Role of home-based transcutaneous electrical acustimulation for treatment of pain in patients with chronic pancreatitis – A Pilot study

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Title: Role of home-based transcutaneous electrical acustimulation for treatment of pain in patients with chronic pancreatitis – A Pilot study

Trial acronym: TEA-CuP (transcutaneous electrical acustimulation in chronic pancreatitis)
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1. Background:

Abdominal pain is the hallmark of chronic pancreatitis (CP) and ~90% of CP patients experience abdominal pain at some point during the disease course [1]. Although medical management with nonopioid analgesics is the first step in the management of painful CP, this is often insufficient. In population-based studies, 25% are prescribed opiates, 22% require endoscopic procedures, and 11% undergo surgery.[2, 3] However, pain in CP is debilitating and often refractory to interventions, resulting in low quality of life, high rates of disability, and increased resource utilization.[4] Therefore, novel methods to reduce pain in CP are needed.

Acupuncture is an alternative non-pharmacologic intervention that has been shown to be effective in treating osteoarthritis[5], irritable bowel syndrome[6], and postoperative ileus[7]. Electroacupuncture (EA) evolved from conventional manual acupuncture and delivers weak electrical current to needles inserted into acupuncture points. Transcutaneous electrical acustimulation (TEA) is a needleless alternative of EA that delivers electrical stimulation noninvasively via surface electrodes placed on acupoints. TEA is one novel form of transcutaneous neuromodulation that has been shown to be a potential non-pharmacologic treatment option for several GI motility disorders[8, 9] and acute pancreatitis[10].

The role of acupuncture methods in CP has been evaluated in 2 prior studies with conflicting results. The first study was conducted 3 decades ago in 23 patients with chronic abdominal pain due to CP and showed that both EA (5 sessions over two weeks) and transcutaneous electrical nerve stimulation (TENS, daily stimulation over 3 weeks using carbon rubber electrodes) failed to show any significant effects on pain as compared to sham treatments.[11] In a more recent study of 15 patients with painful CP, one session of traditional acupuncture led to more pain relief compared with sham stimulation.[12] However, the effect was short-lived, and after 1-week follow-up, there was no difference in clinical pain scores between groups. These conflicting results are likely due to the selection of different stimulation points, stimulation parameters and treatment durations. Similar to other medical therapies, these are important factors determining the efficacy of the EA therapy. In addition, the mechanisms of pain in CP are complex and multifactorial, and some particular pain phenotypes may be more responsive to acupuncture to others.

In this project, we will use a novel TEA device for treatment of abdominal pain in patients with CP. The proposed TEA is based upon a logical progression of preliminary basic mechanistic and clinical studies.[10, 13, 14] We will use specific parameters designed for treating abdominal pain that have been shown to be effective for ameliorating abdominal pain in patients with irritable bowel syndrome (IBS)[15] and acute pancreatitis (AP)[10]. Mechanistically, TEA at these acupoints and with these parameters can improve autonomic function and inhibit inflammation. Clinically, the proposed TEA can be self-administrated at home 1 or more times daily. If TEA is effective in reducing pain in CP, this may be an alternative intervention with better safety profile to other interventions used for painful CP and an attractive non-pharmacological approach for opioid-free pain therapy.

2. Specific aims:

Aim 1: To determine the feasibility and tolerability of delivering TEA to outpatients with painful CP

Approach: We propose to conduct an open-label feasibility trial to understand the feasibility of TEA in patients with painful CP. In this open-label study, all subjects will receive TEA at acupoint ST36 in an unblinded manner. This will inform on recruitment & retention rates, percentage of patients with complete data collection and compliance with study procedures. This will also assist in sample size calculations for a future larger study.

Aim 2: To collect pilot data on the efficacy of TEA on abdominal pain, patient reported outcomes, and quality of life, in patients with painful CP. TEA at ST36 has been shown to be effective in the treatment of patients with abdominal pain due to visceral hypersensitivity and pancreatic inflammation.[10, 15] We will use parameter P100 (100Hz, 0.5ms, 0.1s-on and 0.4s-off, and tolerable current output), which has been found most effective in treating visceral pain in animals and patients with irritable bowel syndrome.[13, 16] TEA at this acupoint may be effective in ameliorating pain in CP by improving pancreatic inflammation or autonomic function.

3. Methods: participants, interventions, and outcomes

In this study, we aim to assess feasibility of TEA, enrollment methods, and data collection tools. All patients will receive TEA via ST36 twice daily (a point below the knee cap) in an unblinded fashion. We will then use this preliminary data to apply for competitive funding to conduct a larger study. The population, intervention and outcome for this study are summarized in ***Table 1***.

