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Open-label pilot study: Non-invasive vagal nerve stimulation improves symptoms and gastric emptying in patients with idiopathic gastroparesis

Andres Gottfried-Blackmore | Emerald P. Adler | Nielsen Fernandez-Becker | John Clarke | Aida Habtezion | Linda Nguyen

Division of Gastroenterology & Hepatology, Department of Medicine, Stanford University, Stanford, CA, USA

Correspondence
Andres Gottfried-Blackmore, Division of Gastroenterology & Hepatology, Department of Medicine, Stanford University, 300 Pasteur Drive, Alway Bld. M215, Stanford, CA 94305, USA.
Email: andresg@stanford.edu

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Abstract

Background: Gastroparesis, a chronic motility disorder characterized by delayed gastric emptying, abdominal pain, nausea, and vomiting, remains largely unexplained. Medical therapy is limited, reflecting the complex physiology of gastric sensorimotor function. Vagus nerve stimulation is an attractive therapeutic modality for gastroparesis, but prior methods required invasive surgery. In this open-label pilot study, we aimed to assess the benefit of non-invasive vagal nerve stimulation in patients with mild to moderate idiopathic gastroparesis.

Methods: Patients self-administered the gammaCore vagal nerve stimulator for 4 weeks. The gastroparesis cardinal symptom index daily diary (GCSI-dd) was assessed during a two-week run-in period, ≥4 weeks of therapy, and 4 weeks after therapy was completed. Gastric emptying and autonomic function testing were also performed. The primary endpoint was an absolute reduction in CGSI-dd of 0.75 after nVNS.

Results: There was a total improvement in symptom scores (2.56 ± 0.76 to 1.87 ± 1.05; $P = .01$), with 6/15 (40%) participants meeting our primary endpoint. Therapy was associated with a reduction in gastric emptying ($T^{1/2}$ 155 vs 129 minutes; $P = .053$, CI −0.4 to 45). Therapy did not correct autonomic function abnormalities, but was associated with modulation of reflex parasympathetic activity.

Conclusions: Short-term non-invasive vagal nerve stimulation led to improved cardinal symptoms and accelerated gastric emptying in a subset of patients with idiopathic gastroparesis. Responders had more severe gastric delay at baseline and clinical improvement correlated with duration of therapy, but not with improvements in gastric emptying. Larger randomized sham-controlled trials of greater duration are needed to confirm the results of this pilot study.

KEYWORDS

autonomic nervous system diseases, gastric emptying, gastroparesis, vagal nerve stimulation

1 | INTRODUCTION

Gastroparesis is a chronic disabling gastrointestinal (GI) motility disorder characterized by delayed gastric emptying of solid food in the absence of a mechanical obstruction. Patients suffer from recurrent nausea, vomiting, abdominal pain, fullness, bloating, and early satiety. Although gastroparesis is considered a neuromuscular disorder of the stomach,[1] it remains a largely unexplained disease. Gastroparesis can have different etiologies including idiopathic, diabetic, iatrogenic, postsurgical or postviral. Idiopathic gastroparesis is the most common, followed by diabetes accounting for about one third of all cases. A US populationbased study in Minnesota in the United States estimated that the ageadjusted incidence of gastroparesis during a 10year period was 2.4 per 100 000 personyears for men and 9.8 per 100 000 personyears for women; prevalence was estimated to be 9.6 per 100 000 men and 37.8 per 100 000 women.[2] Importantly, a recent American hospital-based survey showed a threefold rise in incidence of hospitalizations and 10-fold rising health-care costs associated with gastroparesis.[3]

The primary management of gastroparesis involves patient education and dietary therapy; correcting fluid, electrolyte, and nutritional deficiencies; identifying and treating the cause of delayed gastric emptying (for example, diabetes mellitus; medications); and palliating symptoms with pharmacological agents as first-line therapies. For treatment-refractory patients, the FDA has approved the use of an implantable gastric electrical stimulator (GES) device (Enterra, Medtronic, Minneapolis, Minnesota, USA) for compassionate use in the treatment of chronic, intractable (drug-refractory) nausea. and vomiting secondary to gastroparesis. Results from one of the largest series of patients treated with a GES device (n = 138) showed durable responses a year after implantation, particularly in nausea, early satiety, and loss of appetite.[4] Stimulation parameters approved in clinical practice do not regulate gastric slow-wave activity and have inconsistent effect on gastric emptying.[5] Rather, it has been proposed that gastric electrical stimulation works by decreasing visceral hypersensitivity through modulation of vagal afferent and efferent function,[6] consistent with the major role of vagal innervation in controlling gastric sensorimotor function.

