**Non-invasive Vagus Nerve Stimulation in the treatment of Crohn's disease- A pilot study.**

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Summary of Changes between Version 10 (06.02.2023) and Version 11 (02.01.2024)

1) Updated version number and date in footer. (Version 02.01.2024)
2) Removed the specification of "three ECG leads" from Baseline visit, Week 8 visit, and week 16 visit to allow for either 3 or standard 12 lead ECG collection. (Specific 3 lead ECG is no longer required. A standard 12 lead ECG can be used.)
3) Adding SIBDQ to baseline study activities.

**Background**

Crohn's disease (CD) is a type of inflammatory bowel disease (IBD) characterized by chronic inflammation in the digestive tract. The pathogenesis of IBD involves immunological, genetic and environmental factors. Currently there is no cure for Crohn's disease and available medical and surgical treatments are expensive and often associated with significant side effects. Anti–tumor necrosis factor alpha (anti-TNF-α) agents are widely used for treatment of Crohn's disease. Electrical neuromodulation is a new treatment approach of bioelectronic medicine, involving molecular medicine, neuroscience, and bioengineering. Multiple possible mechanisms have been proposed for electrical neuromodulation in GI diseases, including central, autonomic, and/or enteric mechanisms. Vagal tone is significantly blunted in IBD and is associated with high TNF-α levels. Animal and preliminary human studies have demonstrated that electrical vagal nerve stimulation (VNS), including non-invasive vagal stimulation (nVNS), exerts an anti-inflammatory effect by harnessing the cholinergic anti-inflammatory pathway. In healthy humans nVNS has been shown to decrease tumor necrosis factor-α levels. Invasive VNS has been shown to improve inflammation in preliminary studies in patients with Crohn's disease.

**Study Design**: Single center open label interventional pilot study.

Estimated Enrollment: 12 participants

**Aim**: To assess the safety and efficacy of transcutaneous vagal stimulation in adult patients with active Crohn's disease.

**Hypothesis**: Non-Invasive VNS will decrease inflammation in people with Crohn's disease leading to decrease in inflammatory markers and symptoms of disease.

**Outcome Measures:**

**Primary Outcome Measure:**

1. Change in fecal calprotectin over time [16 weeks]

**Secondary Outcome Measures:**

1. Change in Crohn's disease activity index (CDAI) over time [16 weeks].
2. Change in serum cytokine levels over time [16 weeks]. Cytokine levels within the blood will be assessed and compared to baseline levels. The cytokines being assayed include C- reactive protein, tumor necrosis factor-alpha, Interferon-gamma, Transforming Growth Factor-beta and Interleukins (IL) - 1, 6, 10, 12, 17, 21, 23.
3. Heart Rate Variability (HRV) [Time Frame: 16 weeks]. Evaluating change in HRV from baseline until study completion.
4. Insulin levels will be collected and analyzed to see if there are any insulin changes before and after first stimulation

**Materials and Methods:** Adult patients with Crohn's disease presenting to the Indiana University Medical center will be invited to participate in the study. Additionally, potential participants can receive information about participation at disease specific health fairs, and educational event.

Ages Eligible for Study: 18 to 75 Years, inclusive.

Sexes Eligible for Study: All

**Inclusion Criteria:**

1. Crohn's disease diagnosis for at least 3 months, confirmed by clinical, biochemical, and endoscopic evaluations.
2. Patients with CD involving the small bowel and / or colon with active symptoms with Crohn's Disease Activity Index (CDAI) > 220 despite at least one conventional therapy (corticosteroids and/or immunosuppressives) with a stable dose will be included.
3. Elevated Fecal calprotectin ≥ 200 µg/g within the past 4 weeks prior to enrollment
4. If on corticosteroids, the dose must be stable and ≤ 20mg/day prednisone or equivalent for at least 14 days before entry into study.
5. If on background immunosuppressive treatment the dose must be stable with the following parameters:

6. 56 days (8 weeks) for Immunomodulators (methotrexate, 6-MP, Azathioprine) and small molecules (upadacitinib)
7. 84 days (12 weeks) for biologics (Infliximab, Adalimumab, Vedolizumab, Ustekinumab, Risankizumab)
8. Clinical laboratory evaluations (including a chemistry panel, complete blood count [CBC], and urinalysis [UA]) within the reference range for the test laboratory, unless a typical consequence of CD or deemed not clinically significant by the Investigator. Labs done clinically within the past 30 days will be used for this criterion and will not need to be repeated for inclusion in the study.
9. Colonoscopy within the previous 1 year with no evidence of colonic dysplasia or cancer.
10. Able and willing to give written informed consent and comply with the requirements of the study protocol.

