Self-Administered Transcranial Direct Current Stimulation for Pain in Older Adults With Knee Osteoarthritis: A Phase II Randomized Sham-Controlled Trial

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Protocol Title:	Self-Administered Transcranial Direct Current Stimulation for Pain in Older Adults with Knee Osteoarthritis: A Phase II Randomized Sham-Controlled Trial
Principal Investigator:	Hyochol Ahn , PhD
Co-Investigators:	Hongyu Miao, PhD Luca Pollonini, PhD Salahadin Abdi, MD, PhD
Study Coordinator:	Samuel Payen
Population:	A maximum of 120 community-dwelling older adults with knee osteoarthritis who are 50–85 years old in in Southeast Texas will be enrolled. Participants who meet eligibility criteria will be randomly assigned to either active tDCS (n = 60) or sham tDCS (n = 60).
Number of Sites:	UTHealth School of Nursing is the only site for this study.
Study Duration:	Three years
Subject Duration:	Four months including follow-up assessments

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General Information

- Knee osteoarthritis (OA) is one of the most common pain conditions among people over 45, and the management of OA pain is challenging because the pain is only partially responsive to existing pharmacological approaches, which are often associated with adverse effects. Also, knee OA pain is characterized by increased pain-related brain activation, possibly explaining the limited success of existing peripherally based treatments that target the pain locally in the area of the knee. Therefore, there is growing interest in interventions targeting brain function for this population. One promising treatment is noninvasive transcranial direct current stimulation (tDCS) with the anode over the primary motor cortex (M1) and the cathode over the contralateral supraorbital area (SO) as it can change brain activity in a noninvasive, painless, and safe way. tDCS falls under the category described by the FDA as a “non-significant risk” device. Recent studies suggest that clinic-based M1-SO applied tDCS has promising efficacy for managing chronic pain. However, no investigator to date has examined the effect of the self-administered home-based tDCS on clinical pain. Recent technological advances have increased the portability of tDCS, which creates the potential for home use with real-time monitoring through a secure video conferencing platform of stimulation delivered through electrodes mounted on custom single position headgear to ensure fidelity of treatment localization. The proposed study directly addresses this gap in the literature by investigating the effects of self-administered, remotely supervised M1-SO applied tDCS at home in 120 older adults with knee OA pain using an experimenter- and participant-blinded, randomized, sham-controlled, phase II parallel group (1:1 for two groups) design. The first aim of this study is to

determine the effects of self-administered M1-SO applied tDCS on clinical pain intensity in older adults with symptomatic knee OA. The second aim is to determine the effects of self-administered M1-SO applied tDCS on pain-related cortical response in older adults with symptomatic knee OA. The third aim is to investigate the feasibility and acceptability of self-administered M1-SO applied tDCS in older adults with symptomatic knee OA. This study will provide definite insight into an exciting new modality of nonpharmacological pain self-management in that it will be extremely easy, safe, and noninvasive with minimal side effects.

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 Transcranial Direct Current Stimulation (tDCS), has received significant attention for the treatment of pain in chronic conditions due to its neuromodulatory effect.[12-15] tDCS involves the application of weak direct electric current to the head in a noninvasive and painless manner, leading to the modulation of the resting membrane potentials of neurons and alteration of the endogenous excitability of the targeted cortical area.[16] This stimulation is believed to mediate analgesic effects by modulating pain processing pathways.[17,18] Previous studies indicated that tDCS is effective in reducing pain in chronic conditions, including fibromyalgia,[12] spinal cord injury,[12] and multiple sclerosis.[14] Therefore, we will assess the feasibility, acceptability, and efficacy of this novel nonpharmacological treatment option in older adults with knee OA pain. Our hypothesis is that self-administered M1-SO applied tDCS will reduce clinical pain intensity and pain-related cortical response more than sham tDCS

Objectives

- The purpose of this project is to assess the feasibility, acceptability, and efficacy of the self-administered tDCS in older adults with knee OA. The specific aims are the following: (1) To determine the effects of self-administered M1-SO applied tDCS on clinical pain intensity in older adults with symptomatic knee OA, (2) To determine the effects of self-administered M1-SO applied tDCS on pain-related cortical response in older adults with symptomatic knee OA, and (3) To investigate the feasibility and acceptability of self-administered M1-SO applied tDCS in older adults with symptomatic knee OA. Outcome measures include clinical pain intensity, pain-related cortical response using functional near-infrared spectroscopy, and feasibility and acceptability using tDCS experience questionnaire and side effects questionnaire.