Table 1: Summary of study population, interventions, outcomes and setting

Population	Adult subjects aged 18 to 75 years with chronic pancreatitis and abdominal pain
Intervention	Home-based 30-minute sessions of TEA twice a day for 4 weeks
Control	None
Outcome	Enrollment, retention, and data collection feasibility
Setting	Comprehensive pancreas clinic at the University of Michigan

Eligibility criteria:

Inclusion criteria

1. Age 18 to 75 years of age.
2. Diagnosis of chronic pancreatitis, based on a score $\geq$ 4 using the previously validated Mayo scoring system that uses morphologic and functional criteria[17], or endosonographic features suggestive or consistent with CP based on Rosemont criteria[18].
3. Abdominal pain present at least once a week within the last month
4. Willing and able to provide written informed consent

Exclusion criteria

1. Pregnancy or breastfeeding mother
2. Imprisoned individuals
3. Non-English speaking patients
4. Scheduled for or with a history of pancreatic surgery (e.g. TPIAT, Puestow, Frey, Whipple, other)
5. Currently undergoing or about to start endoscopic therapy with ERCP or EUS
6. Recent history of acute pancreatitis as defined by the Revised Atlanta Classification within a month prior to enrollment
7. Radiologic and clinical findings consistent with symptomatic pseudocyst, wall-off necrosis, infected pancreatic necrosis, or biliary obstruction within the last 6 months
8. Self-reported daily use of opioids for > 12 months for weak opioids (codeine, tramadol and hydrocodone) or > 6 months for strong opioids (other opioids) in the last two years. A similar approach was used in a recent landmark RCT that compared endoscopic therapy vs. surgery in patients with painful chronic pancreatitis.[19]
9. Self-reported ongoing illicit drug use or abuse
10. Suspected or diagnosed pancreatic cancer
11. Receiving chemotherapy for cancer
12. Known allergy to adhesive ECG electrodes
13. Patients with bilateral below the knee amputation
14. Patients with lower extremity paralysis
15. Patients are participating in another clinical trial
16. Patients with an implantable electrical stimulation device.

Interventions

I. Run-in period: 2 weeks (V0)

After initial screening (V0 – virtual or in person) and after the consent form is signed, subjects that fulfill eligibility criteria will be invited to participate to the study.

All eligible subjects will then complete a pre-enrollment run-in period of 2 weeks. Over this run-in period, subjects will be asked to complete a diary with information on daily severity of abdominal pain. Subjects will rate their worst daily abdominal pain intensity over the past 24 hours by putting a mark on a visual analogue scale (scoring 0-10), where 0 represents "no pain" and 10 represents the "worst imaginable pain." Subjects with abdominal pain severity of 4 or greater for at least 5 days in this run-in period will be invited for a site visit to start the intervention (V1). Subjects who don't qualify for this criterion will not be invited to receive the intervention. A similar approach has been used in a prior RCT evaluating the role of antioxidants for pain in CP.[20] Surveys will be completed via RedCap.

II. Visit 1 (V1)

In this initial visit, subjects will complete baseline questionnaires. This visit will either be in-person at the main hospital in Ann Arbor or performed remotely with the study coordinator. After enrolling in the study, subjects will be given the TEA device and receive instructions on how to use this via ST36. If the participant chooses to have the visit be remote, they will receive the study materials by mail prior to the visit and a pregnancy test supplied by the study team. In

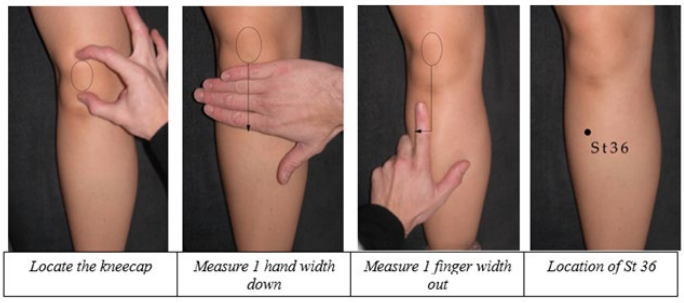
either method of visit, the participant will be given a paid return mailer to give our supplies back. Participants will be subjected to a pregnancy test of they are of child-bearing potential on the day of V1.This will be done in the clinic or self-administered by the subject at home prior to the Zoom appointment. Recommendation to use some form of contraception during the study and birth control options will be discussed. Study participants will use the TEA device for 5 minutes under the supervision of the study coordinator. Subjects will be asked to start the intervention one day after the training received during the initial visit.

III. Home-based treatment period- 4 weeks

TEA will be self-administrated at home over two daily treatment sessions of 30 minutes each. TEA will be performed using a device that measures about 4x6 cm (***Figure 2***), and that is programmed by the study team to deliver a specified weak electrical signal. The subject is able to adjust the stimulation output by pressing the "+" or "-" sign on the device. The stimulation output is adjustable, because the tolerance level varies by individuals and settings will be adjusted based on maximal tolerance. The maximum current output is 10mA. All other parameters, including frequency, pulse width, and time on/time off during the pulsed stimulation, will be fixed. TEA is similar to a transcutaneous electrical nerve stimulation (TENS) unit that is classified by FDA as a non-significant risk device. The device is powered by a small rechargeable battery and the charging will take place only when the device is not in use. This device has been approved for use in two ongoing clinical studies at UofM by the same investigation team (HUM00189911, HUM00217301).

