Pilot Study--The Effects of Non-invasive Vagal Neurostimulation (nVNS) in Adolescents with Postural Orthostatic Tachycardia Syndrome (POTS)

NCT06268288

9March2023

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March 9, 2023

Non-invasive Vagal Neurostimulation in Adolescents with Postural Orthostatic Tachycardia Syndrome (POTS)

Title of project: Pilot Study --The Effects of Non-invasive Vagal Neurostimulation (nVNS) in Adolescents with Postural Orthostatic Tachycardia Syndrome (POTS).

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Project summary: Excessive sympathetic stimulation and reduced vagal modulation is found in patients with postural orthostatic tachycardia syndrome, hyperadrenergic subtype. The use of non-invasive vagal neurostimulation (nVNS) in adolescents as treatment for many POTS- associated diagnoses including irritable bowel syndrome, depression, and chronic abdominal pain has resulted in statistically significant symptom improvement [1-3]. Dana Shiffler's study in 2021 showed that use of transcutaneous VNS for 14 days in 16 adults with hyperadrenergic POTS resulted in an increase in vagal stimulation, a decrease in sympathetic discharge, and improvement in dysautonomia symptoms [4].

Two types of non-invasive vagal neurostimulation devices exist including auricular and neck stimulated devices. Numerous research studies utilizing the device gammaCore [5], a non-invasive handheld medical device that is applied to the side of the neck and sends gentle patented mild electrical stimulation through the skin to activate the vagus nerve, have been conducted to decrease symptoms such as nausea, headache, abdominal pain, tinnitus, and Parkinson symptoms.

Currently the multifaceted mode of management for POTS patients at Mayo Clinic General Pediatric and Adolescent Medicine department (i.e. recovery STEPS) [6], including increasing fluid and salt intake, slowly increasing duration and intensity of exercise, utilizing prescription medications, and implementing biobehavioral modalities can be overwhelming and discouraging for adolescent patients suffering from POTS. Use of GammaCore neurostimulation as an additional treatment modality in addition to the recovery STEPS for POTS may serve to improve cardiac autonomic profile and decrease symptom intensity. It may also help young adults exercise more on a weekly basis and decrease headache frequency.

Specific aims:

Specific Aim 1: To determine if nVNS will decrease autonomic symptom intensity (COMPASS-31 total score) in comparison to standard recovery STEPS management.

Hypothesis: Use of VNS will decrease autonomic symptom intensity compared to control group (decrease the COMPASS score).

Specific Aim 2: To determine if nVNS with result in improvement in functioning (Child Functional Disability Inventory, cFDI, total score).

Hypothesis: Use of nVNS will improve the child function (decrease in the cFDI score)

Specific Aim 3: To determine if nVNS with result in less heart rate variability with tilt table testing.

Hypothesis: HR variability will show less of an increase in treatment group compared to control group.

Secondary aims:

Secondary Aim 1: To determine if utilization of nVNS influences headache frequency.

Hypothesis: Headache frequency will decrease in treatment group more than in the control group.

Secondary Aim 2: To determine if utilization of nVNS will influence weekly duration of aerobic exercise.

Hypothesis: Weekly exercise duration will increase more in the treatment group than in the control.

Background and significance:

The incidence of Postural Orthostatic Tachycardia syndrome in the United States is estimated to be 500,000 to 2 million people [7]. Despite being first described in 1993 [7], this syndrome continues to be underdiagnosed. In addition, institutions with programs designed to help adolescents with POTS by providing education, physical therapy, psychological therapies, and biobehavioral programs are severely limited in number in the United States.

Vagal nerve stimulation has been used since the 1990s for treatment of intractable epilepsy. Auricular neurostimulation therapy to the auricular branch of the vagal nerve utilizes a noninvasive device that delivers transcutaneous electrical nerve stimulation [8]. It has been used in multiple studies to decrease sympathetic nerve activity and augment vagal stimulation [9] in the treatment of conditions such as irritable bowel syndrome, depression, and chronic migraines. [1,10-11]. Other non-invasive vagal stimulation devices, such as gammaCore, have been shown in clinical studies to decrease symptoms such as depression, abdominal pain, tinnitus, and others.