Study Design

- We will conduct a double-blind (participant and experimenter), randomized, sham-controlled, phase II parallel-group study with two groups (sham and active tDCS) in 120 older adults with knee OA.
- Expected duration of study is three years after the IRB approval from CPHS.
- tDCS with a constant current intensity of 2 mA will be applied for 20 minutes per session daily for 2 weeks (Monday to Friday) via the Soterix 1x1 tDCS mini-CT Stimulator device (Soterix Medical Inc., NY; 6.5 inches long, 3 inches wide, 0.7 inches thick) with headgear and 5x7 cm saline-soaked surface sponge electrodes. The FDA has ruled that the aforementioned tDCS stimulator is a "non-significant risk" device, a requirement for Investigational Device Exceptions. The sponge electrodes snap into the custom headgear, which is secured to the participant's head for simple and fail-safe electrode preparation. This single-position headgear with clearly labeled sponge markers eliminates room for user error and helps conserve the placement of the montage. Participants can only administer a stimulation session via the Soterix 1x1 tDCS mini-CT Stimulator device after being provided a single-use unlock code by the research staff once proper contact quality is achieved (only the on/off button will be adjustable by the study participants; they will not be able to adjust the device settings). After the participant enters the unlock code, the screen on the device will show a timer that counts down the minutes until the end of the session. At 20 minutes, the device will turn off automatically, and study staff will instruct the participant to remove the headset and discard the sponges and to safely store all materials for the next session. For sham stimulation, the electrodes will be placed in the same positions as for active stimulation, but the stimulator will only deliver 2 mA current for 30 seconds. This sham stimulation method has been shown to be reliable and indistinguishable from active treatment.[12,19]

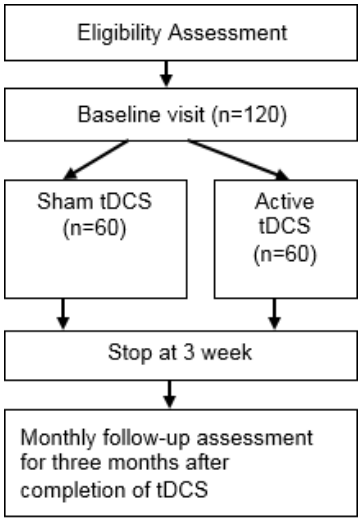

Figure 1. Study flow diagram

Study Population

- A maximum of 120 community-dwelling older adults with knee osteoarthritis (OA) will be enrolled. Similar to our previous work,[20] participants who are 50-85 years old will be considered eligible if they (1) have symptomatic knee OA based on American College of Rheumatology Clinical criteria,[21] (2) have had knee OA pain in the past 3 months with an average of at least 30 on a 0-100 NRS for pain, (3) can speak and read English, and (4) have no plan to change medication regimens for pain throughout the trial. According to American College of Rheumatology criteria,[21] 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 any concurrent medical conditions that could confound the interpretation of outcome measures, pose a safety risk for any of the assessment or tDCS procedures, or preclude the successful completion of the protocol. Specific exclusion criteria are: (1) prosthetic knee replacement or non-arthroscopic surgery to the affected knee, (2) history of brain surgery, brain tumor, seizure, stroke, or intracranial metal implantation, (3) systemic rheumatic disorders, including rheumatoid arthritis, systemic lupus erythematosus, and fibromyalgia, (4) alcohol/substance abuse, (5) current use of sodium channel blockers, calcium channel blockers and NMDS receptor antagonists, (6) diminished cognitive function that would interfere with understanding study procedures (i.e., Mini-Mental Status Exam score ≤ 23), (7) pregnancy or lactation, (8) hospitalization within the preceding year for

psychiatric illness, and (9) no access to a device with internet access that can be used for secure videoconferencing for real-time remote supervision.]

- 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. In addition, we will put our recruitment flyer on the UTHealth official social medial channels (e.g., Facebook, Instagram, Twitter, LinkedIn). 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-administered tDCS at their home or private room for three 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 four times, and each visit will take approximately 2 hours.

