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Transcutaneous Electroacupuncture for Gastrointestinal Motility Disorders (TEA)

Date: 09/15/2022

JHM IRB - eForm A – Protocol

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1. Abstract

a. Provide no more than a one page research abstract briefly stating the problem, the research hypothesis, and the importance of the research.

Gastrointestinal (GI) dysmotility is common in GI motility disorders, such as functional dyspepsia (FD) gastroparesis and chronic constipation. The symptoms of GI dysmotility include abdominal discomfort or pain, early satiety, nausea, vomiting, abdominal distension, bloating, anorexia and reduced bowel movement. . Medical treatment for GI motility disorders is very limited in the US. Acupuncture has frequently been used for treatment of GI ailments in Eastern countries. The most commonly used acupuncture points (acuponts) for focused treatment of GI symptoms are the Neiguan (PC6) and the Zusanli (ST36) points. Electroacupuncture (EA) at PC6 and ST36 has been reported to accelerate gastrointestinal motility in both animals and human.

Recently, we have studied the feasibility of transcutaneous electroacupuncture (TEA): electrical stimulation is applied to acupoints via surface electrodes without needles, similar to the commercial available transcutaneous electrical nerve stimulation (TENS) but applied to acupoints. We hypothesize that TEA as a new treatment option, improves GI symptoms in patients with FD, gastroparesis or constipation, improves GI motility and therefore improves quality of life of the patients.

The success of this project will lead to a noninvasive and convenient therapy for treating GI motility disorders. The proposed TEA method is expected to improve gastric and colonic functions and thus improve quality of life. In addition, the proposed TEA method and device are self-administrative after training during the first office visit. It provides a long-term treatment option for both FD, gastroparesis and chronic constipation.

2. Objectives (include all primary and secondary objectives)

1. Effects of TEA on GI symptoms, in patients with FD or gastroparesis or chronic constipation.

2. Mechanisms of TEA for treating GI motility disorders: TEA improves gastric accommodation, gastric dysrhythmia, and the improvement in these pathological abnormalities may be associated with the enhancement of vagal activity and the release of GI hormones.

3. Background (briefly describe pre-clinical and clinical data, current experience with procedures, drug or device, and any other relevant information to justify the research)

FD affects millions of Americans but is difficult to treat due to its multiple abnormalities in gastric motor and sensory functions. Common treatment options include dietary measures, pharmacologic treatments, such as acid-suppression drugs, prokinetic agents, fundus relaxing drugs, and antinociceptive agents, and psychologic interventions (1-3). In general, targeted therapies directed at the underlying pathophysiology are desirable. However, efficacy of the therapy is usually very limited due to multiple symptoms and pathophysiologies in individual patients. For example, a patient may have impaired accommodation and delayed gastric emptying at the same time; in this case, prokinetic agents can be used to treat delayed emptying but would worsen the symptoms related to gastric accommodation because available prokinetics often impair gastric accommodation. For the same reason, fundus relaxing drugs may be used for treating impaired accommodation; however, these drugs may delay gastric emptying because they relax muscles. The treatment approach to patients with hypersensitivity to gastric distension has not been established. Antidepressants are commonly used in functional GI disorders and were thought to exert a visceral analgesic rather than an antidepressant effect. However, studies of the effects of antidepressants on visceral sensitivity are rare, and the existing data on visceral sensitivity are controversial (4).

Gastroparesis is defined as delayed empting of solids from the stomach. The common symptoms of gastroparesis are similar to FD, resulting from impaired gastric motility. Same as FD, currently very limited treatment options are available for gastroparesis. A number of prokinetics were developed for treating gastroparesis but have been withdrawn from the market due to their side effects.

Constipation is highly prevalent in the US. Currently most patients are dependent on laxatives that do not cure the disease and long-term use may actually worsen the condition. In addition, due to an alarming increase in the use of opiates for pain, opiate-induced constipation became a big medical problem.

