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TITLE: Effectiveness of Gastric Electrical Stimulation in Gastroparesis: Results from a Large Prospectively-Collected Database of National Gastroparesis Registries

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Backgound

Gastric electrical stimulation (GES) for treating gastroparesis symptoms is controversial.

Methods

We studied 319 idiopathic or diabetic gastroparesis symptom patients from the Gastroparesis Clinical Research Consortium (GpCRC) observational studies: 238 without GES and 81 with GES. We assessed the effects of GES using change in GCSI total score and nausea/vomiting subscales between baseline and 48 weeks. We used propensity score methods to control for imbalances in patient characteristics between comparison groups.

Key Results

GES patients were clinically worse (40% severe vs. 18% for non-GES; $P<0.001$); worse PAGI-QOL (2.2. vs. 2.6; $P = 0.003$); and worse GCSI total scores (3.5 vs. 2.8; $P<0.001$). We observed improvements in 48-week GCSI total scores for GES vs. non-GES: improvement by ≥ 1-point (RR = 1.63; 95% CI = (1.14, 2.33); $P = 0.01$) and change from enrollment (difference = -0.5 (-0.8, -0.3); $P < 0.001$). When adjusting for patient characteristics, symptom scores were smaller and not statistically significant: improvement by ≥ 1-point (RR = 1.29 (0.88, 1.90); $P = 0.20$) and change from the enrollment (difference = -0.3 (-0.6, 0.0); $P = 0.07$). Of the individual items, the nausea improved by ≥ 1 point (RR = 1.31 (1.03, 1.67); $P = 0.04$).

Conclusions and Inferences

This multi-center study of gastroparesis patients found significant improvements in gastroparesis symptoms among GES patients. Accounting for imbalances in patient characteristics, only nausea remained significant. A much larger sample of patients is needed to fully evaluate symptomatic responses and to identify patients likely to respond to GES.

Key Words: Gastroparesis; Nausea; Vomiting; Abdominal Pain; Gastric Electrical Stimulation

Introduction

Gastric electrical stimulation (GES) has been approved as a Humanitarian Use Device (HUD) in the US since 2000 for the treatment of gastroparesis of diabetic or idiopathic origin and has been used in several thousand patients in the US and worldwide since then.[1,2] GES systems are expensive, as are for clinical trials, involve invasive surgery, and require additional visits and maintenance, and trials are difficult to be properly designed and executed. GES can be viewed as part of a larger attempt to use bioelectric stimulation as a therapy of the GI Tract as recently reviewed by Payne et al.[3] As noted in this and other recent publications, bioelectric stimulation is being widely applied to the gastrointestinal (GI) tract, including but not limited to: thalamic,[4] spinal cord,[5] vagal (including auricular)[6], and electro-acupuncture,[7] as well as GES, both high[8] and low[9] energy. Despite its HUD approval, the use of GES has been controversial and the data, including controlled trials, has been the source of much debate.[10-15] Given difficulties in conducting placebo-controlled trials for surgical procedures, an alternative approach would be to derive information from prospectively-collected data in cohorts of patients, some of which undergo intervention with GES therapy based on clinical indications and eligibility, while others do not (i.e., a variation on the "pragmatic trial" method). We utilized prospectively-collected data from patients enrolled in the Gastroparesis Clinical Research Consortium (GPCRC) prospective cohort studies to pragmatically evaluate the effectiveness of the GES system implantation for reduction in symptoms of gastroparesis.

Methods

Study data

We examined the data of patients who participated in two National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) Gastroparesis Clinical Research Consortium (GpCRC) prospective cohort studies, Gastroparesis Registry (GpR) (ClinicalTrials.gov identifier: NCT00398801) and Gastroparesis Registry 2 (GpR2) (ClinicalTrials.gov identifier: NCT01696747). Diabetic or Idiopathic gastroparetics as well as patients with gastroparesis-like symptoms were participating in this study. In the GpR study, patients were recruited at 6 academic centers and followed every 16 weeks. In the GpR2 study, patients were recruited at 9 centers and followed every 24 weeks. Prospectively-collected data included medical histories, physical and blood exams, gastroparesis-related symptoms and functional exams, and psychological distress measures. This data included patients who had both delayed and non-delayed gastric emptying, the latter group also referred to as gastroparesis-like syndrome. Patients in GpR 1 and 2 did not have regularly scheduled repeat gastric emptying tests.

GpR and GpR2 patients who did not have the gastric electrical stimulation (GES) system implanted at the enrollment, who were recruited at study centers that implant the GES therapy, and who completed the 48-week follow-up visit, were eligible for this study. We included 6 sites that practice the GES implantation, with a range or 2-16 stimulators in the sites. As of January 2018, 708 patients were enrolled at the GES-practicing clinics. Among those, 321 patients did not have the GES system implanted at enrollment and completed the 48-week visit. For patients who participated in both cohort studies, we used the data of a study in which they had the GES system implanted between enrollment and the 48-week visit. If the GES system was not implanted in both studies, records in the first cohort study (GpR) were used. After removing two incomplete records, our final sample size was 319 (Figure 1).