**Exclusion Criteria:**

1. Expectation to increase corticosteroids and/or immunosuppressive treatment
2. Presence of bowel stricture with pre-stenotic dilatation
3. Presence of intra-abdominal or perirectal abscess
4. Crohn's Disease Activity Index (CDAI) < 220
5. Fistula with clinical or radiological evidence of abscess
6. Perianal CD with or without rectal involvement
7. Ileostomy, colostomy, enteral or parenteral feeding
8. Short gut syndrome.
9. Clinical condition medically or surgically unstable that, at the discretion of the investigator would not be compatible with the patient's participation in the study
10. Any malignant neoplasia, in the year prior to screening, except for nonmelanoma skin cancer.
11. Active treatment with antibiotics
12. Presence of active intestinal infection or documented infection by stool PCR or culture analysis in the previous 6 weeks
13. Continuous treatment with an anti-cholinergic medication, including over the counter medications.
14. Implantable electronic devices such as pacemakers, defibrillators, hearing aids, cochlear implants or deep brain stimulators.

15. Current tobacco or nicotine user within the past 4 weeks (to limit potential confounding effects of exposure to nicotine)
16. Bowel resection surgery within past 90 days prior to study enrollment and on no conventional IBD therapy, or planned surgery within the course of the study
17. Participation in any other Investigational drug and/or treatment currently or planned during the length of the study
18. Any condition which, in the opinion of the investigator, would jeopardize the subject's safety following exposure to a study intervention
19. Pregnancy or Lactation
20. Comorbid disease with high likelihood of requiring corticosteroid use
21. Inability to comply with study and follow-up procedures
22. Non-English speaking.
23. Known cardiac condition causing or with potential to cause arrhythmia
24. Patients diagnosed with narrowing of the arteries (carotid atherosclerosis)
25. Patients who have had surgery to cut the Vagus nerve in the neck (cervical vagotomy)
26. Patients with clinically significant untreated hypertension, hypotension, bradycardia, or tachycardia.
27. Have a metallic device such as a stent, bone plate or bone screw implanted at or near their neck.
28. Are using another device at the same time (e.g., TENS Unit, muscle stimulator)

**Study device and interventions:**


Fig. 1

A handheld device (Fig. 1) (GammaCore; electroCore Inc.; Rockaway, NJ, USA), which consists of a battery powered portable stimulator with a digital control user interface that controls signal amplitude and two steel contact electrodes will deliver the nVNS electrical stimulation to the cervical Vagus nerve. The device has been approved by the U.S. Food and Drug Administration (FDA) for non-invasive Vagus nerve stimulator therapy for adjunctive use for the prevention and treatment of migraine and cluster headaches in adult patients.

The following visits will be held as part of the study

**Visit 1. Screening Visit:**

Subjects identified by the PI or the Sub-I, or who have been given study information at a health care event, who meet the inclusion and exclusion criteria will be consented after the study has been explained in detail to the subject and they are willing to participate in the study. They will complete the Short Inflammatory Bowel Disease Questionnaire (SIBDQ) at this time.

Patients will also be asked to complete a Crohn's Disease Activity Index (CDAI) diary for 7 days prior to the baseline visit to determine eligibility. Patient may repeat CDAI diary up to 4 times if the CDAI score does not fall in the qualifying range.

**Visit 2. Baseline Visit:**

1. Subjects will complete the Short Inflammatory Bowel Disease Questionnaire (SIBDQ).
2. Blood (30 ml/2 tablespoons) is collected under aseptic conditions for the inflammatory markers, cytokine levels, insulin levels, and serum samples for future analysis.
3. ECG electrodes are placed on the chest for measurement of the electrocardiogram (ECG)
4. A baseline ECG recording using the above placed electrodes will be made for 20 minutes. There is no electrical stimulation taking place currently.
5. After 20 minutes of baseline recording, the gammaCore device will be placed on the left side of the neck in line with the vagus nerve. The nerve lies in the carotid sheath along with the carotid artery and the jugular vein. The carotid pulse is easily felt in the neck. Electrical stimulations are applied using the device for 120 seconds followed by another 120 seconds after a 60 second pause. The amplitude of the stimulation to be used is first calibrated using the lowest possible signal and gradually increasing it to the point where there is mild pulling of the ipsilateral (same side) oral commissure (corner of the mouth where the upper and the lower lip meet). This pulling should not cause any pain to the subject but should be just a slight movement. Once the correct amplitude is reached, the two consecutive stimuli of 120 seconds each will be given to the subject. (The amplitude of the stimulation will be adjusted at each stimulation if necessary to achieve a mild pulling of the ipsilateral oral commissure.) During this time the ECG recordings will continue.
6. After the stimulation period has ended another blood sample (30 mL / 2 tablespoon) to measure insulin levels, and serum for future analysis will be collected approximately 20 minutes post stimulation, and the subject will continue to be monitored and recordings will be made for another 20 minutes. The ECG recordings will be saved as part of the research record.
7. Approximately 40 minutes after the stimulation has ended another blood sample (30 mL / 2 tablespoon) will be collected to measure insulin levels, and stored serum samples for future analysis.
8. The subjects will then be trained on the use of the device using the instructions provided by the manufacturer.
9. The device will be set to the appropriate stimulus and sent with the subject.