This study is clinically important because it may improve the symptoms of patients suffering from POTS minimizing both physical and psychological burdens. By improving symptoms, the adolescent patient can start to feel better and be able to function more fully in normal activities. Use of this device may help “jumpstart” improvement and decrease symptoms allowing the adolescent patient to be able to engage earlier in more physical activity. Physical activity which also improves the sympathetic/vagal modulation pathway [12] can then act synergistically to evoke a successful recovery program. A subanalysis looking at total weekly duration of aerobic exercise will also be conducted.

Currently, the pediatric subspecialty groups at Mayo Clinic evaluate these same patients with autonomic dysfunction for a variety of related problems including headaches, migraines, abdominal pain, irritable bowel syndrome, constipation, pelvic pain, back pain, generalized musculoskeletal pain, arthralgias, difficulty concentrating, tremors, temperature dysregulation, dermatological conditions, and syncope. Often treatment modalities and medications provided are limited or are not successful in managing symptoms. The results of this study may also result in interesting subanalysis cohorts looking at specific symptom resolution such as frequency of headaches.

The COMPASS-31 is a questionnaire of autonomic symptoms severity in 6 domains [13]. The scoring system yields individual autonomic domain symptom burden and a total score expressed as a percentage from 0-100 . A higher score indicates greater symptom intensity. The child Functional Disability Inventory (cFDI) evaluates activities of daily living such as walking, going to school, ability to do

homework, etc [14]. Higher scores represent more difficulty. Pre-study, mid-study, and post-study COMPASS-31 and cFDI questionnaires will assess change. Forms to chart daily headache frequency and aerobic exercise will be provided to each participant and evaluated for change over the two months of study duration.

In the independent article "Safety and tolerability of transcutaneous vagus nerve stimulation in humans: a systematic review" by Redgrave et. al [1], they review the safety of these devices in 51 studies. Of the 51 studies, 18 were transcutaneous vagus nerve stimulator devices utilized in the neck. Four studies did not report their side effect rate. The side effects are documented in this review article as percent participants with **any** side effects (%SE) and side effect rate per 100 hours of tVNS (%SE/100 h).

In summary, of the 14 studies, eight had no side effects and 2 had side effect rates less than 1%. Four studies had side effect rates greater than 1 % (bolded). These studies are documented in more detail below.

All studies with neck transcutaneous vagal nerve stimulation:

Altavilla 2015 study for chronic migraine used one dose for 90 seconds with 0%SE and 0%SE/100 h.

Davies 2016 study for hemicrania continua; 0%SE.

Frangos 2016 study involving experimental changes on fMRI had 0%SE and 0% SE/100 h.

Gaul 2015 study for cluster headaches had 25% SE and 4.65 %SE/100 h.

Goadsby 2014 for migraines had 13% SE and nothing recorded (NR) for %SE/100 h.

Grazze 2014 study for migraine had 1% SE and 0% SE/100 h

[Grazzi 2016 study for menstrual migraines had no data]

Grazzi 2016 study for migraine without aura had 0% SE

Kinfe 2015 study for cluster tic syndrome in one patient and 0% SE

Kinfe 2015 study for migraine, sleep disturbance had 4% SE and 1.67 %SE/100 h

[Lerman 2016 study for healthy volunteers' nociceptive effects and no data on SE]

[Magis 2013 study for headaches had no data on SE]

Marin 2016 study for cluster headaches had 0% SE

Paulon 2015 for gastroparesis had 0% SE and 0%SE/100 h

Schulz-Stubner 2011 case report for hiccups had 1% SE

[Silberstein 2016 study for migraine had no data]