Vagus nerve stimulation (VNS) using implantable electric generators has been in clinical use since the 1990s with an excellent safety profile. Implanted VNS was originally indicated for refractory epilepsy, but with newer means of stimulating the vagus nerve, it is now being investigated for a broad array of diseases involving most organ systems of the body.[7] A new generation of non-invasive VNS devices is rising to circumvent the invasive nature of surgical implantation. Cervical transcutaneous non-invasive VNS (nVNS) can be achieved using a battery-powered neurostimulator (gammaCore, electroCore) designed primarily to stimulate myelinated sensory afferent vagus nerve fibers as they ascend through the neck in the carotid sheath. The gammaCore device has been approved and is being prescribed in several countries mainly for the treatment of primary headache and is FDA-approved for migraines and cluster headaches.[8] When studied in patients with primary headache, the device demonstrated a favorable safety profile and was not associated with significant adverse events.[9] Recently, a proof-of-concept study reported clinical improvement in approximately 40% of drug-refractory gastroparesis patients after 3 weeks of nVNS.[10] Building on the proposed mechanism of action of GES and on the work of Paulon et al, the aim of the present open-label pilot study was to assess the impact of short-term nVNS on cardinal symptoms, gastric emptying, and autonomic function in patients with mild to moderate idiopathic gastroparesis.

Key Points

- Medical therapy for gastroparesis is limited, reflecting the complex physiology of gastric sensorimotor function. Vagus nerve stimulation is an attractive therapeutic modality for gastroparesis, but existing methods require invasive surgery.
- We report that 4 weeks of non-invasive cervical vagal nerve stimulation significantly improves the cardinal symptoms of gastroparesis and accelerates gastric emptying in a subset of patients with idiopathic gastroparesis. Clinical responders had more severe gastric delay at baseline, and clinical improvement correlated with duration of therapy.
- This is the first study to show that non-invasive vagal nerve stimulation can improve both symptoms and gastric emptying in a cohort of idiopathic gastroparesis, with an excellent tolerability and acceptance profile.

2 | MATERIALS AND METHODS

2.1 | Study design

This open-label pilot study was conducted at the Stanford Digestive Health Clinic in California. Our registered clinical trial (Clinical Trials.gov NCT03120325) includes idiopathic and diabetic gastroparesis subjects as well as functional dyspepsia patients. Data presented in this report represent the primary clinical outcomes of the idiopathic gastroparesis cohort, as this was the fastest to be enrolled and completed. Adult participants were established patients in our Gastroenterology Motility Clinic, referred from outside centers, or self-referred after learning about the study through gastroparesis patient forums. For study inclusion, adult subjects (age 18-65) had to carry a diagnosis of idiopathic gastroparesis based on delayed gastric emptying at 2 and/or 4 hours based on gastric emptying scintigraphy of a standardized meal.[11] As there is significant overlap between idiopathic gastroparesis and functional dyspepsia,[12] Rome IV criteria[13] were used to assess for functional dyspepsia. All subjects (15/15) met criteria for postprandial distress syndrome, and 73% (11/15) met criteria for epigastric pain syndrome. For purposes of this trial, patients who met Rome IV criteria and also had delayed gastric

emptying were characterized as idiopathic gastroparesis. Patients were excluded if they were actively using opiates or were undergoing titration or changes in any prokinetic/antiemetic medication within four weeks of enrollment and if they had a history of gastric surgery or gastric electric stimulator placement (see full list in Table S1).

The gastroparesis cardinal symptom index daily diary (GCSI-dd) was assessed during a two-week run-in period, during nVNS, and after four weeks following discontinuation of nVNS. Gastric emptying and autonomic function testing were performed immediately before and after nVNS. The primary endpoint was a decrease in the one week mean composite GCSI-dd score of ≥0.75 after at least four weeks of nVNS. Secondary endpoints included changes in GCSI-dd subscales and gastric emptying. Exploratory endpoints included impact of nVNS on autonomic symptoms and function. Based on the 30% response rate to nVNS shown by Paulon et al,[10] it was estimated that 12 subjects would allow sufficient power to detect a clinically significant reduction of >0.75 points in the aggregate GCSI-dd score ($\mu_A = 3$ to $\mu_B = 2.2$, with $\kappa = 1.88$, $\sigma = 0.8$, Type I error rate 5% two-sided). Fifteen were enrolled to account for possible dropout. The use of nVNS in this study was endorsed by an investigational device exemption from the FDA, and this study was approved by the Stanford Institutional Review Board. All examinations, data collection, and follow-up were conducted between June 2017 and February 2019.