Acupuncture is a Traditional Chinese Medicine method which has been used in the treatment of patients for thousands of years. Acupuncture is being increasingly accepted by practitioners and patients in the West as well, especially during the last three decades. Electroacupuncture (EA) is a modification of this technique that stimulates acupuncture points (or acupoints) with electrical current instead of manual manipulations, and appears to have more consistently reproducible results in both clinical and research settings. EA has been used to treat GI symptoms, including acute and chronic gastroenteritis, diarrhea, constipation, vomiting, nausea, and gastroduodenal ulcers by altering acid secretion, GI motility, and visceral pain (5-6).The most commonly used EA points in treating GI symptoms are the Zusanli point of the lower limbs (stomach-36 or ST-36) and the Neiguan point at the wrist (pericardium-6 or PC-6). EA at PC6 and ST36 has been shown to improve gastric motility in both animals and humans (7-8). Recently, a number of studies have been performed to examine the efficacy of EA for the treatment of visceral pain. It has been shown that repeated EA attenuated visceral hypersensitivity in irritable bowel syndrome (IBS) rat model (9), and EA at ST-36 and PC-6 significantly increases the threshold of rectal sensations to rectal distension in IBS patients (10-11). It remains to be investigated whether EA improves GI symptoms, motility in patients with FD or gastroparesis.

Recently, we have studied the feasibility of transcutaneous electroacupuncture (TEA): electrical stimulation is applied to acupoints via surface electrodes without needles. This method is similar to the commercial available transcutaneous electrical nerve stimulation (TENS) but applied to acupoints. Compared to the traditional EA, TEA is needleless, self-administrative, therefore may benefit patients with impaired gastric motility.

We hypothesize that TEA as a new treatment option, improves GI symptoms in patients with FD gastroparesis or chronic constipation, accelerate impaired GI motility and therefore improves quality of life of the patients.

4. Study Procedures

a. Study design, including the sequence and timing of study procedures

A double-blinded crossover design will be used for the study (Fig. 1). Forty patients with FD, forty patients with gastroparesis and forty patients with chronic constipation will be blinded about the treatment regimens and patients who are familiar with the acupoints or meridian will be excluded.

Revisions to the informed consent process are being permanently adopted for this research. Teleconsent will be used as opposed to in person consenting where possible to reduce unnecessary in person encounters specifically for a consent procedure. In the event teleconsent is utilized, participants will be provided with a copy of the Informed Consent prior to the teleconsent meeting either via email, fax, mail or previously provided during an in person visit.

Participants will be given adequate time to consider the research study and ask questions prior to signing the consent form. The consent designee must verify the participant physically signed the consent document either by viewing via video conference, obtaining a photo of the signed consent document; or obtaining verbal confirmation from the participant that he/she signed the consent form or agreed to participate electronically. The participant will sign and date/time the informed consent document. The document is then mailed, emailed or faxed to the consent designee. The participant will be asked to return the original signed document on their first in person visit. If the Informed Consent form is mailed to the consent designee by the participant the study coordinator will sign the copy, which they possess after the participant has acknowledged signature on their copy. Once the original is received by the consent designee the copies will be attached to make a single document. In all other instances, once received, the research coordinator signs, dates/times the informed consent document.

At the time of the first clinical encounter post teleconsent, research coordinator will review any additional study participant questions and discuss the risks, benefits and alternatives of the study in full detail, completing the physician/mid-level component of the consent process. After the Informed Consent process is completed, a study team member will file the consent document in EPIC. The entire consent document is also then filed in the research record.

Upon enrollment, each patient will be randomly assigned to group A or group B. Patients in group A will be treated with TEA at ST36 and PC6 for 4 weeks, followed with a 2-week washout period and another 4-week period with sham TEA. Patients in group B will be treated with TEA and sham-TEA in a reversed order. The previous preliminary studies with EA or TEA were of duration of 2 weeks. To ensure better performance, we choose a treatment period of 4 weeks. A previous study has indicated that a washout period of 2 weeks is sufficient. The patients will not be informed of the exact locations of ST36 or PC6 and will not be informed that TEA at the sham points may be ineffective. The patients will be asked to come to the hospital 4 times: before the study (V1), end of the first 4 weeks (V2), end of washout period or beginning of the second 4-weeks (V3) and end of the second 4 weeks (V4). TEA or sham TEA will be performed three times daily, each initiated immediately after a meal and lasts for 2 hours. Various tests will be performed during each visit (see Fig.1 and Table 1). Symptoms of gastroparesis, assessment of constipation and questionnaire of quality of life (SF-36) as well as

TEA usage questionnaire will be completed during each of the 4 visits. The questionnaires will also be completed by the patient at home at the end of each week including the washout period.

