SU1447

Short-term Non-invasive Vagus Nerve Stimulation (nVNS) in Patients With Treatment-refractory Gastroparesis

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Introduction

- Gastroparesis is a chronic gastric motility disorder characterized by
  - Nausea, vomiting, bloating, early satiety, and abdominal pain
  - Delayed emptying in the absence of mechanical obstruction[1]
- Pharmacological treatments include prokinetics, antiemetics, and antisecretory drugs
- When pharmacological treatment is ineffective, step-up treatment includes enteral or parenteral nutrition and implantation of a gastric neurostimulation (GNS) device (Enterra®, Medtronic plc)
- GNS is reported to improve symptoms in 50% to 70% of patients with treatment-refractory gastroparesis[2] and symptom improvement does not parallel improved gastric emptying[3]
- The *antinociceptive* effect of GNS is thought to be mediated centrally, probably by the neurostimulation of vagal afferents arising from the stomach[3]
- Complications of GNS include pain at the implantation site and, rarely, infection, dislodged electrodes, and intestinal obstruction[4]
- In the United Kingdom, the cost of an implantable GNS device is >£16,000,[5] and funding is limited

Non-invasive Vagus Nerve Stimulation

- A high-frequency/low-energy battery-operated non-invasive vagus nerve stimulation (nVNS) device (gammaCore®, electroCore LLC) is programmed to selectively stimulate *afferent* vagus nerve fibers
- In the European Union, nVNS has a CE mark for the treatment of gastrointestinal disorders and is also used for the treatment of primary headache and medication overuse headache

Study Premise and Objective

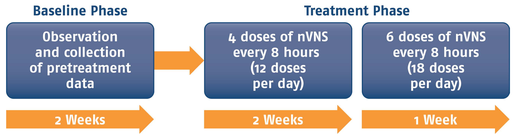
- We hypothesized that if implanted GNS devices act centrally through afferent vagus nerve stimulation, then nVNS applied to afferent vagus fibers traversing the neck may have a similar therapeutic effect
- This compassionate proof-of-concept study assessed whether short-term nVNS therapy influences symptoms in patients with treatment-refractory gastroparesis

Methods

Study Design

- This prospective, 2-phase pilot intervention study evaluated the effects of short-term nVNS on symptoms in patients with treatment-refractory gastroparesis (**Figure 1**)

Figure 1. Study Design



Patients

- All participants had treatment-refractory gastroparesis and were eligible for GNS implantation if funding could be secured

Device

- The nVNS device (**Figure 2A**) delivers a low-voltage electrical signal to the neck parallel with the carotid artery (**Figure 2B**) via a pair of stainless steel stimulation surfaces coated with a small amount of conductive gel

Figure 2A. nVNS Device

Figure 2B. Positioning of the nVNS Device

Images provided courtesy of electroCore, LLC.

- The stimulation intensity is adjusted by the patient using + and − buttons to achieve a comfortable tingling sensation in the tissues underlying the stimulation plates

Intervention

- After training by a medical staff member, patients self-administered nVNS therapy at home
- A single dose of nVNS was programmed as a 120-second stimulation period
- For the first 2 weeks, 2 doses were applied sequentially to the left and right vagus nerve 3 times daily (12 doses/day); during the third week, 3 doses were applied bilaterally 3 times daily (18 doses/day)

Assessments and End Points

- Each day, patients used a diary to record and grade their symptoms on the 9-item Gastroparesis Cardinal Symptom Index (GCSI),[6] which uses a 6-point Likert scale (0 = *no symptoms*; 5 = *very severe symptoms*)
- The mean baseline GCSI aggregate score was compared with the mean aggregate score at the end of each treatment week
- For each of the 3 GCSI subscales, the mean baseline score was compared with the mean score at the end of each treatment week
- A **responder** was defined as a patient who experienced a ≥1-point decrease from baseline in the GCSI aggregate score by the end of the treatment phase
- For each patient, the percentage change from baseline in GCSI aggregate score was calculated for each treatment week
  - Proportions of patients with **>30% and >50% decreases from baseline** in GCSI aggregate score were calculated
- For each GCSI subscale, the **percentage change in mean score** from baseline was calculated for each treatment week
- Patients were asked to report any adverse events they experienced

Results

Patients and Adherence

- 35 patients were enrolled (**Table 1**)
- Twenty-three (66%) patients completed the daily diary for 3 weeks and were adherent to treatment; 7 (30%) of these patients continued treatment for up to 6 weeks

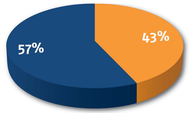
Table 1. Patient Characteristics

	Patients (N=35)
Age, mean (range), y	38.5 (21–81)
Sex, No. (%)	
Female	28 (80)
Male	7 (20)
Gastroparesis Etiology, No. (%)	
Idiopathic	21 (60)
Diabetic	12 (34)
Postsurgical	2 (6)

Effects of nVNS

- 43% (n=10) of patients were considered responders (**Figure 3**)
- Mean GCSI aggregate scores decreased with nVNS therapy (**Figures 4 and 5**)
- Mean scores on all GCSI subscales improved with nVNS therapy (**Figures 6–8**)
- No serious adverse events were reported
- All responders reported symptom recurrence within 1 week after stopping treatment

Figure 3. Responders[a] and Non-Responders to nVNS (n=23)



[a] **Response** was defined as a ≥1-point decrease from baseline in the GCSI aggregate score by the end of the treatment phase.

Figure 4. Mean GCSI Aggregate Scores in All Patients (n=23) and in Responders (n=10)

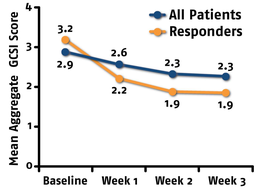


Figure 5. Proportions of Patients With >50% and >30% Decreases in GCSI Aggregate Score (n=23)

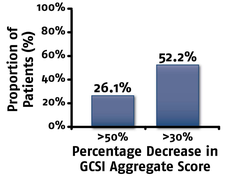


Figure 6. Percentage Change in Mean Nausea/Vomiting Subscale Score for All Patients (n=23) and for Responders (n=10)

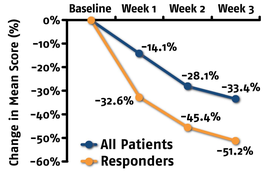


Figure 7. Percentage Change in Mean Postprandial Fullness/Early Satiety Subscale Score for All Patients (n=23) and for Responders (n=10)

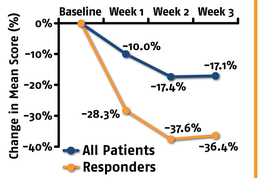
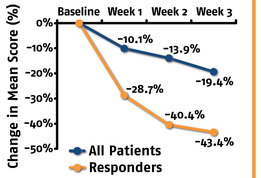


Figure 8. Percentage Change in Mean Bloating Subscale Score for All Patients (n=23) and for Responders (n=10)



Conclusions

- **In this open-label, short-term, proof-of-concept study, nVNS appears to be safe**
- **These results suggest that short-term treatment with nVNS alleviates the cardinal symptoms of gastroparesis**
  - **Improvements were noted in all 3 GCSI subscale scores, most notably for the nausea/vomiting subscale**
- **In responders, symptom relapse occurred within 1 week after treatment cessation**
- **The nVNS dose response and time to response need to be addressed**
- **In treatment-refractory gastroparesis, nVNS may be an alternative to implanted GNS**
- **The scene is set for further evaluation of nVNS in drug treatment-resistant gastroparesis**

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gammaCore® is not currently FDA approved and is not available in the United States