Device Implantation

Gastric stimulators were inserted as previously described in the operating room, either laparoscopically or laparotomy with peri-procedure antibiotics, and indications and contraindications for device placement were left up to each center. The stimulating electrodes were inserted sub-serosally approximately 10 cm proximal to the pylorus along the greater curvature and were placed parallel to one another, one centimeter apart. An upper endoscopy was performed intra-operatively to ensure no penetration of the stimulating electrodes through the mucosa. The GES placement could also involve inserting a jejunostomy feeding tube or performing a pyloroplasty at the discretion of the gastroenterologist and surgeon. Indications for enteral access and/or pyloric therapy in the NIH GpCRC patients was determined by each center. The stimulator was turned on either the same day or the day afterwards and most patients stayed in the hospital for 1-2 postoperative days. Initial stimulator settings were the same for all centers: 5 mA of current, 330 microseconds pulse width, 0.1 seconds on and 5.0 seconds off. Protocols for GES adjustment after implantation was left up to each site. In general, if adjustments are made, often the initial change is to increase the amperage from 5 to 7.5 then to 10 milliamp. If this does not help, then the frequency is increased from 14 Hz to 28 Hz, then to 55 Hz. This follows the suggestions previously reported on adjusting GES devices.[34]

Outcome and exposure variables

The primary outcome was improvements in symptoms of gastroparesis as measured by change in the Gastroparesis Cardinal Symptom Index (GCSI) total score[35] from the enrollment in the cohort study to the 48-week follow-up visit. We used 3 outcome measures of the GCSI total score for the evaluation of

the GES implantation: any improvement (i.e. any decline in the GCSI total score); its improvement by 1-point or more; and its change from the enrollment. The GCSI total score increases with symptom severity and ranges from 0 to 5. It is given by an average of 3 subscales (nausea/vomiting, post-prandial fullness/early satiety, and bloating). Each subscale is calculated as an average of 2-4 items in 6-point Likert scale with a range of 0-5. As the secondary outcome, improvements in symptoms measured by the nausea/vomiting subscale, in aggregate, as well as separately (nausea, retching, and vomiting scores), were assessed and analyzed in a similar manner.

We compared the outcome measures between patients who received the GES system during this 48-week follow-up period (GES patients) and those who did not (non-GES patients). The GES system was implanted at varying times between the enrollment and the 48-week follow-up visit.

We used the following baseline measures, not those measured at the GES implantation, to reduce bias in comparison of the outcomes between GES therapy vs. non-GES patients: GCSI total score, nausea/vomiting subscale, nausea, retching, or vomiting score; gender (female vs. male); age (as two spline terms with a breakpoint at 35 years); race (white vs. non-white); education (post high school education or more vs. less); annual household income ($50,000+ vs. less); BMI (in kg/m^2); delay in gastric emptying (present vs. absent); etiology of gastroparesis (diabetic, idiopathic, other); duration with gastroparesis symptoms (as two spline terms with a breakpoint at 12 years); use of narcotic pain medications (yes vs. no); and total number of classes of medication (0-11). For the age and the duration with gastroparesis symptoms, we used linear splines to accommodate their non-linear association with the outcomes. The total number of classes of used medication were counted from the following 11 classes: antidiabetic; antihyperlipidemic; anticoagulant; systemic corticosteroids; cardiovascular/antihypertensive; proton pump inhibitors/histamine H2 receptor antagonists; prokinetic; antiemetic; pain relieving/analgesics/non-steroidal anti-inflammatory/aspirin; narcotic (opioid) pain medications; and neuropathic pain medications.

Statistical methods

Baseline characteristics were compared between GES therapy and non-GES patients using *t*-test for continuous variables and Fisher's exact test for categorical variables. We analyzed the observed vs. maximum possible follow-up time in each group using Kaplan-Meier plots, in which time of the GES implantation was interpolated as the midpoint between two visits.

Since the GES therapy was not assigned randomly, we used propensity score methods to reduce bias in comparing GES therapy with non-GES patients.[36] Propensity scores for receiving the GES system were estimated using logistic regression with the above-mentioned baseline exposure variables.