The procedure for each visit is as follows: In the morning, GI symptom questionnaire, TEA use and SF-36 will be completed; then chest and abdominal surface electrodes will be placed and the noninvasive measurements of electrogastrogram (EGG) will be recorded for 2 hours. One hour after the recording, a test meal will be consumed by the subject and the recording will be continued for one more hour. Blood samples will be taken to measure gastrointestinal hormones such as NPY, ghrelin, CCK, motilin and VIP at different time points: at the initiation of the baseline recording of the EGG, immediately before the ingestion of the meal, 30 and 60min after the test meal. TEA or sham-TEA (according to the preceding treatment regime) will be performed during the tests for visits 2 and 4. No TEA or sham-TEA will be performed during visits 1 and 3 as these tests will be considered as baseline or control tests. For the patients with chronic constipation, no nutrient drink test will be conducted, symptoms related to constipation will be assessed, EGG will be recorded and blood samples will be collected.

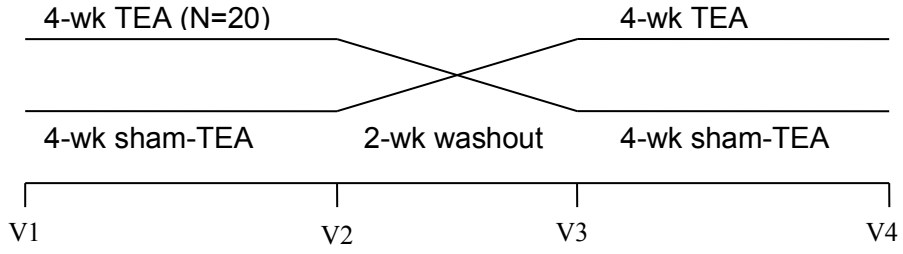

Table 1: Measurements during each of the scheduled visits (For patients with FD or Gastroparesis)

Time	GI Symptom Questionnaire	TEA Use	SF-36	EGG	Blood
Week 0 (V1)	+		+	+	+
Week 1	+	+			
Week 2	+	+			
Week 3	+	+			
Week 4 (V2)	+	+	+	+	+
Week 6 (V3)	+		+	+	+
Week 7	+	+			
Week 8	+	+			
Week 9	+	+			
Week10 (V4)	+	+	+	+	+

Notes:

- Abbreviations: V: visit; EGG: electrogastrogram.
- TEA Use questionnaires will be administered by telephone during weeks 1-3 and 7-9.

Transcutaneous electroacupuncture

Location of acupuncture points: Two acupoints, ST36 (Zusanli) and PC6 (Neiguan) will be chosen for the TEA therapy. These two acupoints have been traditionally used to heal the ailment of stomach and frequently chosen in research studies, including our previous studies (13-15). PC6 is a common acupuncture point used for the treatment of nausea and vomiting,

whereas ST36 is one of the most frequently used acupuncture points for the treatment of gastric diseases. These two points were also used in our previous studies in humans and were shown to be effective in treating dyspeptic symptoms and improving gastric motility (13-15). The location of ST36 (Zusanli) is at the depression inferior to tibia tubercle and one finger-breadth (the patient's thumb finger) from the anterior crest of the tibia. Anatomically, it is between the muscle anterior tibialis and muscle extensor digitorum longus. Superficially, there are the lateral sural cutaneous nerve and the cutaneous branch of the saphenous nerve at this acupoint. Profoundly, there is the deep peroneal nerve (16). PC (Pericardial meridian) 6 (Neiguang) is located at the junction of the distal one sixth and the proximal five sixth from the transverse crease of the wrist to the transverse cubital crease, between the tendons of m. palmaris longus and m. flexor carpi radialis. Superficially, there is muscle flexor digitorum superficialis at the location. Profoundly, there is muscle flexor digitorum profoundus. The medial antebrachial cutaneous nerve, the median nerve (deeper) and the anterior interrosseous nerve (deepest) are distributed at the location.

TEA and sham-TEA: TEA will be performed continuously for 2 hrs immediately after each meal. The patient will be trained by the unblinded stimulator programmer to place electrodes in the right locations of the body and will not be told whether the points are sham or real. Two electrodes will be placed for each acupoint: one right at the acupoint and the other 4 to 6 cm away from the acupoint along the meridian of the acupoint (Fig.2). One PC6 point and one ST36 point will be used. Fig.2 shows the placement of stimulation electrodes and stimulator at the PC6 point. Weak electrical pulses are delivered from the stimulator (the wrist watch-like unit).