Stimulation Session	B	Week 1					Week 2					Week 3					M1	M2	M3
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15			
Pregnancy Test	X																		
MMSE	X																		
Knee Radiograph*	X																		
Medical History Questionnaire	X																		
Clinical Pain Intensity																			
NRS (primary outcome)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
WOMAC (secondary outcome)	X					X					X					X	X	X	X
PCS (secondary outcome)	X					X					X					X			
Pain-related Cortical response																			
fNIRS imaging (secondary outcome)	X					X					X					X			
QST measures	X					X					X					X			
Feasibility and Acceptability																			
tDCS experience questionnaire (secondary outcome)																X			
Side effects questionnaire (secondary outcome)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			

Note: B, Baseline; M, Monthly follow-up phone assessment after completion of tDCS treatment; MMSE, Mini-Mental Status Exam; NRS, Numerical Rating Scale; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index; PCS, Pain Catastrophizing Scale; QST, Quantitative Sensory Testing; fNIRS, functional near-infrared spectroscopy. The baseline visit will occur 3 to 7 days prior to the tDCS intervention, and will include medical history questionnaire, clinical pain intensity, and fNIRS imaging. Each month for three months post-intervention, participants will complete a follow-up telephone

assessments of clinical pain intensity. * Knee radiographs can be scheduled at a different time depending on the participants' availability.

- 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.
- MMSE. MMSE will be used to exclude people with diminished cognitive function (i.e., Mini-Mental Status Exam score ≤ 23).
- Knee Radiograph. Knee radiographs will be taken to determine OA severity using Kellgren-Lawrence scores.
- Medical History Questionnaire. All participants will complete a thorough questionnaire to collect demographic and medical history details, including age, sex, height, weight, duration of knee OA, current and past treatments for knee OA, comorbid conditions, and current medications.
- Clinical Pain Intensity. Clinical pain intensity will be measured by asking participants to rate their average knee pain over the past 24 hours via NRS from 0 (no pain) to 100 (worst pain imaginable). Following Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials recommendations for clinical trials involving chronic pain,[22] pain intensity changes assessed through an NRS will be our primary outcome measure for data analysis purposes. We also measure clinical pain intensity using Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), which ranges from 0 to 96, with higher scores indicating worse OA pain-related symptoms. Moreover, we measure pain catastrophizing using Pain Catastrophizing Scale (PCS), which ranges from 0 to 52, which higher score indicating higher pain catastrophizing.
- 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 locations investigated in previous studies.[23,24] 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). Based on our hypothesis, we believe these cortical areas will exhibit significant hemodynamic activity elicited by pain stimulation. Hemodynamic image reconstruction will be aided by the acquisition of spatial coordinates of all fNIRS optodes with respect to subjects' anatomical landmarks (nasion, pre-auricolar left and right, vertex and inion) using a 3D Digitizer (Polhemus Patriot, Colchester, VT). 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 mm^2 thermode placed onto the forearm. The experimental protocol consists of an initial baseline period of 60 seconds during which no thermal stimulation will be applied (i.e., thermode at room temperature), followed by 20-second stimulation at 45°C and a 30-second resting period. 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. In addition, 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.

- Feasibility. We will calculate the percentage of participants who a) meet the inclusion criteria, b) agree to be randomly assigned, c) complete the full tDCS protocol, and d) attend the follow-up assessment.
- Acceptability. We will collect data on participants' tDCS experience via a questionnaire, at the conclusion of tDCS 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 transcranial electrical stimulation treatment benefited me. Participants will also be encouraged to elaborate their answers in free-form.
- Moreover, 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 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 (details of the data and safety monitoring plan are provided in the Human Subjects section). This approach has been used in our previous study and frequently in other studies.[20,25,26]

Data and Safety Monitoring

- The DSM plan is in accordance with the Policy of the National Institute of Nursing Research (NINR) for Data and Safety Monitoring of Extramural Clinical Trials set forth in 2014. As part of the DSM plan, we have convened a Safety Monitoring Committee (SMC) of which the organization, responsibilities, and operations are mandated by NIH and NINR policy.
- Level of risk of the intervention. We will investigate the effects of self-administered transcranial direct current stimulation (tDCS) on clinical pain in older adults with knee osteoarthritis pain in this study. The FDA determined that the tDCS device as used in those studies is Non-Significant Risk (NSR), and the UTHealth IRB also determined that the tDCS as used in this study is Non-Significant Risk (NSR). To add additional safety measures for this study, we will convene a SMC. This study constitutes minimal risks because: (1) the discomfort is transient in nature and generally subsides immediately after the procedure; (2) participants are instructed that they may stop any procedure at any time with no adverse consequences; and (3) the level of discomfort experienced by participants is below their tolerance level. Also, risks will be minimized by adhering to our exclusion criteria, and the study physician will have full discretion to exclude participants who may be at excessive risk.