We stratified the patients into 3 subclasses so that GES therapy and non-GES patients have similar propensity score values within each subclass. After we verified a balance of baseline exposure variables within subclass, we estimated subclass-specific effects of GES therapy and obtained its total effects using the Mantel-Haenszel relative risk[37,38] for the binary outcomes (any improvement and improvement by ≥ 1-point in GCSI total score, nausea/vomiting subscale, and each subscale component) and the inverse-variance weighted average[39] for the continuous outcome (change in GCSI total score, nausea/vomiting subscale, and its components). Observed and propensity-score adjusted relative risk (relative improvement) and difference in changes between the GES and non-GES patients were reported. Stratified analysis by severity of gastroparesis symptoms (baseline GCSI total score ≥3.0 vs. <3.0) was assessed using linear regression adjusting for patient characteristics. Note that this conventional analysis method was applied since our sample size was too small for propensity-score analyses after stratification. Power and sample size for detecting improvement in GCSI total score by ≥ 1-point was calculated based on the test for two independent proportions. All the analyses used Stata version 15.1 (StataCorp LLC, College Station, Texas).

Results

Of a total of 319 patients, 81 (25%) patients had the GES system implanted between enrollment and 48-week follow-up visit; 238 patients did not. GES patients at enrollment were clinically worse (40% graded as having severe gastroparesis) as compared to the non-GES patients (18%; $P < 0.001$) and had more delayed gastric emptying (80% vs. 68%; $P = 0.05$) (Table 1). Three patients with a post-surgical gastroparesis diagnosis received stimulators, out of 17 total patients with that diagnosis in the study population. Two of 81 patients who received stimulators also received pyloplasties, both at one center. Differences were seen between GES and non-GES patients, with GES patients having higher numbers of medications, including opioids (4.8 vs. 4.1; $P = 0.004$). GES patients had higher (i.e., worse) values in baseline GCSI total score (3.5 vs. 2.8; $P < 0.001$), in all the GCSI sub-scores, and in almost all the PAGI-SYM symptom severity scores. GES patients were with lower (i.e., worse) PAGI-QOL score (2.2 vs. 2.6; $P = 0.003$). GES and non-GES patients did not differ in demographic, socioeconomic, behavioral indicators, and the anxiety scores.

More than half of GES therapy patients were estimated to have received the GES system at 12 weeks (Figure 2); 58%, 62% and 84% had the GES system implanted by 16, 24, 36 weeks, respectively. The follow-up time of the patients with the GES was 2,456 person-weeks, which was 63% of the maximum follow-up time if the GES system had been implanted at enrollment in all patients.

On average, the GCSI total score was higher in GES patients as compared to non-GES patients (Figure 3, top left). In GES patients, a major decline in GCSI total score was observed between enrollment and 16-week visits (Figure 3, top). Propensity scores to the GES system overlapped between GES and non-GES patients (Supplemental Figure 1).

In the unadjusted analysis, 78% of GES therapy patients improved in the GCSI total score, whereas 58% improved among non-GES patients (relative risk (RR) = 1.33; 95% confidence interval (CI) = 1.14, 1.56; $P = 0.002$) (Table 2). Thirty-eight (38) percent of GES patients improved in the GCSI total score by ≥ 1-point, whereas 24% improved among non-GES patients (RR = 1.63; 95% CI = 1.14, 2.33; $P = 0.01$). The observed net change in GCSI total score between the enrollment and the 48-week visit was -0.8 in GES patients and -0.3 in non-GES patients with a difference of -0.5 (95% CI = -0.8, -0.3; $P < 0.001$However, after accounting for the propensity to receive the GES system, the observed improvements were not statistically significant: any improvement between GES vs. non-GES patients with RR = 1.16 (95% CI = 0.98, 1.38); $P = 0.11$); improvement by ≥ 1-point with RR = 1.29 (95% CI = 0.88, 1.90; $P = 0.20$); and a difference in changes of -0.3 (95% CI = -0.6, 0.0; $P = 0.07$). Subclass-specific estimates are presented in Supplemental Figure 2. A similar pattern was observed for nausea/vomiting subscale (Table 2) and the individual subscale symptoms (Table 3). Of the individual subscale measures, only the nausea symptom was improved by ≥ 1-point (RR = 1.13; 95% CI = 1.03, 1.67; $P = 0.04$) although its net change did not differ (-0.1; 95% CI = -0.6, 0.3; $P = 0.52$) (Table 3). In some cases across scores we assessed, improvements of ≥ 1-point were noted even when the mean differences were not different. Patients with GCSI total score ≥ 3.0 tended to improve in GCSI total score more than those with the score < 3.0 (adjusted differences, -0.5 vs. 0.1; $P = 0.02$) (Table 4).

Discussion

Given the difficulties in conducting trials on complex patient populations with devices, alternative methods seem warranted for evaluating devices such as the GES system in patients with the symptoms of gastroparesis. This study is the first to use a propensity score approach to compare patients with the symptoms of gastroparesis who have received GES devices, and compared them with a similar group

of patients who did not undergo neuromodulation. In this study, the patients receiving device differed in several measures of illness, such as being clinically more severely ill, with greater gastric emptying delay at baseline, than those patients not receiving GES. The GES patients also had worse symptoms and quality of life measures at baseline.