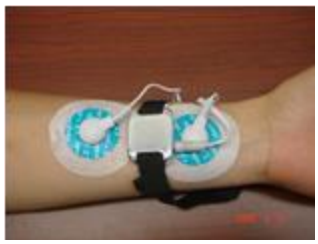

Fig.2: The micro-stimulator (watch-like) to be used for TEA.

Sham-TEA will be performed using sham-points with the same output from the stimulators. The sham points for PC6 and ST36 will be at non-acupoints a few centimeters away from the real points between meridians.

Trains of pulses will be used for TEA or sham-TEA with train on-time of 2sec and off-time of 2sec. Pulses in each train will have a frequency of 25Hz and an amplitude range of 2-10mA, based on patient tolerability. These parameters were previously shown to be effective in treating GI symptoms in patients with scleroderma and FD (13, 14).

When TEA is performed outside hospital, the patient will be asked to continue his or her regular activity. Instructions for the use of the device by the patient at home will be given and include the following: 1) a picture showing the locations where the electrodes should be attached; 2) placement of stimulators; 3) instructions for turning on and off the micro-stimulator (all stimulation parameters will be programmed by the investigator and not alterable by the patient); 4) a timer will be given to the patient and the patient will be reminded when the stimulator should be disconnected to the electrodes; 5) instructions for the removal and storage of the electrodes and stimulator as well as charge of the stimulators.

Assessment of gastroparetic symptoms, quality of life and use of TEA

Dyspeptic and gastroparetic symptom questionnaire will use the previously validated gastroparesis cardinal symptom index (17), including 9 symptoms: nausea (feeling sick to your stomach as if you were going to vomit or throw up), retching (heaving as if to vomit, but nothing comes up), vomiting, stomach fullness, not able to finish a normal sized meal, feeling excessively full after meals, loss of appetite, bloating (feeling like you need to loose your clothes) and stomach or belly visibly larger. Each symptom will be graded from 0 to 5 (none, very mild, mild, moderate, severe and very severe).

Quality of life questionnaire Health-related QOL (HR-QOL, or QOL) symptom assessment will be performed using the validated SF-36 health form questionnaire with its specific scoring system.

TEA use questionnaire 1) How many meals did you eat in the last 7 days? 2) How many of these meals did you apply the TEA? 3) When you use the TEA, about how long do you wear the stimulators?

Assessment of sympoms for patients with chronic constipation

Symptoms: 1) Number of spontaneous complete bowel movement (SCBM) per week. 2) Patient Assessment of Constipation Symptoms (PAC-SYM). Stool diary during the entire experimental period to assess bowel movement, including number and time of defecation, stool quality, straining and medications or any other methods used for defecation; stool consistency will be assessed according to the Bristol Stool Form Scale. PAC-SYM questionnaire will be completed every two weeks. 3) Quality of life (PAC-QoL): the questionnaires will be completed at all visits.

Measurements of EGG and GI hormones

The noninvasive measurement of the EGG will be made and blood samples will be taken in order to answer the following questions: 1) whether there is an alteration or impairment in gastric slow waves, vagal activity and/or certain gastrointestinal hormones in patients with FD or gastroparesis, compared with healthy controls; 2) whether TEA is able to improve the impairment if any; 3) if TEA improves some of these abnormalities, whether the improvement is correlated with the improvement in FD or gastroparesis.

The EGG measurements will be made in each patient during each visit (starting at 9am) with the following protocol: a 30-min baseline recording without TEA or sham-TEA, another 30-min recording with TEA or sham-TEA, consumption of the test meal for the gastric emptying test described above and a 60-min postprandial recording. Blood samples (5ml) will be drawn at the beginning of the tests, beginning of the meal and 30-min and 60-min after the meal.

Recording and analysis of the EGG: A noninvasive method, called electrogastrography, will be used in this study to assess the effects of acute and chronic TEA on gastric slow waves (18). The EGG will be recorded using a multichannel recording device which is a standard piece of FDA-approved clinical equipment. The device consists of four identical amplifiers with cut-off frequencies of 1.8 and 16.0 cpm (19). The data will be converted from analogue to digital with a sampling frequency of 1Hz on line and stored. Patients will remain at 30 degrees head elevation and be required to remain motionless in order to avoid possible artifacts derived from body movements. Four-channel EGG signals will be recorded. Previously validated spectral analysis methods will be used to derive the following parameters from the EGG (19): a) dominant frequency and power of the slow waves; b) the percentage of normal 2-4 cycles/min slow waves and c) the percentage of tachygastria, bradygastria or arrhythmia.