Figure 2: Photo of the existing TEA device

Figure 3: Location of ST36 for TEA



TEA will be delivered through stimulation of acupoint ST36, located four subject's finger widths down from the bottom of the knee cap along the outer boundary of the shin bone (***Figure 3***). TEA will be applied to one leg at a time. Participants may choose to switch legs with each session. Participants will be informed to switch legs if any skin irritation occurs. Subjects will be asked to perform the two daily stimulations at least 6 hours apart but no more than 14 hours apart. This variability in the selected leg or time interval is not expected affect the efficacy of the intervention. Devices will be labeled with unique identifiers and device supply will be tracked upon dispense and retrieval from subjects. For the stimulation of this acupoint, one electrode will be placed right at the acupoint and the other electrode at 3-4 cm below the first electrode along the leg. TEA will be performed using parameter set P100. P100 uses intermittent pulse trains with a train on-time of 0.1s and off-time of 0.4s (2 trains/second), and a pulse frequency of 100Hz and width of 0.5ms within each train, and a sensible but tolerable current output based on the patient's tolerance (maximal current that the patient can tolerate without feeling discomfort or pain by the current used). Previous studies have shown that EA at 2 Hz accelerates the release of enkephalin, beta-endorphin and endomorphin, while EA at 100 Hz selectively increases the release of dynorphin;

a combination of the two frequencies produces a simultaneous release of all opioid peptides, resulting in a maximal analgesic effect.[21, 22] In our Parameter set P100, there are two frequency components: 100Hz pulses and 2Hz trains. EA and TEA with this parameter set have been shown to be effective in reducing abdominal pain.[13, 23, 24] Adherence will be directly monitored through use of the TEA device. The TEA automatically records duration of use, time of the day, and stimulation intensity.

The treatment will be discontinued if the patient develops an adverse event (discussed under *6. Safety Management*) that requires the treatment to be stopped or at the participant request. Subjects will be allowed to start and continue conventional medical therapy for the duration of the study, including any pain medications. This will be at the discretion of the treating physician. This will allow us to assess the addition of TEA to conventional care. The TEA intervention will be discontinued if the patient gets admitted to hospital or if a surgical or endoscopic procedure is performed during the treatment phase of the study. During the 4 weeks of treatment, subjects will complete pain diaries through RedCap. This will take 2 minutes for completion.

IV. Monitoring phone calls

To assess any potential problems with the TEA device, we will contact participants via telephone within 72 hours of starting treatment and then weekly at 1 week, 2 weeks, and 3 weeks from treatment initiation.

V. Visit 2 (V2), 4 Weeks from V1

During this follow-up period subjects will complete the same set of surveys that was completed during the first visit to assess pain, quality of life, and anxiety or depression. Subjects will also return the TEA device using their return mailer (provided during or prior to visit 1). In the event the device is broken or non-functional, participants will still be requested to return the device.

VI. Visit 3 (V3), at 8 weeks from V1

After subjects finish treatment (4 weeks from V1), they will continue completing daily pain diaries for additional 4 weeks. During this phase, subjects will not receive device stimulation. At 8 weeks from V1, subjects will be asked to complete the same set of surveys completed during visit 1 and 2. These will be completed via RedCap.

VII. Close-out phone call, at end of trial

At the end of the trial, study subjects who enrolled and received TEA will be reached out via a phone call to assess on global impression and acceptability of the treatment.

Outcomes

Primary outcomes

1. Enrollment feasibility: how many patients with CP who are assessed meet eligibility criteria. In addition, of these, how many provide informed consent. Of those who consent, how many meet criteria to participate after the run-in period. Of those who meet run-in period criteria, how many start the intervention (TEA).

2. Adherence: of those who start the intervention, how many adhere to the intervention as prescribed. The time of the day and duration of each TEA administration will be automatically recorded by the TEA device.
3. Retention feasibility: how many patients who start the intervention complete follow-up visit at week 4 and return complete follow-up questionnaires at week 8.
4. Visits duration: how long does it take to complete visits 1 and 2.
5. Data collection feasibility: how many patients complete all the surveys. In addition, we will calculate the proportion of study surveys that are completed per protocol