In the GpCRC clinical centers using a pragmatic treatment design of prospectively enrolled patients, we observed improvements in the GCSI, and nausea, retching, and vomiting severity in patients receiving GES. The results of the improvements in the nausea/vomiting subscale were similar to those changes were seen with the GCSI total score. Since, from previous trials, the primary changes seen with GES were in nausea and vomiting, this finding is consistent with previous work on GES. On the other hand, whereas we initially observed significant improvements in the GCSI total score comparing GES therapy and non-GES patients, after propensity score adjustment for imbalances in patient characteristics between two groups of patients, the improvements became smaller and not statistically significant for most measures, with the exception of improvement in nausea symptom by ≥ 1-point. This difference before and after the adjustment was due to the initial GCSI score. Patients with severe symptoms (i.e., with high GCSI total score) were more likely to receive the GES system and more likely to improve in the GCSI total score as compared to patients with mild symptoms. In the previous work from our consortium, we observed a more severe GCSI score at baseline is associated with a better outcome, which could explain the uncorrected results with the GES.[40] We should also note that non-GES groups are likely to have received other therapies. In this sense, we could conclude that GES improved gastroparesis symptoms, but the degree of improvements was not far different from other alternative treatments. However, patients with higher GCSI total scores (≥ 3.0) improved more with GES than did those patients with GCSI < 3.0, when compared to non-GES patients, implying that GES effect may be greater in patients with greater symptoms.

Seven meta-analyses and/or guidances have been published on GES; two are generally positive for both diabetic and idiopathic gastroparesis,[16,17] three are positive for diabetic vs. idiopathic gastroparesis.[18-20] Most studies published on GES have been open-label, and randomized controlled trial (RCT) data has been conflicting, with some trials showing positive effects during RCT trials and other trials not.[10-15,21,22] Including this current study and a newer study (submitted for publication), there are 8 controlled trials of GES among which 6 were randomized. Of these 8 controlled trials, 6 were small or intermediate size[10-14,23] and 2 were larger size, including this and the newest trial.[24] Of the 6 randomized trials, 3 had cross over designs now determined to be unwise.[10,11,13] The other three

randomized trials were reported as positive.[12,14,24] The main problem with cross-over studies that are now viewed as unwise is that the fact that GES effects can occur as quickly as 72 hours, and may not respond to even a prolonged wash out phase, which was not recognized when the trials were designed.[11]

The conclusions in the current study are to be taken with several caveats in mind. Our sample size of GES therapy patients was not large enough to estimate benefits and risks of the GES system implantation; the statistical power was 26% for detecting 1.29-fold likelihood of improvement in GCSI total score by ≥ 1-point. We would need about 1,600 patients, assuming the same ratio of GES and non-GES patients as this study, to detect the same difference with 80% power. Further subset analysis, for example by diagnosis of idiopathic or diabetic gastropareses diagnosis, were not deemed possible due to small sample sizes in this trial. Secondly, although propensity score methods are a valid way to evaluate treatments in complex non-randomized cohort studies, they must be used with caution since the propensity score methods cannot adjust for unobserved patient characteristics, which can be achieved only by randomized control trials.[36] Finally, a small potential source of bias in our data is that GES patients were not followed for full 48 weeks, but an average of 30 weeks, and that patient characteristics at baseline, not at the GES implantation, were used for adjustment.

Hence, it would be indispensable to conduct additional well-designed cohort studies with sufficient sample size, and if feasible, a randomized clinical trial. Conducting these studies is made more difficult as devices, unlike pharmaceuticals, do not have to be provided without charge from the manufacturer for clinical trials in the US. The most recent randomized clinical trial, from France, which showed significant changes between On and Off for GES therapy, may address some of these issues, but is not yet published as a full publication.[24] Other approaches would be to select patients for whom we expect optimal response to GES in terms of a given patient's anatomy and physiology effecting outcome. The anatomic measure of gastric Cajal cells have been reported to effect outcome[41,42] as measured by full thickness biopsy, although this can now be performed less invasively.[43] Several studies have now shown that baseline gastric electrical activity, particularly when done with multi-point (low-resolution) recordings of the gastric mucosa, can predict outcome to temporary and permanent GES.[11,30,44]