Measurement and analysis of GI hormones: A number of GI hormones/neuropeptides are involved in the regulation of gastric motility. The major excitatory neuropeptides include motilin, ghrelin, neuropeptide Y (NPY), cholecystokinin CCK and substance P, whereas vasoactive intestinal peptide (VIP) and nitric oxide are the major inhibitory neuropeptides. Electroacupuncture has been shown to be effective in altering ghrelin, NPY and VIP in rats (22-24). Little information is available on the effects of EA in patients with motility disorders. In our preliminary studies, we observed an increase in NPY with TEA in patients with functional dyspepsia and a decrease in VIP with TEA in patients with scleroderma. In this study, we choose to study the effects of TEA on NPY, ghrelin, CCK, motilin and VIP.

Blood samples will be collected in chilled EDTA tubes, centrifuged at 2°C for 10 minutes, and stored at -70°C until extraction. Plasma NPY, VIP, motilin, CCK and ghrelin levels will be determined using commercially available radioimmunoassay kits. In addition, some blood samples will be reserved for the analysis of other hormones related to GI motility and sensation.

b. Study duration and number of study visits required of research participants.

The study duration will be for 10 weeks, each patient will have 4 visits.

c. Blinding, including justification for blinding or not blinding the trial, if applicable.

Blinding of investigator is not practical as the investigator will be performing the procedure such as locate acupoints or sham-acupoints. However, the patients will be blinded to the TEA/sham TEA treatment.

d. Justification of why participants will not receive routine care or will have current therapy stopped.

Not Applicable.

e. Justification for inclusion of a placebo or non-treatment group.

Not Applicable. All the patients will have TEA treatment.

f. Definition of treatment failure or participant removal criteria.

Treatment failure will be defined as a lack of improvement in symptoms pre and post TEA treatment based on validated questionnaires and gastric motility assessment 6 and 12 months after the last treatment. Participant removal criteria will include any patient with moderate to severe adverse reaction to TEA or inability to tolerate the TEA conforming to standards of usual routine care.

g. Description of what happens to participants receiving therapy when study ends or if a participant's participation in the study ends prematurely.

The participant will follow up with their referring gastroenterologist and continued therapy will be left to the discretion of their provider.

5. Inclusion/Exclusion Criteria

Inclusion criteria for FD patients

1. Bothersome postprandial fullness
2. Symptoms of early satiation, epigastric pain, epigastric burning during the last 3 months
3. No evidence of structural disease including at upper endoscopy that is likely to explain the symptoms.
4. Males and females between ages 18-80 yrs;
5. Subjects with high probability for compliance and completion of the study.

Inclusion criteria for gastroparesis patients

1. At least one severe gastroparetic symptom or two moderate gastroparetic symptoms (see assessment of gastroparetic symptoms);
2. Abnormal gastric emptying diagnosed during the past year;
3. Males and females between ages 18-80 yrs;
4. Subjects with high probability for compliance and completion of the study.
5. Upper endoscopy or upper GI within last 2 years showing no evidence of gastric bezoar,

stricture, or peptic ulcer.

Inclusion criteria for chronic constipation patients

1. Satisfying Rome IV criteria for diagnosis of functional constipation;
2. abdominal X-ray or anorectal manometry test during the past 3 months indicating delayed colonic transit (more than 20% ingested markers are retained) or abnormal colonic motility;
3. ages 18-80 years;
4. no constipation medication for a minimum of 1 week before enrollment except for rescue agents (stimulant laxatives, such as bisacodyl);
5. willing to comply with the treatment regimen.