Silberstein 2016 for cluster headache had 6% SE and no data for %SE/100 hr

Steyn 2013 case study for asthma had 0% SE and 0%SE/100 h

Four studies with side effects greater than 1%:

The Gaul study[2] in 2015 investigating cluster headaches found similar adverse effects in the control group (no VNS) with 13/49 (27%) reporting adverse effects and the test group (with VNS) of 18/48 (38%) reporting any adverse effects. They had four serious side effects (2 in each group) including cholecystitis, hematoma after surgery, genital herpes, and CH exacerbation. None were considered to be related to VNS device. Their mild to moderate side effects included: cluster headaches, headaches, nasopharyngitis, dizziness, oropharyngeal pain, and neck pain. Seven people discontinued the study due to side effects. Four were in the control group and had chest pain, fatigue, depressed mood, or cluster headaches. Three were in the VNS group and had complaints of hot, malaise, hematoma after planned surgery, and depressed mood.

The Goadsby study[3] in 2014 investigating acute migraine in 30 patients had mild stiff neck occur 4 times, frequent urination occur 4 times, lip or facial droop occur 2 times, and shoulder pain or spasm occur 2 times. There were one each of the following: raspy voice, tinnitus in ear, moderate stiff neck, neck twitch, mild neck redness, moderate neck redness, mild neck swelling, cough, mild confusion X 2 hours, moderate dizzy, dizzy up to 60 miutes, fever, and joint pain.

The Kinfe study[4] in 2015 investigating migraines in 20 patients had a 4 % side effect rate with mild adverse effects including neck twitching and skin redness. They recorded a 1.67% side effect rate per 100 hours of use. All these events were transient, occurred with period of stimulation and resolved quickly. There were no severe side effects. Of note, this team used the same device as is planned in our study, the electroCore device, and used it in the same fashion.

The Silberstein study[5] in 2016 investigating cluster headaches was a very large, randomized, double blind, sham controlled trial of 150 people and used a VNS on half and a sham VNS treatment on another half of the patients. This study utilized the electroCore device as well. Adverse device effects (ADEs) were reported by 35/150 (VNS 11 and sham 24) in the double-blind phase. Only one patient had a serious adverse effect during that double blind phase. This patient had a cluster headache, multiple left extremity deep vein thromboses, abdominal aortic aneurysm, pneumonia, anasarca, respiratory failure, and urethral trauma. These were categorized as non-device side effects. The common side effects in the Silberstein study were burning/tingling/soreness in 9 patients, skin irritation/redness in 9 patients, lip, or facial drooping/pulling/twitching in 8 patients and 7 with dysgeusia/metallic taste.

CONCLUSION: Upon review of all the studies utilizing the neck transcutaneous vagal nerve stimulation technique, 71% of these studies had patients that reported a very low rate of any side effects (0-1% of patients). In the studies that had higher than 1% of their patients report any side effects, the common side effects were primarily transient with use of the device and dissipated shortly after the stimulation. They were all primarily mild as well. These are detailed below:

Adverse Effects:

Skin irritation at neck site: Common side effects included mild tingling, mild soreness, mild redness with use of the device. A rare side effects included a stinging sensation.

Neck and facial changes: Common side effects that were concurrent with device usage included: lip or facial drooping, lip pulling, lip twitching, oropharyngeal pain, mild neck twitch, and mild neck stiffness.

There were rare (1-2 person only) reports of raspy voice, tinnitus (ringing) in ear, neck swelling, moderate neck stiffness, and moderate neck/shoulder pain or spasm.

Systemic changes: Common side effects included headache (in these headache prevention studies), mild dizziness, mild oropharyngeal pain, frequent urination, and metallic taste. Rarely, patients have reported changes in temperature, malaise, depressed mood, fever, joint pain, moderate dizziness, transient confusion, and cough.