Exploratory outcomes

1. Pain diary records [timeframe: daily from 2-week run-in period until 8 weeks from treatment onset]: this will be used to measure daily pain experience on an 11-point visual analogue scale (VAS). The recording of daily pain scores will be started during the 2-week run-in period and will end 8 weeks after the intervention is over. Subjects will mark a point along a scale (from no pain [0] to worst imaginable pain [10]) on the VAS related to (a) average pain and (b) worst pain during the last 24 hours on two separate entries. This will be done at a fixed time of the day chosen by the participant. We will measure the change of average and worst pain from baseline to 4 weeks and 8 weeks post-treatment.
2. Brief Pain Inventory—Short Form (BPI-SF) [timeframe - weekly from baseline until 8 weeks from treatment onset]: The BPI-SF is a validated self-reported tool that evaluates pain severity and pain interference with daily activities at the time of assessment. A total of 4 pain intensity items (worst, least, average, and current pain) are rated on an 11-point numerical rating scale (0 = no pain, 10 = worst possible pain). The pain interference subscale includes 7 items evaluating the impact of pain on sleep, mood, walking ability, general activity, work, relationships, and enjoyment of life over the past 24 hours rated on an 11-point scale from 0 = does not interfere to 10 = completely interferes. Possible scores for pain severity range from 0 to 40 (higher scores reflect more severe pain); possible scores for pain interference range from 0 to 70 (higher scores reflect more pain interference with daily life).
3. Comprehensive Pain Assessment Tool Short Form for Chronic Pancreatitis (COMPAT-SF) [timeframe - baseline, 4 weeks from treatment onset, 8 weeks from treatment onset]: The COMPAT-SF is a validated self-reported tool specifically designed for patients with pancreatic disease. The COMPAT-SF carries several sub-scores for pain pattern, pain severity, pain provocation, pain spreading, and pain description. The pain pattern scale ranges from 50-100 with higher scores denoting worse pain. The severity score ranges from 0-100 with higher scores denoting worse pain. The provocation score ranges from 0-70 with higher scores denoting worse pain. The spreading score ranges from 0-90 with higher scores denoting worse pain. The description score ranges from 0-80 with higher scores denoting worse pain. The total score ranges from 15-90 with higher scores denoting worse pain.
4. Number of patients using prescription opioids for pain control at time of assessment [timeframe - baseline, 4 weeks from treatment onset, 8 weeks from treatment onset]: Opioid use (yes/no binary answer) at each assessment.

5. Mean reported daily opioid dose for patients using prescription opioids at time of assessment [timeframe - baseline, 4 weeks from treatment onset, 8 weeks from treatment onset]: Opioid dose (continuous variable in milligrams of morphine equivalent) at each assessment.
6. Overall Quality of Life [timeframe - baseline, 4 weeks from treatment onset, 8 weeks from treatment onset]: Overall quality of life will be assessed using the PROMIS-29 instrument. The PROMIS-29 instrument incorporates 7 domains: physical functioning, fatigue, pain interference, depression, anxiety, ability to participate in social roles and activities, and sleep disturbance. Each of these domains have a score 0-40 with higher scores representing worse quality of life in these domains. There are also 2 summary scores: Physical Health and Mental Health. Z-scores are calculated for these two summary scores with lower scores representing better quality of life.
7. Change from baseline on the Hospital Anxiety and Depression Scale (HADS) [timeframe - baseline, 4 weeks from treatment onset, 8 weeks from treatment onset]: The HADS is a validated self-reported tool that screens for symptoms of anxiety and depression. Possible scores range from 0 to 21 (higher scores reflect more severe symptoms of anxiety or depression).
8. Rates of hospital admission for pancreatitis-related hospital admissions [timeframe – 8 weeks from treatment onset]
9. Rates of treatment-related adverse events [timeframe - 4 weeks from treatment onset]
10. Patient global impression of change (PGIC) [timeframe: end of follow-up]: this is a 1-item question that should take less than 1 minute to complete. This question assesses the overall change on pain by using a 7-point Likert scale that ranges from (1) very much improved to (7) very much worse.
11. Modified abbreviated acceptability rating profile [timeframe: end of follow-up]: this is an 8-item questionnaire that should take 2 minutes (Tarnowski KJ, Simonian SJ. Assessing treatment acceptance: the Abbreviated Acceptability Rating Profile. J Behav Ther Exp Psychiatry 1992;23:101-6). Each item uses a 5-point Likert scale, including Strongly disagree, Disagree, Neutral, Agree, and Strongly agree. A final score ranges from 0-40, with 40 indicating the highest acceptability possible. This will serve to assess how study subjects perceive the acceptability of the TEA treatment for pain in CP.

Participant timeline

After enrollment, participants will have a 2-week run-in period, where they will complete daily pain diaries. If participants fulfill minimal pain requirements, participants will complete V1 to provide baseline data and will start TEA treatment. Participants will undergo TEA therapy twice a day for 4 weeks. During that time, participants will continue completing daily pain diaries and will 3 weekly phone calls to assess adverse events. After 4 weeks of TEA therapy, the participants will return the device and will complete V2, in which participants will complete questionnaires similar to V1. Participants will then continue completing daily pain diaries for additional 4 weeks, while not receiving the TEA therapy. At completion of those 4 weeks, participants will have closure V3, in which they will provide questionnaires similar to V1 and V2. The total participant's duration in the study is 10 weeks (2 weeks run-in, 4 weeks TEA treatment, and 4 weeks post TEA treatment assessment). At the end of the trial, participants will receive a close-out phone call to assess treatment acceptability.