A. Monitoring Entity

Role of the PI and investigative team. Dr. Ahn, the PI, will have primary responsibility for monitoring study research staff, who will receive training on the study design, recruitment, and protocol prior to study initiation. Research staff will receive formal training on the study protocol by Drs. Ahn, Abdi, and Pollonini, which will entail one day of intensive training followed by additional training sessions as needed. The research staff will attend weekly meetings with the PI and monthly team meetings during data collection with the PI and co-investigators to discuss any study issues regarding recruitment and follow-up data collection. These meetings will be used to discuss experiences with the intervention participants, provide consultation, ascertain whether the research staff are following study protocols,

evaluate and reinforce cultural competence, and identify any potential adverse events. Dr. Miao, the study statistician, will coordinate data management and analysis.

Role of the SMC. The SMC will be responsible for oversight of the activities related to implementing the clinical trial to ensure patient safety, conformance to the clinical protocol, overall performance of the trial components, and integrity of the data being collected. The SMC will meet prior to the start of enrollment, and then annually to review study progress (e.g., recruitment, retention, and safety procedures) and participant safety concerns and also as needed to adjudicate any adverse events. All meeting materials will be considered privileged by SMC members. This confidentiality will be maintained at all times to the extent permitted by law.

The SMC will comprise 3 members with expertise in neuromodulation, statistics, and geriatric clinical research: Ricardo Jorge, MD, professor of psychiatry and behavioral sciences at Baylor College of Medicine; Dr. Nikhil Padhye, PhD, associate professor and biostatistician at The University of Texas Health Science Center at Houston Cizik School of Nursing; and Carmel Dyer, MD, Roy M. and Phyllis Gough Huffington Chair in Gerontology and the Nancy P. and Vincent F. Guinee Distinguished Chair in Gerontology at The University of Texas Health Science Center at Houston. The SMC members are independent of the project. These members are appropriately qualified to review the scientific design and conduct of the study, to evaluate safety and risks to participants, to interpret data statistically, and to make recommendations concerning continuation, modification, suspension, or termination of the study.

Annual SMC meetings will begin after the first week of data collection. In addition, should any adverse event occur, the SMC will be informed immediately, and a special session will be scheduled to discuss strategies to deal with the event. The annual meeting will include a synopsis of the protocol and design, discussion of the status of interventions and data collection procedures, a summary of subject contacts, discussion of any adverse events or potential adverse events, status of data entry and verification, and a summary of any descriptive and inferential statistics to date. Details about data quality and completeness and data collection timeliness will be provided to the SMC, including enrollment rates, exclusion rates and reasons, completion of scheduled data collection, reasons for study withdrawal, adequacy of enrollment composition, demographic similarities/differences between the intervention and control groups, protocol deviations and adherence, and compromises in confidentiality. The SMC meetings will be closed sessions without the investigators, during which the SMC will discuss the need for additional procedures to prevent adverse events or ensure data integrity. In the unlikely case that the study needs to be terminated early owing to unexpected adverse events or inadequate conduct of the study, the SMC will make recommendations to the investigators. Recommendations from the SMC meetings will be shared with the UTHealth IRB and the NIH during annual reports and immediately if the SMC identifies adverse events not previously reported or recommends early termination of the study.

Role of the IRB. This study will be approved by the UTHealth IRB. The UTHealth IRB will have the primary oversight of the study, and the PI (Dr. Ahn) will be responsible for reporting the status of the study to the IRB. Annual progress reports and renewals will be completed for the IRBs and will include a summary of the recommendations of the SMC. If adverse reactions related to study procedures are noted, they will be immediately reported to the UTHealth IRB by Dr. Ahn so that the IRB is aware of any risks involved with the study. The IRB will be responsible for ensuring the adequate and appropriate composition of the SMC as specified by NINR policy.