2.2 | Vagal nerve stimulation

Patients self-administered bilateral transcutaneous cervical non-invasive vagal nerve stimulation (nVNS) twice daily for a minimum of four weeks using the gammaCore hand-held vagal nerve stimulator (electroCore Inc). Twice daily stimulation was selected based on a standing prophylactic approach (rather than as needed for acute flares), prior studies showing efficacy with q12h dosing for episodic headaches,[14] and personal communications revealing difficulty maintaining compliance with three times a day dosing, as reported by Paulon et al[10] nVNS was delivered via two stainless steel contact surfaces that were coated with conductive gel before each treatment, and the device was positioned in parallel with the carotid pulse in the neck (Figure S1). A single stimulation of nVNS was programed as a 2-minute period. On day one of treatment, patients were trained on proper positioning and instructed to adjust the stimulation intensity voltage using the + and − buttons to achieve a comfortable tingling sensation in tissues beneath the stimulation plates and engagement of the facial nerve with ipsilateral lip pull. A skilled clinical coordinator provided training on the correct use of the nVNS device. Throughout the treatment period, patients self-administered nVNS at home, two stimulations sequentially to each of the left and right neck overlaying the vagus nerve, two times daily (four stimulations per day) for a minimum of 4 weeks. Compliance was assessed through email reminders, diary completion, and telephone follow-ups. Phone calls were only used when subjects did not reply to reminder emails, showed lag in daily diary completion, and/or reporting adverse events or clinically relevant events. At no time were subjects cued about use, prolongation or cessation of nVNS device use. At the end of the treatment period, study subjects were re-assessed by a gastroenterologist and underwent testing for gastric emptying and autonomic function. All subjects were instructed to continue recording daily symptoms for an additional four weeks without therapy (washout period), after which they were re-assessed in clinic by a gastroenterologist and underwent repeated autonomic function testing.

2.3 | Symptom scoring

For each patient that completed the study (defined as a patient who returned a diary containing symptom data of at least four weeks of nVNS, and two weeks of washout), a mean GCSI-dd aggregate score (0-5) was calculated for the two-week pretreatment phase (ie, baseline), the last week of nVNS, and the last week of washout. We defined a responder for this study as a patient who experienced a ≥0.75 point decrease from baseline in GCSI-dd aggregate score after at least four weeks of nVNS. In addition, scores for nausea/vomiting, fullness/early satiety/appetite, and bloating/abdominal pain GCSI-dd subscales were assessed independently at each study visit via the Patient-Reported Outcomes Measurement Information System (PROMIS) Global Health and Pain Interference scales (PROMIS© Global Health) and the 12-item Short-Form Health Survey (SF-12) physical (SF12-PCS) and mental scales (SF12-MCS). Autonomic symptoms were scored using the validated 31-question scoring instrument, composite autonomic symptom score (COMPASS 31).

2.4 | Gastric emptying

Gastric emptying rate was assessed using the Spirulina gastric emptying breath test (GEBT) (Cairn Diagnostics), which is based on the absorption of spirulina labeled with ^{13}C, and measurement of this isotope in the breath over four hours postmeal challenge.[15] GEBT was performed at baseline and after nVNS.

2.5 | Autonomic function testing

Study subjects underwent autonomic function testing (AFT) at baseline, on the last day of treatment approximately 3-6 hours after last nVNS application, and after the washout period. All subjects were tested at approximately the same time (10 AM ± 1 hour), under same fasting conditions, in the same position (comfortably seated with both feet parallel on the ground, following a very strict protocol), and instructed to avoid alcohol, smoking, and caffeine for at least 24 hours. Menstrual cycle was not monitored or controlled for in this small pilot study. AFT was conducted using the ANX 3.0 (ANSAR Medical Technologies Inc). The ANX is a non-invasive, digital, real-time, heart rate variability and

respiratory variability-based monitor of the autonomic nervous system (ANS).[16] Three leads are used to capture EKG & respiratory signals. The ANX measures the ANS by detection and recording variations in the R-R, or beat-to-beat, interval and respiratory activity. Automated software performs spectral analysis to identify high- and low-frequency components of the heartbeat interval to precisely locate the parasympathetic signal. Respiratory activity analysis provides independent and more specific measurements of sympathetic activity and parasympathetic activity: at rest to determine baseline power and balance between the branches, during individual cardiovascular challenges to each branch, and a combined challenge to both branches to detect degrees of neuropathy or ANS branch suppression or excess. Eleven out of 15 subjects completed all three AFT time point recordings.