One of the other difficulties with device trial for gastroparesis is that the mechanism of action of GES has not been well understood. Besides a documented central effect in several studies,[25,26] recent NIH DiaComp work has reported other mechanisms of action of temporary and permanent GES, including

an early and sustained anti-emetic effect; an early and durable gastric prokinetic effect in delayed emptying patients; an early anti-arrhythmic effect that continues over time; a late autonomic effect; a late hormonal effect; an early anti-inflammatory effect that persists; and an early and sustained improvement in health-related quality of life.[27] Older work has shown that GES can also improve pancreatic function in patients with the symptoms of gastroparesis, likely via a vagal mechanism.[14] Recent work with temporary and permanent GES has reported an effect on the small bowel[28] and colon.[29,30] However, one randomized sensory study did not reveal a central effect of GES in humans.[31] Other work, however, has demonstrated effect of GES on GI peptides.[32] Previous work has shown an effect on survival for patients receiving GES versus controls,[33] which when combined with other recent publications, implies that GES may have an effect on disordered pathophysiology in some patients with gastroparesis symptoms.

Several additional aspects of neuromodulation need to be addressed as pertaining to this study. One aspect, which is used for the majority of all neuromodulation device trials worldwide, is to use a temporary phase first, but this was done in only 1 of the 6 randomized controlled trials. Temporary GES, using non-surgical leads placed on the gastrointestinal mucosa, has been used for a number of years on a variety of patients, including those of pediatric age, but is an off-label use in the US.[9] A recent publication has presented long term follow up of GES in patients who received temporary GES first,[11] and which suggests that temporary GES may be able to predict permanent GES response.[45]

Another aspect of the treatment of gastroparesis is the emerging area of pyloric therapies.[46-50] Without evidence based data on the role of pyloric therapy for gastroparesis, it is difficult to know how this approach may have changed the outcome of the patients in this study. Presumably, additional patients likely would have benefited from pyloric therapy, but at this time one can only speculate as to how many patients this would be as only 2 patients in this series had pyloric therapy. Newer approaches to decisions about pyloric therapy, using pyloric physiologic measures have been reported[47,51] but have not been systematically explored. In addition, a number of patients in the GpCRC have the symptoms of gastroparesis but do not have delayed solid gastric emptying, and thus, with the current approach to pyloric therapy, would not have been considered for that intervention. In terms of GES and pyloric therapy, recent publication has presented an algorithmic approach that could be considered as a way to integrate GES and pyloric (and other) therapies.[45] However, long term follow up data on this proposed approach is not yet available.

It is also important to mention that the current approval of GES in the US is for drug refractory diabetic and idiopathic gastroparesis and that HUD approval is based on the criteria of being safe and probably effective. This HUD designation, awarded in 2000, was based on one open label and one double-blinded study, both international studies of moderate sample size.[1,12]

From the latest available data, approximately 18,000 GES devices have been implanted worldwide with a current device system cost of about $13,500. Of those, about 90 % are in the US [52] and of those, approximately 50 % were implanted in 20 US centers. As detailed in this report, GES is currently more likely to be given to patients with more severe drug-refractory gastroparesis symptoms. The question of whether the HUD designation is still appropriate is one that will likely continue to be debated. Newer, less invasive, and less costly ways of delivering GES have been proposed[53,54] and with other bio-electric therapies being currently trialed, it may be some time before the optimal role of GES in the therapy of patients with gastroparesis, particularly predominant nausea and vomiting, symptoms can be determined.

Conclusions

In the NIDDK GpCRC multi-center cohort study of 319 patients with gastroparesis, of whom 81 received GES, we observed significant improvements in the GCSI, and nausea, retching, and vomiting severity in patients receiving GES versus patients not receiving GES. However, accounting for baseline gastroparesis severity and other factors, observed improvements attenuated, and only the improvement in nausea score by ≥ 1 point remained significant. Patients with greater symptoms scores at baseline improved more with GES than those with lesser symptoms. A much larger sample of patients with the GES in either a cohort study or randomized clinical trial is needed to fully evaluate symptomatic responses to GES and to precisely identify the patients more or less likely to respond.

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References

1. Abell TL, Van Cutsem E, Abrahamsson H, et al. Gastric electrical stimulation in intractable symptomatic gastroparesis. *Digestion.* 2002;66(4):204-212.
2. Shada A, Nielsen A, Marowski S, et al. Wisconsin's Enterra Therapy Experience: A multi-institutional review of gastric electrical stimulation for medically refractory gastroparesis. *Surgery.* 2018.
3. Payne SC, Furness JB, Stebbing MJ. Bioelectric neuromodulation for gastrointestinal disorders: effectiveness and mechanisms. *Nature reviews Gastroenterology & hepatology.* 2019;16(2):89-105.
4. Luyten L, Welkenhuysen M, van Kuyck K, et al. The effects of electrical stimulation or an electrolytic lesion in the mediodorsal thalamus of the rat on survival, body weight, food intake and running activity in the activity-based anorexia model. *Brain Res Bull.* 2009;79(2):116-122.
5. Song GQ, Sun Y, Foreman RD, Chen JD. Therapeutic potential of spinal cord stimulation for gastrointestinal motility disorders: a preliminary rodent study. *Neurogastroenterol Motil.* 2014;26(3):377-384.