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Silberstein SD, Mechtler LL, Kudrow DB, Calhoun AH, McClure C, Saper JR, et al. Non-invasive vagus nerve stimulation for the acute treatment of cluster headache: findings from the randomized, double-blind, sham-controlled ACT1 study. Headache. 2016:56:1317-32. Doi.org/10.1111/head.12

Experimental Design and Methods:

Study Participants: Patients will be recruited from the Mayo Clinic GPAM clinic. We will aim to recruit 40 participants ages 12-19 years with Postural Orthostatic Tachycardia as diagnosed from a positive Mayo Clinic Autonomic Reflex Screen. Patient will have a 40 or greater increase in their heart rate during the tilt test without corresponding orthostatic hypotension (a fall in BP of >20 mmHg SBP or 10mm Hg DBP).

Exclusion criteria: Exclusion criteria includes orthostatic hypotension, pregnancy, prior neck surgery, any metallic implant near the stimulation site, known cardiac disorder (structural anomaly, prolonged QT interval, arrythmia or history of documented dysrhythmia), or use of feeding tubes. Additional exclusion criteria includes: patients on other autonomic medications other than Metoprolol or Midodrine, inability to independently utilize the GammaCore device, inability to independently complete surveys, or patients receiving hormonal treatments other than OCPs.

I**nformed consent**: Participants (age 12-17 years of age) and guardians will review the informed assent/consent form (approved by Mayo Clinic's institutional review board) with our study coordinator

and signage is required by both the participant and a guardian prior to participation. Participants (age 18-19 years of age) may sign their own consent forms.

Stipend for return visit: A stipend of $60 will be provided to each patient who completes the repeat tilt table testing within 0-14 days of the study exit.

Recruitment of subjects: Adolescent patients aged 12-19 years of age referred for autonomic dysfunction evaluation are recruited as potential subjects. The study coordinator will contact the patients prior to their arrival for the initial ARS and provide information regarding the possibility of enrolling in the research study if the patient meets the criterial for enrollment after clinic evaluation.

Patients will undergo standard 3-part autonomic reflex screening (ARS). Those patients with a positive tilt test showing a heart rate increase of 40 or above (and no evidence of orthostatic hypotension) will be eligible for the study. Confirmation of negative pregnancy will be determined for each female participant prior to enrollment.

Study design:

A baseline Composite Autonomic Symptom Score (COMPASS-31) and a Child-Functional Disability Inventory will be completed upon enrollment. Subjects will also complete a patient health questionnaire (PHQ-9) for baseline observation. This will be completed every 2 weeks to monitor new onset or worsening depression as a side effect with the use of the device. For secondary analysis, our team will ask the participants to chart their daily aerobic exercise (minutes) and daily headache frequency (hours) plus estimated headache severity (mild, moderate, severe).

All participants will be provided with our current standard POTS management recommendations including 4 key areas: non-caffeinated fluid intake of 90 ounces a day, increased intake of salty foods, recommendations to slowly increase daily aerobic exercise, and addition of medication (either metoprolol 25 mg po BID or Midodrine 5 mg po TID) per physician preference. See recovery STEPS protocol [6].

Patients will be randomly assigned to a group that receives the nVNS or a group that does not. Assignments will be stratified by sex.

Enrolled patients will be taught how to use the vagus nerve stimulator on the right side of the neck for two 2-minute stimulations (termed “GammaCore intervention”). The nVNS should be self-administered 3 times throughout each day utilizing two 2-minute stimulations per GammaCore intervention.

At 4 and 8 weeks, each patient will again complete the COMPASS -31 symptoms list and the Child Functional Disability Inventory. The forms for charting daily headache frequency/severity and daily aerobic activity will be collected at 8 weeks.

A repeat visit to Mayo Clinic is strongly encouraged at 8 weeks after baseline ARS testing for additional tilt table testing.

Potential risks:

Vagal neurostimulator possible adverse effects: pain, tingling, pruritus, and skin irritation.