2.6 | Statistical analysis

Comparison of the three time points (pretreatment, nVNS, and washout) was done with repeated-measures one-way ANOVA followed by Tukey's post hoc multiple comparisons test (GraphPad Prism) on the absolute value of the mean composite and subscale GCSI-dd, and AFT endpoints. GEBT half-emptying time ($T^{1/2}$) and responder vs non-responder comparisons were done with paired and unpaired t test analyses, respectively. The Spearman correlations and linear regressions were performed to assess the relationship of symptom response (delta GCSI-dd) and gastric emptying (delta $T^{1/2}$) with selected study variables (voltage, duration of therapy, etc).

3 | RESULTS

Seventeen patients (14 women, 3 men) enrolled in the study. Of these, 2 (12%) opted out of the study during the baseline measures period prior to starting nVNS. Fifteen subjects completed the baseline assessment, and at least four weeks of treatment. Due to subject-related scheduling conflicts for posttherapy gastric emptying and autonomic function testing, subjects were instructed to continue therapy until their post-treatment visit. Fourteen subjects completed the post-treatment and washout assessments. Subject characteristics are presented in Table 1 and comorbidities in Table S2, with gastroesophageal reflux, migraines, anxiety, and asthma being the most common. At baseline, the GCSI-dd fullness/early satiety/appetite subscale was the most severe (median 3.3), followed by the bloating/abdominal pain subscale (median 2.6) (Table 2).

3.1 | nVNS is associated with improvement of cardinal symptoms of gastroparesis

Six out of 15 subjects (40% responders) achieved the primary endpoint of ≥0.75 absolute reduction in the composite GCSI-dd after ≥4 weeks of nVNS (Table 1). The mean absolute change in all 15 subjects was −0.69, which was driven mainly by improvement in the fullness/early satiety/appetite subscale (mean decrease of −0.87) (Table 2, Figure 1). After four weeks of washout, the reported composite CGSI-dd was still improved compared with baseline (−0.45) but not statistically significant (Table 2, Figure 1). We also found a 40% response rate (6/15 subjects) according to the FDA's most recent guidelines for GCSI-dd,[17] in which a meaningful response is considered to be a 30% decrease or >0.50 absolute decrease from baseline in at least 50% of the days or weeks of treatment (Figure S2). nVNS was very well-tolerated and no adverse events were reported during or after treatment. Responders showed significant symptom improvement in the Patient-Reported Outcomes Measurement Information System (PROMIS) gastrointestinal and pain symptom subscales (Figure 2), but not on the global health assessment (Figure S3). Responders also showed a trend of improvement in the 12-item Short-Form Health Survey (SF-12) physical symptom scale, but not the SF-12 mental health scale (Figure S3).

Duration of nVNS correlated with treatment response and was significantly different between responders and non-responders (Figure 3). Mean voltage was greater in the responder group (21.2 vs 15.8 mV; P = .16), though not statistically significant. Baseline GCSI-dd, age, BMI, and gender were not different between responders and non-responders (Table 1). However, responders had a greater median baseline SF-12 mental health symptom score (Figure S3), and greater delay in prior scintigraphy and baseline gastric emptying on the Spirulina breath test compared to non-responders (median $T^{1/2}$ 187 vs 144 minutes) (Table 1).

3.2 | nVNS is associated with improvement of gastric emptying

Treatment with nVNS led to an absolute reduction in gastric emptying half time ($T^{1/2}$ 155 minutes vs 129 minutes; P = .053, CI −0.4 to 45) (Figure 4). However, there was no difference in the improvement of gastric emptying between clinical responders vs non-responders (Figure S4A), nor was gastric acceleration associated with duration of nVNS or voltage (Figure S4B-C). Further, improvement in GCSI-dd did not correlate with improvement in gastric emptying (Figure S5).

3.3 | Short-term nVNS was not associated with improvement of autonomic dysfunction

At baseline, subjects presented with autonomic abnormalities, mainly, low sympathetic response to challenge (64% of subjects) and parasympathetic excess response to cardiovascular challenge (91%). Short-term nVNS did not normalize autonomic dysfunction during cardiovascular challenge testing (Table S3), nor did it improve symptoms associated with autonomic function (Figure S6).

