Outcomes of Treatment with Vagal Nerve Stimulation in Post-COVID Syndrome: A Pilot Study

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MAYO CLINIC

General Study Information

Principal Investigator: Ryan T. Hurt MD, PhD

Study Title: Outcomes of Treatment with Vagal Nerve Stimulation in Post-COVID Syndrome: A Pilot Study

Mayo Clinic IRB approved as of: 29 May 2024

Research Question and Aims

Hypothesis: Vagal nerve stimulation improves outcomes in patients with post-COVID syndrome.

Aims, purpose, or objectives:

1. To evaluate the impact of vagal nerve stimulation in the treatment of post-COVID syndrome

Background:

Post-COVID syndrome is a constellation of symptoms that persist greater than 28 days after the initial onset of symptoms of SARS-CoV-2 infection.(1) The constellation of symptoms bears a striking resemblance to the "central sensitization syndromes", a group that includes fibromyalgia, chronic fatigue syndrome, and postural orthostatic tachycardia syndrome (POTS).(1, 2) This syndrome is likely to occur in upward of 10% of the population who has been infected with COVID-19, likely affecting hundreds of millions across the world.(2, 3) The etiology of this condition is poorly understood at this time, but it has been linked to immune dysregulation, which likely mediates its effects via neuroinflammation, as demonstrated by the strikingly consistent hypometabolic pattern seen on brain PET.(3-7)

At this time, we have no effective treatment options for post-COVID syndrome. Sympathetic hyperactivity has been a reliable feature of these central sensitization conditions and many of our treatment modalities are directed at reducing the sympathetic drive.(8) Parasympathetic nervous system activation thereby presents an attractive therapeutic intervention.

The Gammacore vagal nerve stimulator has been used in several clinical settings and has demonstrated decreased frequency and severity of headaches. Some studies have also shown a decrease in fatigue.(9-11) We hypothesize that VNS may also decrease post-COVID symptoms, particularly fatigue. If this proves beneficial, these findings could drive an individualized approach to treating post-COVID syndrome.

Whereas multiple studies have previously described common Point-of-Care Ultrasound (POCUS) findings in acute COVID-19, to date no description has been made of POCUS findings in the post-COVID syndrome. In the acute setting, POCUS has been shown to perform similarly to CT for diagnostic and prognostic purposes both in COVID-19 and other pulmonary conditions. POCUS has also previously been shown to usefully augment the physical exam for volume status and left ventricular function. In the post-COVID setting, questions often exist regarding ongoing pulmonary parenchymal disease, cardiac disease, and cardiovascular manifestations of autonomic dysfunction. Often the evaluation for these problems requires multiple outpatient imaging studies which are costly and time consuming. As such, the use of POCUS in the post-COVID

syndrome evaluation may provide an opportunity to simplify and expedite the patient evaluation while reducing cost.

Study Design and Methods

Methods:

20 patients will be recruited from the Post-COVID Care Clinic (PCOCC) at the Mayo Clinic in Rochester. After providing informed consent to this study as well as our post-COVID patient registry and biorepository, patients will perform baseline clinical questionnaires including the Post-COVID Functional Status Score, PHQ-9, GAD-7, PROMIS-F, and COMPASS and have a blood sample taken for analysis for cytokine panel including high sensitivity IL-6, DHEA, and am cortisol. A Point-of-Care Ultrasound (POCUS) will be performed, if one has not been performed clinically within the previous two weeks, and enrollees will have PET-CT of the brain performed to evaluate brain metabolism.

They will then be randomized to either receive VNS treatment or not to receive VNS treatment. For those randomized to use the Gammacore, the device will be applied to the neck (by the study participant) for 2-minute intervals, two sets, administered three times daily. The people who contact the patients for follow-up as part of the PCOCC treatment program (nurses and health coaches) will be blinded, but patients will not be blinded in this open-label study. All patients will complete the above questionnaires at 2, 4, 6, and 12 weeks, lab draws at 6 and 12 weeks, and a repeat POCUS will be completed as well as a PET-CT of the brain at 12 weeks.

Study Outline

Subject Information

Target accrual: 20

Subject population: Adult Patients from the Post COVID Care Clinic at Mayo Clinic, Rochester MN

Inclusion Criteria:

1. Age ≥ 18 years old
2. Presence of fatigue with post exertional malaise
3. Presence of headache
4. Clinical diagnosis of post COVID syndrome
5. They have consented to participate in the study
6. Have the ability to participate in all aspects of the study

Exclusion Criteria:

1. Age < 18 years old
2. Pregnant
3. Prior adverse reaction to ^{14}FDG
4. Active implantable medical device e.g., pacemaker, hearing aid implant
5. Metallic device e.g., stent, orthopedic hardware in neck
6. Using another electronic device at the same time e.g., TENS, mobile phone
7. Any other condition deemed exclusionary by the study principal investigator

Biospecimens

From healthy, non-pregnant, adult subjects who weigh at least 110 pounds. For a minimal risk application, the amount of blood drawn from these subjects may not exceed 550ml in an 8 week period and collection may not occur more frequently than 2 times per week.

Volume per blood draw: _30_ml

Frequency of blood draw _every 6 weeks x 3 occurrences

Review of medical records, images, specimens

☒ The study involves data that exist at the time of IRB submission **and** data that will be generated after IRB submission.

Data Analysis

Data Analysis Plan:

Data will be collected and stored in a de-identified RedCAP database. Data to be abstracted from the electronic health record includes demographics, medical history, and laboratory results. Experimental data will be added to the database as generated.

Outcomes will be compared across groups. Changes from baseline to week 12 will be analyzed using analysis of covariance, with the baseline value included as the covariate. Distributional assumptions will be assessed and transformations or nonparametric methods used as appropriate. A p-value of <0.05 will be considered significant. Power calculations were not performed as this is a pilot study for use in post COVID syndrome and there is limited data to base these calculations upon.

Endpoints

1. *Primary:* Post-COVID Functional Status Score
2. *Secondary:* PROMIS_F
3. *Exploratory:*
    a. PET-CT
    b. Lab values – cytokine panel, high sensitivity IL-6, DHEA, cortisol
    c. PHQ-9, GAD-7, and COMPASS
    d. Point-of-Care Ultrasound

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