Skin irritation at neck site: Common side effects included mild tingling, mild soreness, mild redness with use of the device. A rare side effects included a stinging sensation.

Neck and facial changes: Common side effects that were concurrent with device usage included: lip or facial drooping, lip pulling, lip twitching, oropharyngeal pain, mild neck twitch, and mild neck stiffness. There were rare (1-2 person only) reports of raspy voice, tinnitus (ringing) in ear, neck swelling, moderate neck stiffness, and moderate neck/shoulder pain or spasm.

Systemic changes: Common side effects included headache (in these headache prevention studies), mild dizziness, mild oropharyngeal pain, frequent urination, and metallic taste. Rarely, patients have reported changes in temperature, malaise, depressed mood, fever, joint pain, moderate dizziness, transient confusion, and cough.

Tilt table side effects: symptoms of dizziness, visual changes, lightheadedness, nausea, vomiting, syncope.

Confidentiality: All information, data, results will be used for research purposes only and confidentiality will be assured by use of identification codes. Electronic data will be kept in a secure database, requiring a password for entry, and limited to study investigators only.

Protection: Volunteers will be assessed for concerns or symptoms at 4 weeks into the study. All participants have been provided contact information for the study coordinator. Subjects will also complete a patient health questionnaire (PHQ-9) for baseline observation. This will be completed every 2 weeks to monitor new onset or worsening depression as a side effect with the use of the device.

Benefits: Participants all contribute to additional medical understanding of treatment modalities to alleviate or lessen POTS symptoms. Participants randomized to the use of the Gamma Core device may have less symptoms and decreased symptom intensity. Patients will receive remuneration for the study of $60 after completing the second tilt table test.

Statistical Analysis:

Aim #1 COMPASS 31 score improves 10 vs 20% from mean of 25.

Two group t-test of equal means (equal n's)

Column	1	2	3	4	5	6	7
Test significance level, α	0.050	0.050	0.050		0.050		0.050
1 or 2 sided test?	2	2	2		2		2
Group 1 mean, μ_1	2.500	2.500	2.500		2.500		2.500
Group 2 mean, μ_2	5.000	5.000	5.000		5.000		5.000
Difference in means, $\mu_1 - \mu_2$	-2.500	-2.500	-2.500		-2.500		-2.500
Common standard deviation, σ	3.125	5.000	12.500		2.750		10.000
Effect size, $\delta = \lvert\mu_1 - \mu_2\rvert / \sigma$	0.800	0.500	0.200		0.909		0.250
Power (%)	80	80	80		80		80
n per group	26	64	394		20		253

Aim #2 FDI questionnaire with 10 % vs 20% improvement from mean of 30.

nQuery Advis

Two group t-test of equal means (equal n's)

Column	1	2	3	4	5	6	7
Test significance level, α	0.050	0.050	0.050		0.050	0.050	0.050
1 or 2 sided test?	2	2	2		2	2	2
Group 1 mean, μ_1	6.000	6.000	6.000		6.000	6.000	6.000
Group 2 mean, μ_2	3.000	3.000	3.000		3.000	3.000	3.000
Difference in means, $\mu_1 - \mu_2$	3.000	3.000	3.000		3.000	3.000	3.000
Common standard deviation, σ	3.750	6.000	15.000		3.000	4.000	5.000
Effect size, $\delta = \lvert\mu_1 - \mu_2\rvert / \sigma$	0.800	0.500	0.200		1.000	0.750	0.600
Power (%)	80	80	80		80	80	80
n per group	26	64	394		17	29	45

Aim #3 Tilt table heart rate decrease 0 vs 20% from mean of 40.