TABLE 1 Study subject demographics

	All[a]		Responders (RE)[a]	Non-responders (NR)[a]	
n	15		6 (40%)	9 (60%)	
Age	34	(23-59)[b]	36	34	P[c] .64
Gender	87%	Female	83%	88%	P .8
Race	80%	White	100%	66%	P .11
A1C	5.3	(4.7-5.5)[b]	5.1	5.3	P .14
BMI	24.6	(18-30)[b]	27	22.3	P .35
Years diagnosed	3	(1-16)[b]	3	5	P .56
Baseline scintigraphy[d]	2 h: 70.2% 4 h: 30.7%	(92%-42%)[b] (63%-9%)[b]	85% 55%	67% 26%	P = .065 P = .011*
Baseline GCSI-dd	2.4	(1.5-3.9)[b]	2.4	2.6	P .8
Baseline GEBT T½ (min)	160	(59-200)[b]	187.7	144.3	P .05*
Days nVNS	35	(28-46)[b]	42.5	33	P .04*
Days washout	22.5	(9-39)[b]	30	17	P .001**
Days total	85	(59-148)[b]	89	68	P .051
VNS voltage	17	(7.5-30)[b]	18	16	P .16

Abbreviations: A1C, hemoglobin A1C; BMI, body mass index; GCSI-dd, gastroparesis cardinal symptom index daily dairy score; GEBT, gastric emptying breath test; nVNS, non-invasive vagal nerve stimulation.

[a]Median or %.

[b]Range.

[c]Chi-square test or t test.

[d]All subjects met criteria of >60% retention at 2 h and/or > 10% retention at 4 h.

*Significance set at $P \leq .05$.

**$P \leq .01$.

TABLE 2 Composite and subscale GCSI-dd scores

Median					Mean of differences					
GCSI-dd	Pre	nVNS	Wash		Pre vs nVNS	Adj. P	Pre vs Wash	Adj. P	nVNS vs Wash	Adj. P
Aggregate	2.4	1.65	2		−0.69	.0105*	−0.46	.08	0.23	.21
Std. dev.	0.76	1.05	1.09	CI	0.17 to 1.22		−0.05 to 0.96		−0.58 to 0.11	
Nausea	1.2	0.85	1		−0.41	.014*	−0.26	.11	0.15	.39
Std. dev	0.80	0.55	0.81	CI	0.085 to 0.74		−0.05 to 0.58		−0.44 to 0.14	
Fullness	3.35	2.2	2.65		−0.87	.03*	−0.65	.12	0.22	.43
Std. dev	0.89	1.42	1.32	CI	0.087 to 1.66		−0.15 to 1.46		−0.67 to 0.23	
Bloating	2.63	2	2.24		−0.64	.02*	−0.4	.09	0.25	.2
Std. dev	1.15	1.43	1.47	CI	0.074 to 1.21		−0.062 to 0.86		−0.66 to 0.16	

Abbreviation: CI, confidence interval.

*$P \leq .05$, Repeated-measures one-way ANOVA with Tukey's multiple comparison test (adj. P).

4 | DISCUSSION

This open-label pilot study suggests that short-term nVNS may have important clinical utility in mitigating the cardinal symptoms of gastroparesis in a subset of patients. Although our findings are consistent with a prior proof-of-concept study in medically refractory gastroparesis,[10] our results are tempered by a lack of placebo control group, a small cohort, and a prophylactic daily dosing regimen vs an on-demand-for-flare design of this study. Follow-up placebo-controlled, larger trials will be instrumental in determining if nVNS will become a clinical modality for gastroparesis therapy.