Table 2: schedule of study visits									
Visit ID	**V0**	**V1**	**Phone call 1**	**Phone call 2**	**Phone call 3**	**Phone call 4**	**V2**	**V3 ^**	**Close-out**
Target time	**- 2 weeks**	**0**	**Within 72h**	**+1w**	**+2w**	**+3w**	**+4 weeks**	**+8 weeks**	**End of trial**
Time window	**2 weeks**	**+ 1 week**					**+ 1 week**	**+ 1 week**	
Procedure									
Eligibility evaluation	x								
Medical history and demographics	x								
Consent	x								
Pain diary (daily average & worse pain, weekly BPI-SF)	x	x					x	x	
Pain assessment (COMPAT-SF, opioids)		x					x	x	
Quality of life (PROMIS-29)		x					x	x	
Anxiety and depression (HADS)		x					x	x	
Adverse events			x	x	x	x	x		
Pancreatitis-related hospital admissions							x	x	
Patient global impression of change (PGIC)									x
Modified abbreviated acceptability rating profile									x

Recruitment

Participants will be identified using different methods. 1) We will use DataDirect to identify potential participants with chronic pancreatitis who do not have major exclusion criteria and who are actively following at the University of Michigan. This will provide a retrospective list of patients with chronic pancreatitis seen at the University of Michigan in the past 1 year. 2) The study coordinator will also identify potential participants from the list of patients scheduled for clinic visits with Dr. Machicado, Dr. DiMagno, or other members of the pancreas clinic. This will be done using MiChart. 3) The study investigators (Drs. Machicado and Dr. DiMagno) and physician colleagues seeing patients at the Comprehensive Pancreas Program will refer potential subjects to the study team. The research team will review potential study participants' medical history through the electronic medical record (MiChart) to assess patients' eligibility.

Once a subject is identified through any of the above methods, the subject will be contacted by phone using a phone script or approached in person in the outpatient clinic. The study team will follow a script and go through the pre-screen questions. If the patient is determined to be ineligible via the pre-screen questions they will be excluded from the study and logged as contacted by the study team but ineligible to participate. In doubt, the study investigator will

determine eligibility. If the subject meets eligibility criteria, the subject will be invited to participate in the study. If the subject is interested, an informed consent will be given either in person if the subject is in clinic or mailed for review & signature via eConsent or SignNow.

4. Methods: data collection

All data will be collected using active and passive methods, including patient interviews, physical examinations, and review of electronic medical records. A trained research coordinator will collect data using standardized forms via RedCap. Research coordinators will follow the manual of operations for all study procedures. All forms will include essential instructions and definitions of variables.

A. Pre-screening form: this will include questions on inclusion and exclusion criteria, pertinent for study eligibility. Initial screening will be based on chart review, in person or telephone patient interview, endoscopic results, and radiologic data that are consistent with the study definition of CP. Screening data will be obtained by the research coordinator before enrollment. This is uploaded into section 8-1.8

B. Pain diary: this will be directly completed by patients. Daily pain scores will be recorded during the 2-week run in period. In those patients who are eligible and are started in TEA, patients will complete the pain diary for 4 weeks during the TEA therapy and will continue for 4 weeks after the intervention is over. The patients will report (a) average pain during the last 24 hours using a VAS, (b) maximal pain during the last 24 hours using a VAS, and (c) weekly BPI-SF (only after intervention started). The survey is uploaded into section 29.1.

C. Baseline form: this will include data on demographics, clinical profile of CP, laboratory biomarkers, radiologic findings, and prior therapeutic interventions, all of which will be recorded from the medical records and by patients filling up a survey. In addition, patients will complete a form pertaining to pain, quality of life, anxiety and depression using the instruments described in secondary outcomes.

D. First follow-up form: this form will be used to assess pain, quality of life, anxiety and depression after the intervention, using the instruments described in secondary outcomes. Adverse events of the intervention will also be recorded in this form. These surveys are uploaded into section 29.1.

E. Second follow-up form: This form will be given to participants during the first follow-up (V2). Subjects will be asked to complete and mail the follow-up questionnaires and diary. This form will be used to assess pain, quality of life, anxiety and depression after the intervention has been discontinued. These surveys are uploaded into section 29.1.

All data will then be captured in a password-protected database through Redcap. Several methods will be used to promote data quality and integrity including database development, proper training of study team members, and use of data quality rules and validation. Each subject will be assigned a unique random number, and Protected Health Information will be coded to

ensure no one outside the study team will be able to identify a subject's identity. This database will be stored in a password-protected database, in a password-protected folder on a secure server behind the University of Michigan firewall. The information will, at all times, only be able to be accessed by the study investigators.

F. After enrollment is completed, study subjects who enrolled and received TEA will be reached out via a phone call to assess on global impression and acceptability of the treatment. Study subjects will be asked the following questions in relation to the use of TEA on their chronic pancreatitis pain.

- Patient global impression of change (PGIC): this is a 1-item question that should take less than 1 minute
- Modified abbreviated acceptability rating profile: this is an 8-item questionnaire that should take 2 minutes (Tarnowski KJ, Simonian SJ. Assessing treatment acceptance: the Abbreviated Acceptability Rating Profile. J Behav Ther Exp Psychiatry 1992;23:101-6).
- Two open questions: (i)"How did the TEA device help you in managing your pancreatitis pain?" and (ii)"What modifications would you suggest to improve the TEA treatment?"