6. Paulon E, Nastou D, Jaboli F, Marin J, Liebler E, Epstein O. Proof of concept: short-term non-invasive cervical vagus nerve stimulation in patients with drug-refractory gastroparesis. *Frontline Gastroenterol.* 2017;8(4):325-330.
7. Wang CP, Kao CH, Chen WK, Lo WY, Hsieh CL. A single-blinded, randomized pilot study evaluating effects of electroacupuncture in diabetic patients with symptoms suggestive of gastroparesis. *Journal of alternative and complementary medicine (New York, NY).* 2008;14(7):833-839.
8. Forster J, Sarosiek I, Delcore R, Lin Z, Raju GS, McCallum RW. Gastric pacing is a new surgical treatment for gastroparesis. *Am J Surg.* 2001;182(6):676-681.
9. Abell TL, Chen J, Emmanuel A, Jolley C, Sarela AI, Tornblom H. Neurostimulation of the Gastrointestinal Tract: Review of Recent Developments. *Neuromodulation.* 2015;18(3):221-227.
10. McCallum RW, Sarosiek I, Parkman HP, et al. Gastric electrical stimulation with Enterra therapy improves symptoms of idiopathic gastroparesis. *Neurogastroenterol Motil.* 2013;25(10):815-e636.
11. Abell TL, Johnson WD, Kedar A, et al. A double-masked, randomized, placebo-controlled trial of temporary endoscopic mucosal gastric electrical stimulation for gastroparesis. *Gastrointest Endosc.* 2011;74(3):496-503.e493.
12. Abell T, McCallum R, Hocking M, et al. Gastric electrical stimulation for medically refractory gastroparesis. *Gastroenterology.* 2003;125(2):421-428.
13. McCallum RW, Snape W, Brody F, Wo J, Parkman HP, Nowak T. Gastric electrical stimulation with Enterra therapy improves symptoms from diabetic gastroparesis in a prospective study. *Clin Gastroenterol Hepatol.* 2010;8(11):947-954.
14. Luo J, Al-Juburi A, Rashed H, et al. Gastric electrical stimulation is associated with improvement in pancreatic exocrine function in humans. *Pancreas.* 2004;29(2):e41-44.
15. Abell TL, McCallum RW, May KP, et al. Effectiveness of Gastric Electrical Stimulation in Gastroparesis: Results From a Large Prospectively Collected Database of a National Gastroparesis Registry (Abstract). *Gastroenterology.* 2015;148(4):S65.
16. O'Grady G, Egbuji JU, Du P, Cheng LK, Pullan AJ, Windsor JA. High-frequency gastric electrical stimulation for the treatment of gastroparesis: a meta-analysis. *World J Surg.* 2009;33(8):1693-1701.
17. Kong MF. NICE Guidance on gastroelectrical stiumlation for diabetes. *Br J Diabetes Vasc Dis.* 2015;15:34-36.

18. Chu H, Lin Z, Zhong L, McCallum RW, Hou X. Treatment of high-frequency gastric electrical stimulation for gastroparesis. *Journal of gastroenterology and hepatology.* 2012;27(6):1017-1026.
19. Camilleri M. Treatment of Gastroparesis. *UpToDate.* 2019.
20. Camilleri M, Parkman HP, Shafi MA, Abell TL, Gerson L. Clinical guideline: management of gastroparesis. *Am J Gastroenterol.* 2013;108(1):18-37.
21. Soffer E, Abell T, Lin Z, et al. Review article: gastric electrical stimulation for gastroparesis--physiological foundations, technical aspects and clinical implications. *Aliment Pharmacol Ther.* 2009;30(7):681-694.
22. Yin J, Abell TD, McCallum RW, Chen JD. Gastric neuromodulation with Enterra system for nausea and vomiting in patients with gastroparesis. *Neuromodulation.* 2012;15(3):224-231; discussion 231.
23. Cutts TF, Luo J, Starkebaum W, Rashed H, Abell TL. Is gastric electrical stimulation superior to standard pharmacologic therapy in improving GI symptoms, healthcare resources, and long-term health care benefits? *Neurogastroenterol Motil.* 2005;17(1):35-43.
24. Ducrotté P, Coffin B, Mathieu N, et al. Gastric Electrical Stimulation (Ges) for Refractory Vomiting: Results of a Prospective Multicenter Double-Blinded Randomized Controlled Cross-Over Trial. *Gastroenterology.* 2017;152(5):S167.
25. Zhang J, Chen JD. Systematic review: applications and future of gastric electrical stimulation. *Aliment Pharmacol Ther.* 2006;24(7):991-1002.
26. Tang M, Zhang J, Chen JD. Central mechanisms of gastric electrical stimulation involving neurons in the paraventricular nucleus of the hypothalamus in rats. *Obesity surgery.* 2006;16(3):344-352.
27. Abell TL, Kedar A, Stocker A, et al. Gastroparesis syndromes: Response to electrical stimulation. *Neurogastroenterol Motil.* 2019;31(3):e13534.
28. McKenzie P, Stocker A, Du P, et al. The Effect of Gastric Electrical Stimulation on Small Bowel Motility in Patients With Gastroparesis and Concomitant Pancreatic and Small Bowel Dysfunction: From Animal Model to Human Application. *Neuromodulation.* 2018.
29. Agrawal A, Francis SL, Deveneau NE, et al. Gastric Electrical Stimulation and Sacral Electrical Stimulation: A Long-Term Follow-Up Study of Dual-Device Treatment. *Dig Dis Sci.* 2016;61(1):176-180.
30. Elmasry M, Hassan H, Atassi H, et al. Baseline Predictive Factors for Fore and Hind Gut Response to Long-Term GI Electrical Stimulation (Abstract, In Press). 2019.