Reporting to NINR. Dr. Ahn, the PI, will be responsible for submitting necessary reports to the NINR. Summaries of the protocol and design, the status of the intervention group, data collection procedures, a summary of subject contacts, discussion of any adverse reactions or any potential adverse reactions, the status of data entry and verification, a summary of any descriptive statistics to date, and the recommendations of the SMC will be included in each annual report to the NINR. The NINR will be

notified within 7 days if the human subjects research or the DSM plan is changed prior to or during implementation of the clinical trial for approval. In addition, should any adverse reaction occur or should the SMC recommend terminating the study early, the information will be immediately reported to the NINR program officer. All personal identifiers will be removed from any documentation sent to the NINR. Timely reports to the NINR will be generated for:

- Unanticipated problems or unexpected serious adverse events that may be related to the study protocol
- IRB-approved revisions to the study protocol that indicate a change in risk for participants
- A summary of recommendations made by the SMC or other monitoring entity as appropriate and (if applicable) the action plan for response
- Notice of any actions taken by the IRB or regulatory bodies regarding the research and any responses to those actions

B. DSM Procedures

B1. Monitoring study safety.

Monitoring schedule. All the stimulation and testing sessions will be supervised by trained research staff who will monitor potential adverse events and symptoms. At each stimulation, participants will be asked to report any adverse events they have experienced. A study physician (i.e., Dr. Abdi) will also be available to evaluate the participant if needed. Based on information obtained at this visit, participants will then be referred for follow-up assessment and/or treatment with the appropriate healthcare provider. Drs. Ahn, Pollonini, Abdi, and Miao will meet every month (by phone and/or in person) to monitor study progress including data collected from participants on any serious health events that caused them to seek medical attention and if any of these resulted in hospitalizations overnight. Any adverse reactions noted by any of the team members will be reported to the PI, the UTHealth IRB, SMC, and NINR. All adverse events will be reviewed monthly by the research team and annually by the SMC. Also, in keeping with NIH guidelines, minority status and gender will be included in these reports to allow for the detection of differential effects.

Auditing selected cases for compliance with IRB requirements. 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.

Conformance with informed consent requirements. This study will be approved by the UTHealth IRB and registered on ClinicalTrials.gov, and written informed consent will be obtained from all participants prior to study commencement. The informed consent document will thoroughly describe the procedures and any associated risks, and study staff will verbally review the information with each participant before enrollment into the protocol. They will also be informed that they can withdraw their consent at any time without penalty. Individuals will participate in the study only after they provide verbal and signed consent. Consent will be obtained by trained research personnel in a private space. The informed consent form will be reviewed in detail with each potential participant, and they will be provided a copy of the informed consent form to review prior to providing consent. Informed consent will be documented in writing via the participant's and investigator's signatures.

Verification of source documents. 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. All identifying information will be archived on a password-protected server in password-

protected folders and files. Only study staff will have access to these files. We will use the double data entry module in REDCap for self-report data. Computer-generated reports of variable frequencies and participant lists will be reviewed, leading to possible corrections to coding or entry. After data within a given group are checked for accuracy, the data will be stored in the password-protected folders. Investigator compliance. All of investigators will complete Protection of Human Subjects certification and receive additional education on research and ethics as needed.

B2. Minimizing research-associated risk.

Location of data collection. All procedures involving human participants will be performed at the PI's laboratory at UTHealth.

Storage of collected data. All electronic data will be stored in password-protected, secured computer systems. 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. Data collected from research participants will be stored in a secured, password-protected computer file. All paper data (e.g., participant contact information, consent forms, etc.) will be placed in a locked file cabinet within 24 hours of their acquisition as designated by the study's research assistant. All data will remain confidential.

Data entry requirements. The data entry system will require a login identification and password to gain access to the data. Where appropriate, validation and range rules will be applied to the actual entry fields. Only the PI and designated research staff will be able to view the data in its raw state.

Data management and analysis. Our research team 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. Dr. Miao, the study statistician, will coordinate data management and analysis.

Data quality control. All staff involved in data collection will be trained and certified to ensure their competence and re-certified periodically throughout the study, as we have done in similar trials. Data will be collected and numerically coded using pre-tested electronic entry forms. 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. 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. As we have done in prior studies, we will develop a manual of procedures during the initial study start-up period that explicitly describes the specific procedures related to intervention delivery, data collection, and quality assurance.

Measurement and reporting of participant accrual and adherence to eligibility criteria. The rate of participant accrual as well as adherence to inclusion/exclusion criteria will be reviewed 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.

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.