5. Statistical methods

Sample size calculation

We will conduct an open-label pilot study of 10 subjects with CP that fulfill eligibility criteria and that receive the TEA device during visit 1. This will serve to inform feasibility on enrollment, adherence, retention, and completion of data collection. Data obtained in this study will lead to protocol changes for a larger randomized controlled trial that we will plan in the future. The study will be under powered to address any clinical outcomes. We anticipate attrition of approximately 10% for a study of this nature.

Statistical analysis

All analyses will be performed according to the intention-to-treat principle. All primary outcomes will be measured using descriptive statistics as absolute values (percentage), mean ± standard deviation (SD), and median (interquartile range [IQR]), as appropriate.

Primary outcomes

A. Enrollment feasibility:
    - Proportion of approached participants who meet eligibility criteria.
    - Proportion of those who meet eligibility criteria and who provide informed consent
    - Proportion of participants who meet the criteria after the run-in period among those who provided informed consent.
    - Proportion of participants who start the intervention among those who meet run-in period criteria.

B. Adherence: proportion of participants who adhere to the intervention as prescribed among those who start the intervention

C. Retention feasibility: proportion of patients who complete follow up visit at 4 weeks and return complete follow-up questionnaires at week 8, among those who started the intervention

D. Visit duration:

- For visit 1, median (IQR) of the time that takes to complete visit 1.
- For visit 2, the median (IQR) of the time that takes to complete visit 2.

E. Data collection feasibility:
- Proportion of participants who come for visit 1 and complete all the surveys involved in the study.
- Proportion of study surveys that are completed per protocol

Exploratory endpoints

- Worst pain on visual analogue scale
  - Mean ± SD of worst pain during the run-in period (baseline)
  - Mean ± SD of worst pain during the treatment period (week 0-4)
  - Mean ± SD of worst pain during the last week of treatment (week 4)
  - Mean ± SD of worst pain after completion of treatment (week 5-8)
  - Mean ± SD of worst pain during the last week without treatment (week 8)
  - Mean difference of worst pain score from the last week of treatment compared to baseline worst pain.
  - Rank-sum test or paired t test depending on data distribution to compare worst pain score from the last week of treatment compared to baseline worst pain.
  - Mean difference of worst pain score after completion of treatment compared to worst pain during the last week of treatment
  - Rank-sum test or paired t test depending on data distribution to compare worst pain score after completion of treatment compared to pain severity from the last week of treatment.

- Average pain on visual analogue scale
  - Mean ± SD of average pain during the run-in period (baseline)
  - Mean ± SD of average pain during the treatment period (week 0-4)
  - Mean ± SD of average pain during the last week of treatment (week 4)
  - Mean ± SD of average pain after completion of treatment (week 5-8)
  - Mean ± SD of average pain during the last week without treatment (week 8)
  - Mean difference of average pain score from the last week of treatment compared to baseline average pain.
  - Rank-sum test or paired t test depending on data distribution to compare average pain score from the last week of treatment compared to baseline average pain.

- Mean difference of average pain score after completion of treatment compared to average pain during the last week of treatment
- Rank-sum test or paired t test depending on data distribution to compare average pain score after completion of treatment compared to pain severity from the last week of treatment.

- Pain severity on BPI-SF
  - Mean ± SD of pain severity during the run-in period (baseline)
  - Mean ± SD of pain severity during the treatment period (week 0-4)
  - Mean ± SD of pain severity during the last week of treatment (week 4)
  - Mean ± SD of pain severity after completion of treatment (week 5-8)
  - Mean ± SD of pain severity during the last week without treatment (week 8)
  - Mean difference of pain severity from the last week of treatment compared to baseline pain severity.
  - Rank-sum test or paired t test depending on data distribution to compare pain severity from the last week of treatment compared to baseline pain severity.
  - Mean difference of pain severity after completion of treatment compared to pain severity during the last week of treatment
  - Rank-sum test or paired t test depending on data distribution to compare pain severity after completion of treatment compared to pain severity from the last week of treatment.

Pain interference on BPI-SF
- Mean ± SD of pain interference during the run-in period (baseline)
- Mean ± SD of pain interference during the treatment period (week 0-4)
- Mean ± SD of pain interference during the last week of treatment (week 4)
- Mean ± SD of pain interference after completion of treatment (week 5-8)
- Mean ± SD of pain interference during the last week without treatment (week 8)
- Mean difference of pain interference from the last week of treatment compared to baseline pain interference.
- Rank-sum test or paired t test depending on data distribution to compare pain interference from the last week of treatment compared to baseline pain interference.
- Mean difference of pain severity after completion of treatment compared to pain severity during the last week of treatment
- Rank-sum test or paired t test depending on data distribution to compare pain severity after completion of treatment compared to pain severity from the last week of treatment.