Exclusion criteria:

1. History of gastric bezoar or diverticulitis.
2. Severe daily abdominal pain requiring narcotic medications.
3. Previous gastro-esophageal surgery including vagotomy, fundoplication, gastric bypass, ulcer surgery.
4. Prior GI surgery except for uncomplicated appendectomy and laparoscopic cholecystectomy;
5. Surgery within the past 3 months.
6. pregnant or preparing to conceive a child;
7. Female of childbearing age who is not practicing birth control and/or is pregnant or lactating. (Confirm with urine pregnancy test).
8. Those who have been treated with acupuncture or those who are familiar with acupuncture points.
9. Anyone with an implantable cardiac pacemaker or defibrillator.
10. Allergic to skin preparation
11. unable to give informed consent;
12. taking prokinetics, anticholinergic or dopaminergic agents;
13. history of gastrointestinal surgery;

6. Drugs/ Substances/ Devices

a. The rationale for choosing the drug and dose or for choosing the device to be used.

We have chosen previously validated questionnaires as our tools to monitor symptom response to TEA/Sham TEA. The tests used in the current protocol are also been validated and are part of the routine clinical care.

The microstimulator device used in the current protocol is a non-invasive device. It is developed under the support of previous NIH funding and has been used in the clinical study in an earlier project funded by NIH (Fig. 2)

b. Justification and safety information if FDA approved drugs will be administered for non-FDA approved indications or if doses or routes of administration or participant populations are changed.

N/A

c. Justification and safety information if non-FDA approved drugs without an IND will be administered.

N/A

7. Study Statistics

a. Primary outcome variable.
The primary outcome of this study is GI symptoms including weekly GI symptom questionnaire; number of spontaneous complete bowel movement (SCBM) per week; and Patient Assessment of Constipation Symptoms (PAC-SYM), once every two weeks.

b. Secondary outcome variables.
The secondary outcome measure of the study will include:

1. TEA use questionnaire.
2. Monthly assessment of quality of life questionnaire.
3. Autonomic functions,
4. GI hormones.

c. Statistical plan including sample size justification and interim data analysis.

Analysis of the outcomes will use a repeated measures regression model including fixed effects for treatment, patient and time period. The model will be estimated using 8 weekly observations (weeks 1-4 and 7-10) on percentage changes in symptoms score from baseline visit (V0) levels for each subject. Results will be expressed as least squares means for the percentage change in symptoms score observe under each treatment, and statistical significance of any difference between these means will be determined with a model-based t-test. A weekly estimate of percentage compliance with the prescribed TEA-use regimen based on patient response to the TEA-use questionnaire will be included in the estimated model as a covariate to address possible confounding of treatment and compliance effects.

In the current protocol, 40 FD patients, 40 gastroparesis patients and 40 constipation patients will be enrolled. The accuracy of the planned patients sample in each disease was assessed by Monte Carlo stimulation. Each simulated sample assumed the percentage change in symptom score outcome is normally distributed with a standard deviation of 38 and a correlation of 0.4 across repeated observations on the same subject. This parameterization was based on previous data from a similar cross-over study by Liu et al. comparing the effects active and sham TEA administered with a conventional TENS device on changes in the same gastrointestinal symptom score in functional dyspeptic patients (14). Results of the power simulation indicate that with complete follow-up the planned sample provides an 80% chance of detecting a cross-treatment difference in symptom score change equal to 10-11 percentage points with a two-sided significance level of 0.05. Even if 40% of follow-up data are missing at random due to drop-outs or missed follow-up contacts, the simulation results indicate the planned experiment would still have an 80% chance of detecting a cross-treatment difference in symptom score change of 13-14 percentage points with a two-sided significance level of 0.05.

d. Early stopping rules.

The Principal Investigator and Co-Investigators, will monitor the safety and wellbeing of subjects throughout each study. As part of the safety plan for this study, the PI and the Co-Investigators will review individual study subject records to ensure that appropriate mechanisms to protect the safety of study participants are being followed, that protocol requirements are

being adhered to, and that data is accurate, complete, and secure. All study data will be collected by the research team, recorded on data flow sheets or case report forms, and stored in locked file cabinets or databases in a secure area of the PI's office. Electronic files (databases, narrative descriptions, online discussions, etc) will be password-encoded to allow access only to designated research personnel. Interim data will be collected continuously, i.e. when data become available, and reviewed by the PI. The subject's right to confidentiality will be protected at all times and no subject will be identified by name in any publication that results from this research.