B3. Protecting the confidentiality of participant data. Confidentiality will be maintained by assigning each participant a number, which will be used in all data tabulation and subsequent publications. The list linking this number to the participant's identity will be maintained in a password-protected data file, accessible only by authorized research personnel associated with the human testing components of this project. The PI will oversee the compliance of the study, maintaining strict adherence to the requirements of the law, UTHealth and federal regulations, research protocols, and health information security. Only trained research team members designated in the IRB-approved study protocol will collect data. Research Electronic Data Capture (REDcap; http://www.project-redcap.org) will be used to capture and store participant data, and the data will be stored on the secure data file server at UTHealth, accessible only by research team members via an encrypted and password-protected computer. All research data will be labeled using the participant's unique identifier. No name or other identifying information will be used on research data. All paper data (e.g., participant contact information, consent forms) will be placed in a locked file cabinet at the UTHealth Cizik School of Nursing within 24 hours of their acquisition.

C. Adverse Events and Unanticipated Problems

Adverse event identification. The research staff will receive one day of training prior to initiating recruitment procedures for this study to assure that all protocols and procedures are followed. Research staff will have ongoing supervision in how to handle participants' discomfort. Participants can choose whether to be in the study or not. They may withdraw at any time without consequences of any kind. They may also refuse to answer any questions they do not wish to answer and still remain in the study. There may be occasions when study participants exhibit stronger and more serious signs of emotional distress. Research staff will be trained to identify and respond to signs of acute distress. We will emphasize to research staff at all study team meetings that if a participant becomes upset, they should be offered the option of discontinuing participation in the study without penalty (i.e., still receiving payment) or continuing at a later time after a break. Our study physician (Dr. Abdi) and Dr. Ahn will be available for immediate consultation in the event of encountering an unexpected acute psychological issue.

Adverse event reviewing. Adverse events will be reviewed at each study team meeting to assure all participant safety and reporting protocols were followed. The SMC will meet annually to review reports on adverse events and unanticipated problems, discuss participant safety concerns, and review general study progress.

Adverse event reporting. Study participants will be encouraged to immediately report any "emergencies or events" by calling the study contact number. These instructions will be included on the consent forms. The study team will record all reported events in the adverse events and unanticipated problems log (including the subject's name, the date, and an event description). All members of the study team will inform the PI, Dr. Ahn, immediately of any adverse events and unanticipated problems, and he will consult with co-investigators and the SMC members on the necessary action. The PI will report the incident to the UTHealth IRB within one week. The action and date of implementation will also be recorded in the adverse events and unanticipated problems log. The entire investigative team and SMC will participate in classifying events as "serious" or "non-serious" (see list below), as well as "non-attributable," "possibly attributable," or "attributable" to the intervention. The SMC will advise the PI and the study team on actions to be taken to minimize further adverse events and unanticipated problems within 2 weeks of reviewing the reports.

1. Serious events include any event or condition that is life threatening or results in a hospitalization or a physical or cardiac event serious enough to require medical attention. These events may be:

a. Fatal

b. Life threatening

c. Permanently disabling
d. Required or prolonged hospitalization (admission, not ER visit)
e. Overdose
f. Significant hazard to the patient
2. Non-serious events include all other events.

D. This is a single site study.

E. Ongoing assessments that may impact the safety or ethics of the study.
The research team is active in clinical pain research and will continue to monitor the literature, attend national and international conferences, and consult with colleagues to assure that we are aware of any emerging data that may impact the safety or the ethics of the study.

F. Advanced plans for interim/futility analysis
One focus of the investigator meetings will be to continuously monitor and develop strategies to prevent adverse reactions, monitor the research staff, and protect data integrity. Accrual data will be reviewed by the team and the UTHealth IRB. The study team will make amendments to the protocol should accrual fall below 15% of the target or should drop-outs exceed projections by 15%.

Statistics

- In this study, we will randomly assign 120 individuals to two groups, i.e., 60 participants to each group. With this sample size, we will be able to detect the expected effect size of 0.89 with more than 99% power at a significance level of 0.05 after accounting for 10% attrition. The minimum effect size we can detect with this sample size is 0.54 with 80% power at a significance level of 0.05 after accounting for 10% attrition. Thus, our sample size will provide sufficient power to detect a clinically meaningful effect.
- All data will be analyzed using the intention-to-treat approach. All demographic and clinical variables will be summarized using descriptive statistics, such as mean ± standard deviation (SD) or median (interquartile range, IQR) as appropriate for continuous variables and frequency and percentage for categorical variables. The distribution of all variables will be examined to check the validity of distribution assumptions before any analysis, using measures of central tendency and a visual inspection of histograms and quantile-quantile plots. If the normality assumption is not met, equivalent non-parametric approaches will be employed. SAS 9.4 (SAS Institute, Cary, NC) will be used to perform the proposed statistical analyses.

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.

Quality control and assurance

- 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.

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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