Two group t-test of equal means (equal n's)

Column	1	2	3	4	5	6	7
Test significance level, α	0.050	0.050	0.050		0.050	0.050	0.050
1 or 2 sided test?	2	2	2		2	2	2
Group 1 mean, μ_1	8.000	8.000	8.000		8.000	8.000	8.000
Group 2 mean, μ_2	0.000	0.000	0.000		0.000	0.000	0.000
Difference in means, $\mu_1 - \mu_2$	8.000	8.000	8.000		8.000	8.000	8.000
Common standard deviation, σ	10.000	16.000	40.000		8.000	7.000	6.000
Effect size, $\delta = \lvert\mu_1 - \mu_2\rvert / \sigma$	0.800	0.500	0.200		1.000	1.143	1.333
Power (%)	80	80	80		80	80	80
n per group	26	64	394		17	14	10

Statistics may include the following methods. Fisher exact test for comparison of simple categorical data between two groups. Two-sided two sample t test for normal, continuous data, presented as mean +/- 1 SD. Two-sided 2 sample Mann Whitney test for non- normal, continuous data, presented as median. Significance calculated as p values of <.05 and 95% confidence intervals.

Summary: There are not published data for mean and variance COMPASS 31 and cFDI data in adolescents with POTS. This makes power and number-to-treat estimates difficult.

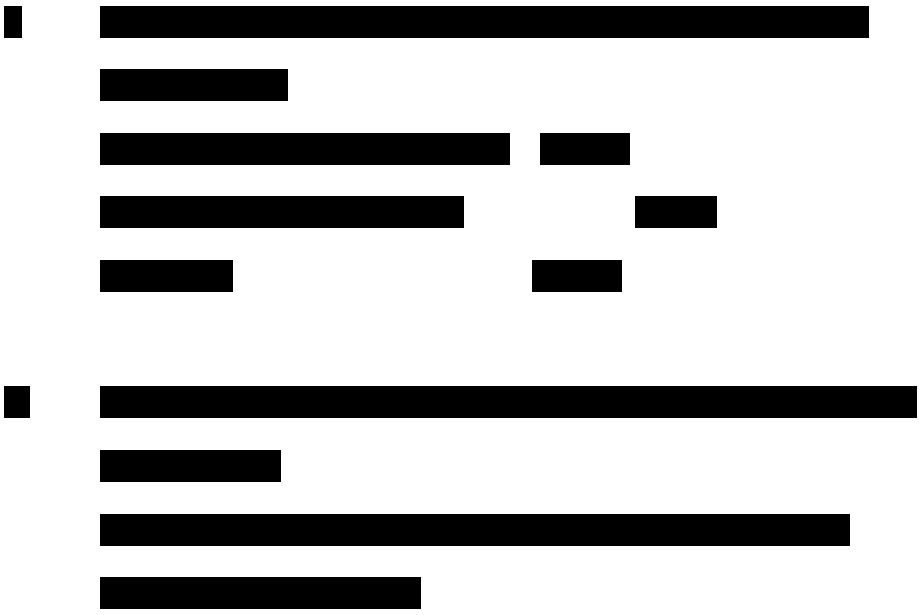
Project timeline:

Participants are to be recruited into the study starting in May 2023 with a goal of 40 participants. Survey questionnaires and daily forms will be obtained at 4 and 8 weeks after entry. Second tilt table tests will be performed at 0-14 days post study completion. Data analysis will be performed after completion of the program by the 40 participants.

Expected Outcomes:

The use of noninvasive vagal nerve stimulation in adolescent patients with postural orthostatic tachycardia syndrome will result in a decrease in autonomic symptoms as per COMPASS-31 questionnaire and a decrease in heart rate variability as seen in repeat tilt table testing. We expect to see a decrease in symptoms (COMPASS-31) in our standard care group of 10% and an additional decrease of symptoms in our Gamma Core group of 10% (total decrease of 20% in the GammaCore group). We expect to see a 10% decrease in cFDI scores and an additional 10% decrease in cFDI scores in our Gamma Core group (total of 20% decrease). We expect to see a 20 % decrease in heart rate increase with repeat head up tilt table testing in the GammaCore group only.

[redacted]



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