This study is considered to be minimal to low risk. Monitoring for and documentation of adverse events, whether anticipated or unanticipated, will be the responsibility of the Principal Investigator and Co-Investigators. Possible, non-serious, anticipated adverse events associated with this study include: minor bruising, pain, or infection associated with venipuncture, and minor discomfort associated with electrical stimulation. If one of these adverse events occurs, the PI and his co-Is will be immediately notified and a note will be entered into the subject's EMR chart. The PI will be responsible for evaluating each adverse event and determining attribution as well as the impact of the adverse event on the risk/benefit ratio using an attribution scale. Each event is graded according to the following criteria:

- Mild – events that do not suggest injury; discomfort is noted but no disruption of daily activities; no therapy, or only symptomatic therapy required.

- Moderate – events indicating injury without long-term risk, discomfort sufficient to modify normal daily activity, specific therapy required (i.e. more than symptomatic).

- Serious – events indicating a serious health threat or permanent injury, incapacity, inability to work, or to perform normal daily activity, hospitalization required or prolonged, emergency treatment required, life-threatening events, death.

The attribution scale assesses the relation of the event to the study procedures. The PI and his co-Is will judge whether or not an adverse event is: 1) not related; 2) possibly related; 3) probably related; 4) definitely related to the study interventions. Anticipated adverse events that are not serious will be reported in aggregate form to the IRB.

All unanticipated, serious, fatal and/or life-threatening adverse events or problems will be reported to the IRB within 24 hours of occurrence or recognition. The Principal Investigator will follow the reporting requirements for serious and unexpected adverse events outlined in the Johns Hopkins University IRB Adverse Event Policy.

8. Risks

a. Medical risks, listing all procedures, their major and minor risks and expected frequency.

The potential risks from participation in the study are minimal. Physical risks of participating in the study may include: A) Mild skin irritation and allergic reaction at the site of electrodes for TEA and EGG; which is less likely to happen and is not serious. B) Pain, bruising, feeling faint and slight risk of infection following blood withdrawal; which is more likely to happen and may be serious.

Nonphysical risks of participating in the study may include: Inability to work on the day of the clinical visit.

b. Steps taken to minimize the risks.

The potential risk is minimal and no special procedure to protect against it. There may or may not be direct medical benefit to the participant. We hope that the information learned from this study will benefit patients with FD, gastroparesis or chronic constipation. This potential minimum risk is really small compared with the potential benefit for people with FD, gastroparesis or chronic constipation.

c. Plan for reporting unanticipated problems or study deviations.

If a serious or unexpected adverse event (AE) occurs, it will be reported to IRB within 24 hours by email or telephone. Serious adverse events include: hospital stay> 24 hours, bleeding requiring transfusion, death or any event resulting in prolonged significant disability or incapacity

d. Legal risks such as the risks that would be associated with breach of confidentiality.

There are no legal risks associated with participation in this study. All measures to protect confidentiality will be taken.

e. Financial risks to the participants.

N/A

9. Benefits

a. Description of the probable benefits for the participant and for society.

Potential improvement in treatment option for FD, gastroparesis and chronic constipaiton and ultimately patient outcome.

10. Payment and Remuneration

a. Detail compensation for participants including possible total compensation, proposed bonus, and any proposed reductions or penalties for not completing the protocol.

There will be no payment or remuneration.

11. Costs

a. Detail costs of study procedure(s) or drug (s) or substance(s) to participants and identify who will pay for them.

All procedures are part of routine clinical care and will be billed to the patient's insurance company.

References:

1. Maggi CA. Therapeutic potential of capsaicin-like molecules: studies in animals and humans. Life Sci. 1992;51:1777–1781.
2. Bortolotti M, Coccia G, Grossi G, et al. The treatment of functional dyspepsia with red pepper. Aliment Pharmacol Ther. 2002;16:1075–1082.