31. Frokjaer JB, Ejskjaer N, Rask P, et al. Central neuronal mechanisms of gastric electrical stimulation in diabetic gastroparesis. *Scand J Gastroenterol.* 2008;43(9):1066-1075.
32. Meleine M, Melchior C, Prinz P, et al. Gastrointestinal Peptides During Chronic Gastric Electrical Stimulation in Patients With Intractable Vomiting. *Neuromodulation.* 2017;20(8):774-782.
33. Anand C, Al-Juburi A, Familoni B, et al. Gastric electrical stimulation is safe and effective: a long-term study in patients with drug-refractory gastroparesis in three regional centers. *Digestion.* 2007;75(2-3):83-89.
34. Abidi N, Starkebaum WL, Abell TL. An energy algorithm improves symptoms in some patients with gastroparesis and treated with gastric electrical stimulation. *Neurogastroenterol Motil.* 2006;18(4):334-338.
35. Revicki DA, Rentz AM, Dubois D, et al. Development and validation of a patient-assessed gastroparesis symptom severity measure: the Gastroparesis Cardinal Symptom Index. *Aliment Pharmacol Ther.* 2003;18(1):141-150.
36. Rosenbaum PR, Rubin DB. Reducing Bias in Observational Studies Using Subclassification on the Propensity Score. *Journal of the American Statistical Association.* 1984;79(387):516-524.
37. Rothman K, Boice JD. Epidemiological analysis with a programmable calculator. *Washington, DC: US Dept of Health, Education, and Welfare, Public Health Service, National Institutes of Health.* 1979;79-1649.
38. Robins J, Breslow N, Greenland S. Estimators of the Mantel-Haenszel Variance Consistent in Both Sparse Data and Large-Strata Limiting Models. *Biometrics.* 1986;42(2):311-323.
39. Hartung J, Knapp G, Sinha BK. *Statistical Meta-Analysis with Applications.* Hoboken, NJ: Wiley; 2008.
40. Pasricha PJ, Yates KP, Nguyen L, et al. Outcomes and Factors Associated With Reduced Symptoms in Patients With Gastroparesis. *Gastroenterology.* 2015;149(7):1762-1774.e1764.
41. Heckert J, Thomas RM, Parkman HP. Gastric neuromuscular histology in patients with refractory gastroparesis: Relationships to etiology, gastric emptying, and response to gastric electric stimulation. *Neurogastroenterol Motil.* 2017;29(8).
42. Omer E, Kedar A, Nagarajarao H, et al. Cajal Cell Counts are Important Predictors of Outcomes in Drug Refractory Gastroparesis Patients with Neurostimulation. *Journal of Clinical Gastroenterology (In Press).* 2018.