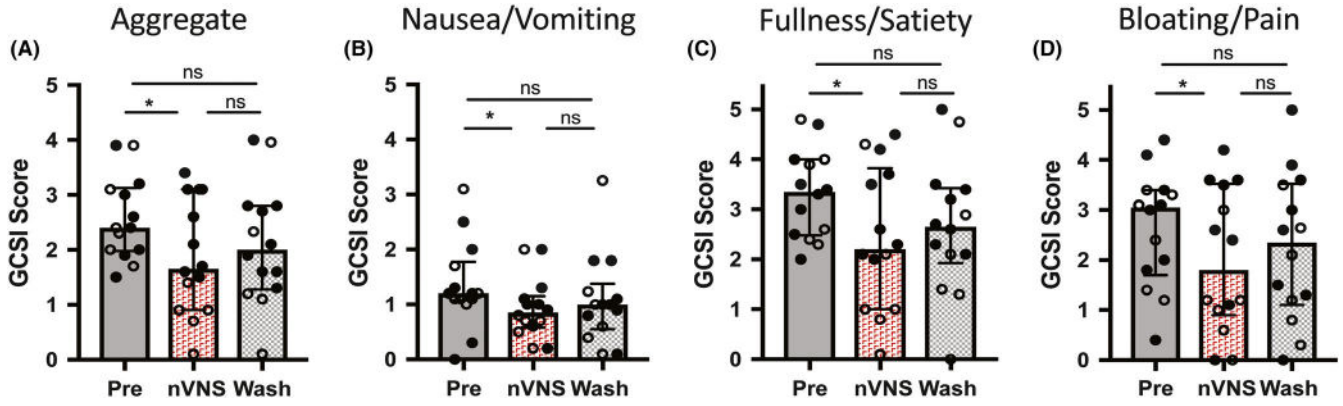

FIGURE 1 A, nVNS is associated with gastroparesis cardinal symptom improvement. Median GCSI-dd aggregate (A) and subscale scores (B-D). Empty symbols reflect clinical responders who had a ≥0.75 reduction in GCSI-dd aggregate score, solid circles reflect non-responders. (*$P \leq .05$; ns = non-significant, repeated-measures One-Way ANOVA Tukey's post hoc test for multiple comparisons)

Symptom management in gastroparesis remains a major challenge for both patients and clinicians. In the USA, approved therapy is restricted to a single prokinetic dopamine-2 receptor antagonist (metoclopramide) that carries a black box warning, as chronic use (>12 weeks) may lead to extrapyramidal side effects and potential irreversible tardive dyskinesia.[18] Therefore, gastroenterologists resort to a combination of nutritional recommendations, herbal therapy, off-label antiemetics, prokinetics and antidepressants, and endoscopic pyloric interventions (botox injections or myotomies) to best manage and prevent symptom flares.[19-21] Currently, several agents are under various stages of clinical trials including selective serotonin 5-HT4 receptor agonists, neurokinin-1 receptor antagonists, and ghrelin receptor agonists.[1] GES through continuous high-frequency/low-energy pulses is offered as a last resource for medically refractory patients and significantly decreases vomiting frequency and gastrointestinal symptoms in patients with severe gastroparesis.[22] Several mechanisms have been proposed to explain the symptomatic benefit of gastric neurostimulation including fundic relaxation, increases in vagal efferent and afferent activity, and central nervous system plasticity in the thalamic and caudate nuclei.[23] A central role for the vagus has been invoked based on (a) spectral analysis of heart rate variability showing that GES increases vagal activity in both rats and humans[24,25]; (b) vagotomy blocks its antiemetic effect in dogs[26]; and denervation of vagal afferents abolishes its enhancive effect on vagal efferent activity.[24]

The vagus nerve provides a bidirectional link between the brain and the gastrointestinal tract, and as such, is involved in maintaining the homeostasis of gut functions such as sensitivity, motility, and immunity both through its sensing and modulatory roles.[27] Being a major component in the control of upper gastrointestinal motility, low vagal tone has been associated with gastrointestinal motility disturbances.[28] The importance of vagal dysfunction in gastroparesis is further supported by evidence of autonomic neuropathy in diabetic gastroparesis[29] and the well-documented development of gastroparesis following iatrogenic surgical vagal nerve damage or transection.[30] Given its extensive innervation of the stomach[31] and its predominant role in parasympathetic regulation of inflammation and motility, the vagus nerve may be utilized as a powerful therapeutic target to restore upper gastrointestinal dysmotility and visceral hypersensitivity.[32] In fact, VNS is safe, well-tolerated, and effective in the treatment of inflammatory disorders associated dysautonomia, such as rheumatoid arthritis[33] and Crohn's disease.[34] The therapeutic effect of VNS in these disorders is based on stimulation of the cholinergic anti-inflammatory pathway,[35,36] which specifically targets pro-inflammatory macrophages in the myenteric plexus,[27] which have been implicated in the pathogenesis of gastroparesis.[37] As such, nVNS could potentially act as a disease modifier in gastroparesis, but this needs to be further investigated.

