterally, consistent with the locations investigated in previous studies.^{25,26} In addition, a few optical channels will be located to the primary auditory cortex as a control region that remains inactive during pain stimulation (i.e., both fNIRS and thermal stimulation devices run silently). Optical recordings will be collected during thermal pain stimulation according to the following protocol. A temperature-controlled pain generator (Medoc TSA-II Neurosensory Analyzer) will be used to produce thermal stimulation through a 16×16 mm² thermode placed onto the index knee. The experimental protocol consists of an initial baseline period of 60 seconds during which no thermal stimulation will be applied (i.e., the thermode at room temperature), followed by 20-second stimulation at 45°C. This experimental block will be repeated six times, for a total experimental duration of 390 seconds that includes a 60-second resting period at the end of the stimulation chain. The experimental session will last about 20-25 min, including the brain imager setup time. fNIRS data will be obtained at two time points: baseline, at the end of the intervention.

Data and Safety Monitoring

- A data and safety monitoring plan (DSMP) will be implemented to ensure the safety of all participants involved in the study and to ensure the validity and integrity of the data. The PI will be responsible for coordinating activities of the DSMP, including arranging meetings and communication and identifying and reviewing relevant participant materials. The data and safety information obtained from each study participant will be reviewed weekly. The primary goal of the DSMP will be to monitor the progress of the study and safety of participants and, if necessary, recommend modifying the study or terminating the study as appropriate.
- Concerns that might dictate the modification or termination of the study include: participant safety, outcome data, data quality, data integrity, intervention efficacy, recruitment, and performance. Both the PI and the study staff will review the study weekly and examine reports of adverse incidents and reports of study participant recruitment and follow-up. Throughout the study, information regarding issues deemed critical to the study or to the safety of research participants will be provided to the PI. Upon receiving this critical information, a meeting to discuss this information may be convened. Information deemed critical would include: serious and non-serious adverse events that may occur, suspicion of scientific fraud or misconduct, and any other issues that may warrant protocol changes or modifications.
- The research team will follow the procedures for data safety and monitoring as required by the Institutional Review Board at UTHealth. To ensure data integrity and the safety of human subjects, all adverse events will be reported to the UTHealth Institutional Review Board. Any subsequent recommendations regarding protocol changes will be implemented. In addition, the investigators will review the reported adverse events every 3 months and conduct interim data analyses every 6 months to minimize the risk to the study participants.
- Safety Review Plan. Study progress and safety will be reviewed monthly (and more frequently if needed) by the PI. Progress reports, including participant recruitment, retention/attrition, and adverse events (AEs), will be provided the UTHealth IRB for annual review. In addition, the reports will address (1) whether AE rates are consistent with pre-study assumptions; (2) reasons for

dropouts from the study; (3) whether all participants met entry criteria; (4) whether continuation of the study is justified on the basis that additional data are needed to accomplish the stated aims of the study; and (5) conditions whereby the study might be terminated prematurely.

- Monitoring Health and Safety. All the stimulation and testing sessions will be supervised by trained research staff who will monitor potential adverse experiences and symptoms. At each stimulation, participants will be asked to report any adverse events they have experienced. Specifically, they will be asked about any adverse events, including itching, pain, nausea, and headache, they have had.
- Adverse Event Reporting. An adverse event (AE) is any unfavorable and unintended sign, symptom, or disease temporally associated with the intervention irrespective of whether it is considered related to the intervention. Non-serious AEs are conditions that may be unpleasant and bothersome to the participant that do not require discontinuing the study. Serious adverse events (SAEs) are events that may be harmful to the participant and/or may be serious enough to warrant either temporary or permanent discontinuation of the study intervention, either because they are intolerable or because they are judged to be potentially harmful. All SAEs require immediate reporting and an assessment of the implications for the continuation of the study and/or modification of the consent form. The following are considered SAEs: (1) it is acute or life threatening; (2) it results in prolonged, permanent, or severe disability; (3) it is another severe illness including worsening of a pre-existing condition, injury, or accident; (4) it is an inpatient hospitalization or surgical procedure or a treatment to prevent an SAE; (5) it results in death; and (6) it is a clinically significant abnormal laboratory or diagnostic test.
- The PI will evaluate AEs for their seriousness, expectedness, severity, and relationship to the study intervention at each study visit. The primary mechanism for ensuring participant safety will be clinical observation of symptoms. The study will be conducted and supervised by trained study staff and will monitor potential adverse experiences and symptoms. All AEs will also be categorized according to the likelihood that they are related to the study intervention. Specifically, they will be labeled either definitely, probably, possibly, or unrelated to the study intervention. The classification of potential relationship to the intervention is shown in Table below.

Adverse Event (AE) Classification

Adverse Event (AE) Classification	
Definite	Temporal pattern + known or expected AE response pattern + confirmed by stopping the intervention + reappearance of AE on re-challenge
Probable	Temporal pattern + known or expected AE response pattern + confirmed by stopping the intervention + could not be explained by participant’s clinical state
Possible	Temporal pattern + known or expected AE response pattern + could have been produced by a number of other factors
Unknown	Relationship for which no evaluation can be made
Not related	AE for which sufficient information exists to indicate that the cause is unrelated to the study intervention

- SAEs that are unanticipated, serious, and possibly related to the study intervention will be reported within 24 hours of the study staff’s knowledge of the SAE to the IRB in accordance with the regulatory requirements. Anticipated SAEs or those unrelated to the study intervention will be reported to the same individuals/entities in accordance with regulatory requirements.
- Minor events will be reported to the IRB. Both the PI and the study staff will review the study weekly and examine reports of adverse incidents and reports of study participant recruitment and follow-up. Throughout the study, information regarding issues deemed critical to the study or to the safety of research participants will be provided to the principal investigator and other study investigators

as needed. As a result of receiving this critical information, a meeting to discuss this information may be convened. Information deemed critical would include: (1) serious and non-serious AEs that may occur; (2) suspicion of scientific fraud or misconduct; and (3) any other issues which may warrant protocol changes or modifications. AE and SAE determination and monitoring will be achieved via administration of structured questionnaires. Standardized forms for referring and treating study participants who experience AEs will be in place.