The subject will be asked to apply one set of 2 consecutive stimuli, lasting 120 seconds each, 3 times a day till the next visit in 8 weeks.

**(Week 1-week 7)**

1. Subjects will continue to stimulate the left vagus nerve, one set of two stimulations 120 seconds each, 3 times a day, one in the morning after waking up, one in the afternoon after lunch and one an hour before going to bed.
2. Stool sample for the week 8 visit can be collected and sent to the IU Health pathology lab by the subject. Request for the stool sample collection will be provided to the subject at the baseline visit. Stool for week 8 can be collected within a week of Visit 3 (Week 8 +/- 1 week)
3. Subjects will complete a CDAI diary for each week. During weeks 1-7 to be collected at Visit 3 (Week 8 +/- 1 week).

**Visit 3 (8 week or 56 days +/- 5 days)**

1. Subject will take one set of two stimulations during the visit to verify compliance and appropriate use of the device.
2. Subjects will complete the Short Inflammatory Bowel Disease Questionnaire (SIBDQ).
3. Blood (29 ml/2 tablespoons) is collected for the inflammatory markers, cytokine levels, and serum samples for future analysis.
4. ECG electrodes are placed on the chest for measurement of the electrocardiogram (ECG)
5. The gammacore device will be placed on the left side of the neck in line with the vagus nerve. Electrical stimulations are applied using the device for 120 seconds followed by another 120 seconds after a 60 second pause. During this time the ECG recordings will continue.
6. After the stimulation period has ended, the subject will continue to be monitored and after 20 minutes post stimulation subject will be allowed to go home.
7. The subject will be asked to continue applying one set of 2 consecutive stimuli, lasting 120 seconds each, 3 times a day till the next visit in 8 weeks.

**(Week 8-week 15)**

1. Subjects continue to stimulate the left vagus nerve with one set of two stimulations, 120 seconds each ,3 times a day, one in the morning after waking up, one in the afternoon after lunch and one an hour before going to bed.

2. Stool sample for the week 16 visit can be collected and sent to the IU Health pathology lab by the subject. Request for the stool sample collection will be provided to the subject at the week 8 visit. Stool for week 16 can be collected within a week of Visit 4 (Week 16 +/- 1week)
3. Subjects will complete a CDAI diary for each week. During weeks 8-15 to be collected at Visit 4 (Week 16 +/- 1week).

**Visit 4 (16 week or 112 days +/- 5 days)**

1. Subject will take one set of two stimulations during the visit to verify compliance and appropriate use of the device.
2. Subjects will complete the Short Inflammatory Bowel Disease Questionnaire (SIBDQ).
3. Blood (29 ml/2 tablespoons) is collected for the inflammatory markers, cytokine levels, and serum samples for future analysis.
4. ECG electrodes are placed on the chest for measurement of the electrocardiogram (ECG)
5. The gammacore device will be placed on the left side of the neck in line with the vagus nerve. Electrical stimulations are applied using the device for 120 seconds followed by another 120 seconds. During this time the ECG recordings will continue.
6. After the stimulation period has ended, the subject will continue to be monitored and after 20 minutes post stimulation subject will be allowed to go home.
7. The subject will be asked to return the device at the end of the visit.

**Safety/Risk:**

1. Non-invasive vagus nerve stimulation with Gammacore device may cause device-related adverse events (AEs) including:

- Discomfort at the application site
- Redness or irritation at the application site
- Pain at the application site
- Pain in the face/head/neck area (including toothache)
- Muscle twitching and/or contractions in the face/head/neck area
- Dizziness
- Headache/migraine

- Facial Drooping and/or lip pull
- Tingling, pricking, or a feeling of "pins and needles" on the skin where the device is applied (paresthesia/dysesthesia).
- Coughing
- Gastrointestinal discomfort
- Headache
- Hoarseness or change in voice
- Irregular heartbeat (arrhythmia)
- Light-headedness/dizziness
- Metallic taste
- Muscle twitching and or contractions of head/neck/face
- Nausea
- Pain
- Shortness of breath (dyspnea)
- Skin irritation

2. Tingling, pricking, or a feeling of "pins and needles" (paresthesia/dysethesia) the patient may experience discomfort, pain, bruising, swelling, blood clot formation, and very rarely infection at the site where the skin is punctured by the needle. Patient may also experience dizziness, nausea or fainting during the blood draw. The procedure is performed under aseptic conditions.
3. There may be slight discomfort and irritation at the site of the ECG electrode placement. The patient might experience itching, redness, and skin irritation. There might be a slight sting for a few seconds when the electrodes are removed.
4. Subjects may feel discomfort completing the CDAI diary, during answering the SIBDQ questionnaires or collecting stool samples.
5. Potential loss of confidentiality. This is explained further under "Privacy/Confidentiality Issues" below.