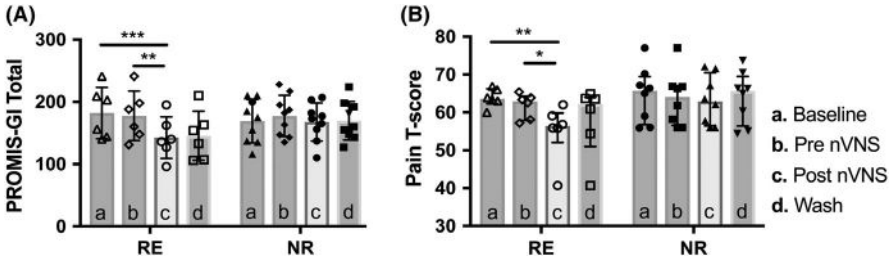

FIGURE 2 nVNS is associated with improvement in PROMIS GI and pain symptoms. Median PROMIS scores for gastrointestinal (GI) (A) and pain (B) symptoms. Responders (RE); non-responder (NR); (*$P \leq .05$; **$P \leq .01$; ***$P \leq .001$; ns = non-significant, repeated-measures 2-Way ANOVA Tukey's post hoc test for multiple comparisons)

Harnessing the potential benefits of VNS through non-invasive means dramatically reduces the risk/benefit ratio and makes this therapy available to a much broader patient population. In this study, we focused on idiopathic gastroparesis, as this comprises the largest, and least understood, cohort of this disorder. Short-term nVNS was safe, well-tolerated, and resulted in a 40% response rate in clinical symptoms, as well as improvement in gastric emptying. There is no clear consensus regarding the definition of response to short-term therapy for gastroparesis. We chose a moderate definition (≥0.75 point decrease from baseline in GCSI-dd aggregate score) for the current study based on existing literature at the time of trial design suggesting that a meaningful response may be defined by a minimally important difference of a 0.73 point decrease from baseline in GCSI-dd aggregate score.[38] The validity of our definition was supported by the clear divergence in scores between responders and non-responders, and was consistent with a similar 40% response rate using the most up-to-date FDA-recommended guideline for GCSI-dd,[17] in which a meaningful response is considered to be a 30% decrease or >0.50 decrease from baseline in at least 50% of the days or weeks of treatment. In a mixed cohort of medically refractory gastroparesis patients awaiting GES implantation, Paulon et al reported a similar 43% aggregate GSCI improvement after 3-6 weeks of nVNS with the gammaCore device, with the largest symptom benefit occurring in the nausea/vomiting GCSI-dd subscale.[10] In our study of idiopathic gastroparesis, the largest symptom improvement occurred in the fullness/early satiety/appetite subscale, which also happened to be the most severe in our cohort. Future larger studies should clarify if this is an effect size, or if nVNS leads to distinct symptom improvement profiles based on the treatment population (ie, idiopathic, diabetic, and surgical gastroparesis).

Beyond symptom improvement, responders were distinguished by increased baseline gastric emptying delay and higher mental health scores on SF-12 compared with non-responders. However, as reported in prior studies,[39,40] symptom improvement in our subjects was not significantly associated with changes in gastric emptying after treatment, and responders and non-responders did not differ significantly in reduction of gastric emptying time. Although we are the first to report that nVNS may improve gastric emptying, our results need to be validated in a larger cohort, as our 17% rate reduction is within the reported intra-individual variability reported for repeated gastric emptying testing.[41] Therefore, the role of nVNS in accelerating gastric emptying should be further investigated, but holds potential for improving dietary tolerability, oral medication pharmacokinetics, and glycemic indices in diabetic gastroparesis.

Although optimal dosing and duration of therapy need to be established, duration of therapy was positively correlated with symptom improvement. The strong correlation between duration of treatment and responder status may reflect a natural bias of responders to continue therapy beyond the minimum 4 weeks, and the inverse for non-responders. It is still unclear whether long-term therapy may have a higher response rate, as has become evident for GES therapy where symptomatic improvement requires months.[22] Because of the small sample size, a relationship between voltage dosing and likelihood of response could not be determined. For the majority of study subjects, cessation of nVNS was associated with relapse in symptoms, but at the end of the four-week washout period there was still a noticeable difference