- Pain by COMPAT-SF
  - Mean ± SD of COMPAT-SF score at onset of treatment (at baseline during visit 1)
  - Mean ± SD of COMPAT-SF score at end of treatment (at 4 weeks during visit 2)
  - Mean ± SD of COMPAT-SF score at end of follow-up without treatment (at 8 weeks)
  - Mean difference of COMPAT-SF score from end of treatment compared to score at baseline.
  - Rank-sum test or paired t test depending on data distribution to compare COMPAT-SF score from end of treatment compared to baseline score

  - Mean difference of COMPAT-SF score at end of follow-up without treatment compared to score at baseline
  - Rank-sum test or paired t test depending on data distribution to compare COMPAT-SF score from end of follow-up without treatment compared to baseline score
  - Mean difference of COMPAT-SF score at end of follow-up without treatment compared to score at end of treatment
  - Rank-sum test or paired t test depending on data distribution to compare COMPAT-SF score from end of follow-up without treatment compared to score at end of treatment

- Proportion of patients using opioids
  - Proportion of patients using prescription opioids for pain control at onset of treatment (at baseline during visit 1)
  - Proportion of patients using prescription opioids for pain control at end of treatment (at 4 weeks during visit 2)
  - Proportion of patients using prescription opioids for pain control at end of follow-up without treatment (at 8 weeks)
  - McNemar Test to compare proportion of patients using opiates at end of treatment compared to baseline
  - McNemar Test to compare proportion of patients using opiates at end of follow-up without treatment compared to baseline
  - McNemar Test to compare proportion of patients using opiates at end of follow-up without treatment compared to end of treatment

- Reported dose of opiates b y milligrams of morphine equivalent (MME)
  - Mean ± SD of MME at onset of treatment (at baseline during visit 1)
  - Mean ± SD of MME at end of treatment (at 4 weeks during visit 2)
  - Mean ± SD of MME at end of follow-up without treatment (at 8 weeks)
  - Mean difference of MME from end of treatment compared to baseline.
  - Rank-sum test or paired t test depending on data distribution to compare MME from end of treatment compared to baseline
  - Mean difference of MME at end of follow-up without treatment compared to baseline
  - Rank-sum test or paired t test depending on data distribution to compare MME from end of follow-up without treatment compared to baseline
  - Mean difference of MME at end of follow-up without treatment compared to MME at end of treatment
  - Rank-sum test or paired t test depending on data distribution to compare MME from end of follow-up without treatment compared to MME at end of treatment

- Physical quality of life (QOL)
  - Mean ± SD of physical QOL at onset of treatment (at baseline during visit 1)
  - Mean ± SD of physical QOL at end of treatment (at 4 weeks during visit 2)
  - Mean ± SD of physical QOL at end of follow-up without treatment (at 8 weeks)
  - Mean difference of physical QOL from end of treatment compared to baseline.
  - Rank-sum test or paired t test depending on data distribution to compare physical QOL from end of treatment compared to baseline

  - Mean difference of physical QOL at end of follow-up without treatment compared to baseline
  - Rank-sum test or paired t test depending on data distribution to compare physical QOL from end of follow-up without treatment compared to baseline
  - Mean difference of physical QOL at end of follow-up without treatment compared to physical QOL at end of treatment
  - Rank-sum test or paired t test depending on data distribution to compare physical QOL from end of follow-up without treatment compared to physical QOL at end of treatment

- Mental quality of life (QOL)
  - Mean ± SD of mental QOL at onset of treatment (at baseline during visit 1)
  - Mean ± SD of mental QOL at end of treatment (at 4 weeks during visit 2)
  - Mean ± SD of mental QOL at end of follow-up without treatment (at 8 weeks)
  - Mean difference of mental QOL from end of treatment compared to baseline.
  - Rank-sum test or paired t test depending on data distribution to compare mental QOL from end of treatment compared to baseline
  - Mean difference of mental QOL at end of follow-up without treatment compared to baseline
  - Rank-sum test or paired t test depending on data distribution to compare mental QOL from end of follow-up without treatment compared to baseline
  - Mean difference of mental QOL at end of follow-up without treatment compared to mental QOL at end of treatment
  - Rank-sum test or paired t test depending on data distribution to compare mental QOL from end of follow-up without treatment compared to mental QOL at end of treatment

- Hospital anxiety and depression scale (HADS)
  - Mean ± SD of HADS score at onset of treatment (at baseline during visit 1)
  - Mean ± SD of HADS score at end of treatment (at 4 weeks during visit 2)
  - Mean ± SD of HADS score at end of follow-up without treatment (at 8 weeks)
  - Mean difference of HADS score from end of treatment compared to baseline.
  - Rank-sum test or paired t test depending on data distribution to compare HADS score from end of treatment compared to baseline
  - Mean difference of HADS score at end of follow-up without treatment compared to baseline
  - Rank-sum test or paired t test depending on data distribution to compare HADS score from end of follow-up without treatment compared to baseline
  - Mean difference of HADS score at end of follow-up without treatment compared to HADS score at end of treatment
  - Rank-sum test or paired t test depending on data distribution to compare HADS score from end of follow-up without treatment compared to HADS score at end of treatment

- Pancreatitis related hospitalizations
  - Proportion of patients who had a pancreatitis related hospitalization during the treatment period

  - Proportion of patients who had a pancreatitis related hospitalization during the follow up period without treatment
  - Proportion of patients who had a pancreatitis related hospitalization during the study period

- Adverse events
  - Proportion of patients who had an adverse event due to the intervention

- Patient Global Impression of Change
  - Proportion of patients who consider their pain improved (PGIC ≤3)

- Treatment acceptability
  - Proportion of patients who agree or strongly agree that the treatment was an acceptable intervention for dealing with chronic pancreatitis pain

For missing data, we will use multiple imputation methods. Statistical significance will be defined as $P<0.05$.