Statistics

- This protocol adopts a randomized controlled trial design. A maximum of 30 community-dwelling older adults (50-85 years old) with knee osteoarthritis will be enrolled. The treatment group will receive CES, and the control group will receive sham-CES. To balance the distributions of subjects' age, race, and gender between the treatment and control groups, a minimization procedure will be adopted. Power calculation is based on two-sample t-test assuming equal variance. For a significance level of 0.05, 15 subjects per group correspond to a power of 0.91, given a 25% difference in means between the two groups and a standard deviation of 20% of the mean.
- Statistical analyses will be performed on data from all enrolled subjects using SAS 9.4. Data will be summarized and checked for outliers and missing values before statistical analyses. The descriptive statistics will be derived for the feasibility and tolerability measures. The clinical pain intensity measures and the experimental pain sensitivity measures will be compared between two groups using univariate or multivariate tests (e.g., Wilcoxon rank test).

Ethics

- IRB approval will be sought from CPHS.
- Participation in this study is completely voluntary. All participants will be informed of the nature of the procedures and associated risks. Also, participants will be informed that they can withdraw from the study at any time and that this will have no adverse impact on the study or on their own future medical treatment. Subjects will participate in the study only after they provide verbal and signed consent. Trained research personnel will obtain consent in a private room where participants feel comfortable. Informed consent will be documented in writing via the participants' and investigators' signatures.

Data handling and record keeping

- Procedure for Collection and Storage of Data. A number of quality control procedures will be used to ensure the validity and integrity of the data and the safety of all participants involved in the study. Relevant data and safety information obtained from each study participant will be verified against the original source documents by the study coordinator and any identified discrepancies will be reviewed at these weekly meetings. The primary goal of these meetings will be to monitor the progress of the study and safety of participants, and if necessary, recommend modifying the study or terminating the study as appropriate. All identifying information will be archived on a password-protected server. Only study staff will have access to these files.
- Location of Data Collection. All procedures involving human participants will be performed using equipment and resources available at the Dr. Ahn's (PI's) laboratory at UTHealth.
- Storage of Collected Data. All electronic data will be stored in password-protected, secured computer systems. All paper data will be stored in a locked file cabinet. Only the participant's study identification number will appear on any data forms. Only research team members will have access to the completed data forms and electronically stored data. All data will be considered part of the

participant's confidential record. All data will remain confidential. A file will be maintained that associates the participant's name with that participant's study identification number. This file will be kept in a locked cabinet separate from the study data.

- Data Entry Requirements. The data entry system will require a login identification and password to gain access to the data. Only the PI and designated research staff will be able to view the data in its raw state.

Quality control and assurance

- Audit/Verification of Entered Data. All data designated as primary outcome data will be subject to a 100% cross-referencing between electronic and paper forms. This audit must have an error rate less than 1%. If the verification fails the audit, all data will be re-entered, the original computer files will be discarded, and the newly re-entered data will be audited. This process will continue until the audit no longer exceeds the maximum allowable error rate. All audits will be supervised and documented by the PI.
- Data Management and Analysis. PI has substantial experience in the design and implementation of data management procedures that provide accurate recording and storage of data, participant confidentiality, and timely analysis. Based on our experience, we believe that the major data management and analysis needs for the proposed project can be met by using a high-end PC, equipped with SPSS and SAS for Windows and appropriate spreadsheet programs. All data files will be automatically backed up daily.
- Data Quality Control. At the time of collection, there will be an initial clerical review of all data for accuracy and completeness. Every effort will be made to ensure that missing data are kept to a minimum. Data entry programs with range checking and response validation will be used for all data entered. Under supervision from the PI, the research assistant will conduct error-checking procedures and preliminary analyses on all data to ensure their accuracy. The research assistant will be trained to avoid omissions in data entry, and computer entry protocols will be programmed to avoid accidental skipping of question items. We believe that the quality control system to be used will ensure a complete and accurate database and will maximize the likelihood that the intervention will be delivered correctly and efficiently.
- Frequency of Data Review. Relevant data and safety information obtained from each study participant will be verified against the original source documents by the primary study coordinator on a bi-weekly basis. As noted above, any identified discrepancies will be discussed with the PI and reviewed at weekly meetings.
- Measurement and Reporting of Participant Accrual and Adherence to Eligibility Criteria. Review of the rate of participant accrual as well as adherence to inclusion/exclusion criteria will occur weekly during the recruitment phase and then every month to assure that participants meet the eligibility criteria and ethnic diversity goals outlined in the grant proposal.
- Final Storage of Paper Data. All paper data (e.g., consent forms) will be housed at a facility that specializes in the storage of medical/research information. The destruction date of these files will be at least 7 years from the termination of the study and will be authorized by the PI of the research study.
- Access to Cleaned Computer Data. Once the study is complete, and all data have been collected, entered, and passed the audit process, the data will be available to the PI and his designates for analysis. Only the PI can give permission for the release of aggregated study data. No confidential information may be released without the express written consent of the study participants. Only copies of the finalized data will be released. The original data file will remain in its pristine state.

Publication Plan

- We will publish research results at the peer-reviewed journal and/or scientific conferences. After completion of the study, results will be returned to research subjects if they want.

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