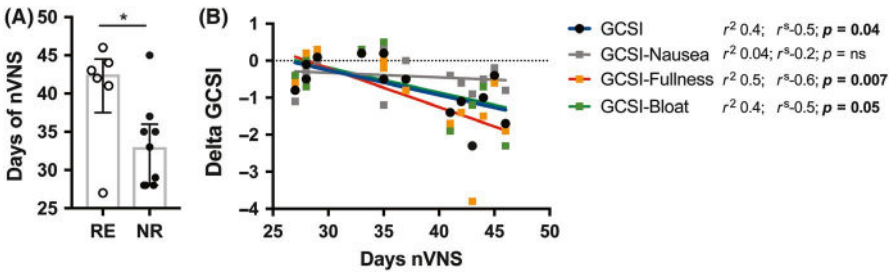

FIGURE 3 Duration of nVNS correlates with improved symptom scores. A, Responders (RE) had significantly increased days of nVNS compared with non-responders (NR). B, Linear regression (r^2) and Spearman's correlation (r^s) for composite GCSI-dd and its three symptom subscales with duration of nVNS therapy (RE, responders; NR, non-responder). (*$P \leq .05$, unpaired t test)

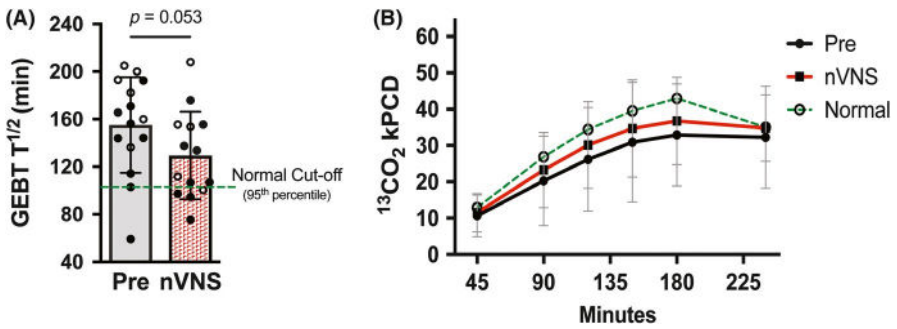

FIGURE 4 nVNS is associated with improvement in gastric emptying. A, Spirulina C^{13} gastric emptying breath test (GEBT) median emptying half time ($T^{1/2}$); empty symbols reflect responders, solid circles reflect non-responders. B, nVNS accelerated GEBT at most time points of the 4 h assay. (P = .053, unpaired t test)

from baseline. Future sham-controlled studies of longer duration will be needed to establish the impact of nVNS in patients with idiopathic gastroparesis.

Both diabetic and idiopathic gastroparesis are associated with autonomic dysfunction,[42] which our baseline AFT confirmed. Although long-term GES and implanted VNS can improve autonomic function,[43,44] short-term nVNS did not improve cardiovascular dysautonomia or autonomic symptoms in our gastroparesis cohort. Whether this was due to underpowering, duration of nVNS, differential vagal fiber engagement, or dosing (continuous high-frequency/low-energy pulses) is difficult to ascertain. Conversely, alternate measures of autonomic function may be more appropriate than heart rate variability-based assays to assess the impact of nVNS on gastrointestinal tract function.

In summary, this pilot open-label study validates nVNS as a potential therapy to improve gastric emptying and the cardinal symptoms of mild to moderate idiopathic gastroparesis. There are no therapies to date that have the potential to reverse underlying pathologic abnormalities in gastroparesis. nVNS, through its neuromodulatory and prokinetic effects, may offer a safe and well-tolerated therapy for the treatment of gastroparesis.

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DISCLOSURES

This was an investigator-initiated study that was generously funded by a philanthropic gift from Colleen and Bob Haas. ElectroCore only provided the devices to carry out the proposed research and participated in discussions about optimal dosing parameters during trial design. Electrocore had no role in data analysis or drafting of the manuscript.

AUTHOR CONTRIBUTIONS

AGB conceived and directed the study, established sample collection protocol, analyzed data, and wrote the manuscript; EPA helped establish sample collection protocol, coordinated enrollment, obtained patient consents, taught subjects to use the gammaCore device, ran experiments, coordinated sample collection, and collected subject information, and reviewed the manuscript; NFB assisted with subject enrollment, performed clinic visits, and reviewed the manuscript; JC assisted with subject enrollment, performed clinic visits, and reviewed the manuscript; AH helped conceive study and edited the manuscript; and LN helped conceive the study, identified patients for the study, performed clinic visits, performed clinical analysis of patients, and edited manuscript.

ORCID

Andres Gottfried-Blackmore https://orcid.org/0000-0002-3563-3727
Linda Nguyen https://orcid.org/0000-0002-3498-6897

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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