6. Safety management

Safety monitoring

The risks of TEA are minor, including possible allergic response to the standard ECG electrodes. The likelihood of this risk is low, approximate incidence of <1%. Since TEA uses current flow through the skin, there is a possibility of uncomfortable sensation or pain at the skin, abnormal or involuntary movements (chorea, dystonia, dyskinesia), gastrointestinal disturbances or nausea. However, the stimulation output will be set at a level that is well tolerated by the participant. In very rare occasions, the participant might experience rash or minor infection at the stimulation point that can be treated locally if needed. If this occurs, the device can be moved to the opposite leg at the same location. If the patient develops a local rash or minor infection in the opposite leg, the patient will discontinue the treatment and notify the study team. To protect subjects against risks, subjects will be instructed to avoid manipulating or rubbing the electrodes to avoid any electrode deformations or breakage. Subjects will be instructed to stop the TEA therapy immediately once they experience uncomfortable sensation or pain at the electrode site.

Participants may develop discomfort related to reporting daily symptoms and repeated surveys where they are asked about their health and well-being. In order to decrease this risk, the number of surveys have been prioritized to the most relevant surveys necessary to assess compliance. Finally, there is a risk for embarrassment from responding to the questionnaires, as many of the questions are pertaining to negative experiences such as pain, anxiety, depression, and quality of life. The participants will be allowed to skip question that cause them to feel discomfort.

Finally, there is a small risk of compromised confidentiality, which is associated with analysis and sharing of medical data. The likelihood of this risk is low, estimated to be <1%. To reduce this risk, each subject will be assigned an ID number, and all data will be stored with the subject ID number only and not the subject's name. All data records entered into the study electronic data capture (EDC) system will be stored on the HIPAA- compliant cloud data server, which is

encrypted and password protected, and the EDC system will comply with the 21 CFR Part 11 requirements for electronic record keeping. All locally-stored data will be on a password-protected computer. Subject charts with medical history and assigned subject numbers will be kept in locked file cabinets stored at the clinical site. Access to charts will be granted only to study investigators. Charts will be kept confidential and will not be shared with any third parties without permission from the subject.

Patients who develop a serious adverse event (SAE), as defined by the Food Drug Administration (FDA) [25], will have the study intervention discontinued, and be managed medically as deemed appropriate by the patient's clinical team. A SAE is defined by the FDA if the AE results in any of the following outcomes: death, a life-threatening AE, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. For related, unexpected, serious device events resulting in death and life threatening outcome (per IRBMED guidelines) these will be submitted as soon as possible but within 7 calendar days of becoming aware of the event.

The study team will submit to the reviewing IRB a report of any unanticipated adverse device effect occurring during an investigation as soon as possible, but in no event later than 14 calendar days after the investigator first learns of the effect.

7. Ethics and dissemination

TEA is similar to a transcutaneous electrical nerve stimulation unit that is classified by FDA as a non-significant risk device. Therefore, an investigational device exemption (IDE) for the FDA will not be needed.

The study will require approval by the IRB of the University of Michigan. Any protocol amendments will be communicated to the IRB. Informed consent will be obtained by the study coordinator face to face or by phone from eligible participants or authorized surrogates. If consent is obtained remotely, subjects will be sent a copy of the consent via mail and sign the consent virtually using eConsent or SignNow. Data will be captured in a password protected database. Each subject will be assigned a unique random number, and Protected Health Information will be de-identified after complete data extraction. The final dataset will only be accessible by the primary investigator and data analyst.

The final results may be presented at meetings, in publications, or in future funding applications; however, such presentations will be of aggregate data only without disclosure of any individual subject identities or PHI. The results of the trial will be posted in Clinicaltrials.gov. After study results are disseminated, deidentified participant data and the analytic code can be requested by external researchers to the principal investigator.

8. Timeline and feasibility

Over the past 3 years, the Comprehensive Pancreas Program of the University of Michigan has provided care to 314 new patients with CP or roughly 104 new patients per year. In addition, our program provides longitudinal care to patients with CP, resulting in 608 return visits for CP over the past 3 years or roughly 203 returns visits per year. Among these patients, it is expected that

87% have chronic abdominal pain.[26] Dr. Jiande Chen (CO-I), leads two research studies using TEA in patients with irritable bowel syndrome and diabetic gastroparesis as the University of Michigan (HUM00189911, HUM00217301).

Our proposed timeline is to complete the study in 12 months. This study will ensure feasibility of interventions, enrollment methods, and data collection tools. Results of this study will support a larger and longer study.

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