3. Talley NJ, Meineche-Schmidt V, Pare P, et al. Efficacy of omeprazole in functional dyspepsia: double-blind, randomized, placebo-controlled trials (the Bond and Opera studies). Aliment Pharmacol Ther. 1998;12:1055–1065.
4. Peghini PL, Katz PO, Castell DO. Imipramine decreases oesophageal pain perception in human male volunteers. Gut. 1998;42:807–813.
5. Diehl DL. Acupuncture for gastrointestinal and hepatobiliary disorders. J Altern Complement Med 5: 27-45, 1999.
6. Ouyang H, and Chen JD. Review article: therapeutic roles of acupuncture in functional gastrointestinal disorders. Aliment Pharmacol Ther 20: 831-841, 2004.
7. Ouyang H, Yin JY, Wang ZS, Pasricha PJ, Chen JDZ. Electroacupuncture accelerates gastric emptying in association with changes in vagal activity. Am J Physiol 282(2):G390-6, 2002
8. Xu SP, Hou XH, Zha H, Gao ZR, Zhang YX, Chen JDZ. Electroacupuncture accelerates solid gastric emptying and improves dyspeptic symptoms in patients with functional dyspepsia. Dig Dis Sci. 2006 Dec;51(12):2154-9.
9. Tian SL, Wang XY, and Ding GH. Repeated electro-acupuncture attenuates chronic visceral hypersensitivity and spinal cord NMDA receptor phosphorylation in a rat irritable bowel syndrome model. Life Sci 83: 356-363, 2008.
10. Takahashi T. Acupuncture for functional gastrointestinal disorders. J Gastroenterol 41: 408-417, 2006.
11. Xing J, Larive B, Mekhail N, and Soffer E. Transcutaneous electrical acustimulation can reduce visceral perception in patients with the irritable bowel syndrome: a pilot study. Altern Ther Health Med 10: 38-42, 2004.
12. Janssen P, Vos R, Van Oudenhove L, Tack J. Influence of the 5-HT3 receptor antagonist ondansetron on gastric sensorimotor function and nutrient tolerance in healthy volunteers. Neurogastroenterol Motil. 2011 May;23(5):444-9, PMID: 21199175
13. Sallam H, McNearney TA, Doshi D, Chen JD. Transcutaneous Electrical Nerve Stimulation (TENS) Improves Upper GI Symptoms and Balances the Sympathovagal Activity in Scleroderma Patients. Dig Dis Sci. 2007 May;52(5):1329-37.
14. Liu S, Peng S, Hou X, Ke M, Chen JD. Transcutaneous electroacupuncture improves dyspeptic symptoms and increases high frequency heart rate variability in patients with functional dyspepsia. Neurogastroenterol Motil. 2008 Nov;20(11):1204-11.
15. Lin X, Liang J, Ren J, Mu F, Chang M, Chen JDZ. Electrical stimulation of acupuncture points enhances gastric myoelectrical activity in humans. Am J Gastroenterol 1997;92:1527-1530.
16. Zhang EQ, ed. Chinese acupuncture and moxibustion. Publishing house of shanghai college of Traditional Chinese Medicine. Shanghai 1990.
17. Revicki DA, Rentz AM, Dubois D, Kahrilas P, Stanghellini V, Talley NJ, Tack J. Gastroparesis Cardinal Symptom Index (GCSI): development and validation of a patient reported assessment of severity of gastroparesis symptoms. Qual Life Res.2004 May;13(4):833-44.
18. Chen J, McCallum RW, ed. Electrogastrography: principles and applications. New York: Raven, 1995.
19. Chen JDZ, Zou X, Lin X, Ouyang S, Liang J. Detection of gastric slow wave propagation from the cutaneous electrogastrogram. American Journal of Physiology 1999; 277(Gastrointes. Liver Physiol. 40): G424-G430.
20. Lu CL. Zou XP, Orr WC, Chen JDZ. Postprandial changes of sympathovagal balance measured by heart rate variability. Dig Dis Sci 1999, 44:857-861

21. Liu JS, Qiao X and Chen JDZ. Vagal afferent is involved with short pulse gastric electrical stimulation. Dig Dis Sci 2004;49:729-737
22. Tian N, Wang F, Tian DR, Zou Y, Wang SW, Guan LL, Shi YS, Chang JK, Yang J, Han JS. Electroacupuncture suppresses expression of gastric ghrelin and hypothalamic NPY in chronic food restricted rats. Peptides. 2006 Sep;27(9):2313-20.
23. Stener-Victorin E, Waldenstrom U, Wikland M, Nilsson L, Hagglund L, Lundeberg T. Electro-acupuncture as a peroperative analgesic method and its effects on implantation rate and neuropeptide Y concentrations in follicular fluid. Hum Reprod. 2003 Jul;18(7):1454-60.
24. Shen GM, Zhou MQ, Xu GS, Xu Y, Yin G. Role of vasoactive intestinal peptide and nitric oxide in the modulation of electroacupucture on gastric motility in stressed rats. World J Gastroenterol. 2006 Oct 14;12(38):6156-60.