**Data Safety Monitoring:**

A study safety monitoring board consisting of the PI along with the study team will be constituted and meet once after the first subject enrollment and thereafter every 5 subjects to ensure the safety of study subjects. As part of the Data Safety Monitoring Plan (DSMP) data quality, subject recruitment, accrual, retention, outcome and adverse event data, assessment of scientific reports,

results of related studies that may impact subject safety, and procedures designed to protect the privacy of subjects will be evaluated. All the data will be secured on a web based platform like RedCap and OnCore to maintain data security.

**Reporting of Adverse Events or Unanticipated Problems involving Risk to Participants or Others:**

The principal investigator (PI) will assess whether an adverse event represents an unanticipated problem following the guidelines described in the IU SOP titled "Unanticipated Problems and Noncompliance". If the investigator determines the adverse event represents an unanticipated problem and requires changes to the protocol or informed consent document or other actions are needed to protect the subjects or others as defined in the IU SOP, the investigator will use the Prompt Reporting Form to report it to the IRB. The reporting will take place within 5 business days after the PI is aware of the event. The form will be submitted via the KC IRB electronic system as an FYI.

The PI will report other unanticipated problems that meet the criteria for prompt reporting as defined in the above IU SOP within 5 business days of becoming aware of the event using the Prompt Reporting Form. This form will be submitted via the KC IRB electronic system as an FYI.

**Study Withdrawal/Discontinuation:**

Enrollment in the study will be voluntary. Subjects may choose not to participate in or leave the study after consenting at any time. Not participating or leaving the study will not result in any penalty or loss of benefits to which the subjects are entitled. In case a subject decides to withdraw from the study, the termination will be documented by the investigator to indicate that the subject chose to withdraw consent. The subject may withdraw himself or herself from the study in person, on the phone or in writing to the PI, a sub-investigator, or the research coordinator.

This study may be terminated by the investigators or the treating physician if they feel that it is no longer safe for a specific patient to participate. The termination will be documented by the investigator to indicate that the subject was withdrawn from the study and reason the subject was withdrawn.

If a subject experience a Crohn's disease flare they will be withdrawn from the study and considered a non-responder. If the subject changes their Crohn's disease medication they will be withdrawn from the study.

**Privacy/Confidentiality Issues:**

Participation in this study may cause a loss of privacy. To minimize this risk, the following steps will be implemented. All the subject's personal and medical data will be considered confidential to the extent allowed by law and therefore every effort will be made to keep all information strictly confidential. Only authorized personnel will have access to the samples, databases, and results. People who may review the information include the investigators, study staff, study monitors and the IUPUI Institutional Review Board or its designees. In addition, personal information may be disclosed if required by law. The samples collected from this study will be deidentified prior to being sent to the testing lab. The samples will be labeled with a code and not with the subject's name. All subject information will be stored in locked cabinets and on the principle investigator's and research coordinator's computers that are password protected. When the study is published, no subject names will be used.

**Follow-up and Record Retention:**

Research records, including signed informed consent documents, signed release of health information authorization forms and other documents that will facilitate reconstruction of study events by the IRB if necessary, will be stored for 7 years after the study or otherwise as required by Indiana law.

**Additional Research Collection**

An extra serum sample will be collected at each blood draw (15ml/ 1 tablespoon) and kept for future analysis under this protocol or in a similar protocol. The samples will be de-identified and stored at Indiana University Health University Hospital, Indianapolis, IN.

The manager of these samples will ensure they are properly used throughout their usable life and will destroy the samples at the end of the scheduled storage period, no longer than 15 years after the end of the study or the maximum allowed by applicable law. De-identified samples may be

shared with Purdue University Laboratories for analysis. No subject identifiers will be shared. Samples will be de-identified per HIPAA standards. Only the research study team will have access to the identification key and sample storage. Subjects will not be able to obtain future access to the stored biospecimens for information that may be of clinically relevant to him/her.

If a subject chooses to withdraw from the study, the investigators will continue to use data already collected up to the point of withdrawal. Biospecimens will be kept, and all personal identifiers removed upon withdrawal.

There will be no whole genome sequencing of the samples. These specimens will not be used for commercial profit.

**Study Funding:** The study devices for transcutaneous vagal nerve stimulation will be obtained through a grant from the manufacturer GammaCore; ElectroCore Inc.; Rockaway, NJ, USA. Study procedures involving stool calprotectin assay, cytokine assays and electrocardiograms will be funded by the Indiana University Division of Gastroenterology

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