43. Othman MO, Davis B, Saroseik I, Torabi A, McCallum RW. EUS-guided FNA biopsy of the muscularis propria of the antrum in patients with gastroparesis is feasible and safe. *Gastrointest Endosc.* 2016;83(2):327-333.
44. Shine A, Ahmed S, McElmurray L, Stocker A, Pinkston C, Abell TL. Electrogastrography at Baseline and Response to Temporary Gastric Electrical Stimulation--A Comparison of Cutaneous with Mucosal Recordings (Abstract, In Press). 2019.
45. Atassi H, Abell TL. Gastric Electrical Stimulator for Treatment of Gastroparesis. *Gastrointestinal endoscopy clinics of North America.* 2019;29(1):71-83.
46. Xue HB, Fan HZ, Meng XM, et al. Fluoroscopy-guided gastric peroral endoscopic pyloromyotomy (G-POEM): a more reliable and efficient method for treatment of refractory gastroparesis. *Surg Endosc.* 2017;31(11):4617-4624.
47. Saadi M, Yu D, Malik Z, Parkman HP, Schey R. Pyloric sphincter characteristics using EndoFLIP((R)) in gastroparesis. *Revista de gastroenterologia de Mexico.* 2018;83(4):375-384.
48. Szarka LA, Gostout CJ. Expanding submucosal endoscopy with applied knowledge. *Gastrointest Endosc.* 2017;85(1):140-142.
49. Lee AA, Hasler WL. G-POEM for Gastroparesis: Is There Pressure to Go with the Flow? *Dig Dis Sci.* 2018;63(9):2165-2167.
50. Sarosiek I, Forster J, Lin Z, Cherry S, Sarosiek J, McCallum R. The addition of pyloroplasty as a new surgical approach to enhance effectiveness of gastric electrical stimulation therapy in patients with gastroparesis. *Neurogastroenterol Motil.* 2013;25(2):134-e180.
51. Gourcerol G, Tissier F, Melchior C, et al. Impaired fasting pyloric compliance in gastroparesis and the therapeutic response to pyloric dilatation. *Aliment Pharmacol Ther.* 2015;41(4):360-367.
52. Burlen J, Runnels M, Mehta M, et al. Efficacy of Gastric Electrical Stimulation for Gastroparesis: US/European Comparison *Gastroenterology Research.* 2018;11(5):349-354.
53. Deb S, Tang SJ, Abell TL, et al. An endoscopic wireless gastrostimulator (with video). *Gastrointest Endosc.* 2012;75(2):411-415, 415.e411.
54. Camilleri M. Novel Diet, Drugs, and Gastric Interventions for Gastroparesis. *Clin Gastroenterol Hepatol.* 2016;14(8):1072-1080.

Table 1 Comparison of baseline patient characteristics between GES and non-GES patients ($N = 319$)

Baseline patient characteristics	GES patients (n = 81)		Non-GES patients (n = 238)		*P**
	N (%) or mean (±SD)		*N* (%) or mean (±SD)		
Demographic and behavioral					
Gender (female)	67	(83%)	204	(86%)	0.56
Age					0.06
18-29	14	(17%)	50	(21%)	
30-44	33	(41%)	58	(24%)	
45-59	25	(31%)	95	(40%)	
60+	9	(11%)	35	(15%)	
Race and ethnicity (%)					0.07
Non-Hispanic white	67	(83%)	172	(72%)	
Non-Hispanic black	7	(9%)	15	(6%)	
Hispanic	6	(7%)	40	(17%)	
Other	1	(1%)	11	(5%)	
Marital status, married or with partner (%)	51	(63%)	130	(55%)	0.20
Education (% college or higher)	22	(27%)	81	(34%)	0.27
Household annual income, $50,000+ (%)	36	(44%)	126	(53%)	0.20
Current smoker (%)	31	(38%)	71	(30%)	0.17
Alcohol intake, 2-4 times a month or more (%)	10	(12%)	48	(20%)	0.13
BMI (kg/m^2)	26.1	(±6.6)	27.6	(±7.9)	0.11
Medical history					
Gastroparesis severity, grade 3 (%)	32	(40%)	43	(18%)	<0.001
Hospitalized for gastroparesis in past year (%)	49	(60%)	74	(31%)	<0.001
Gastroparesis etiology (%)					0.27
Diabetic	27	(33%)	59	(25%)	
Idiopathic	51	(63%)	164	(69%)	
Other	3	(4%)	15	(6%)	
Duration with gastroparesis symptoms (year)	5.4	(±5.3)	4.9	(±5.9)	0.54
Use of narcotic pain medication	40	(49%)	81	(34%)	0.02
Total number of classes of medication† (0-11)	4.8	(±2.1)	4.1	(±2.0)	0.004
PAGI-QoL‡ (0-5)	2.2	(±1.2)	2.6	(±1.1)	0.003

Baseline patient characteristics	GES patients (n = 81) *N* (%) or mean (±SD)	Non-GES patients (n = 238) *N* (%) or mean (±SD)	*P**
State anxiety inventory score	43.8 (±14.4)	42.9 (±13.7)	0.62
Trait anxiety inventory score	44.4 (±13.6)	41.9 (±12.4)	0.12
Gastric emptying (mean % retained)			
2-hour emptying	55.7 (±21.6)	53.6 (±22.8)	0.47
4-hour emptying	28.2 (±23.3)	22.7 (±20.6)	0.05
Delayed gastric emptying§ (%)	65 (80%)	163 (68%)	0.05
PAGI-SYM¶ symptom severity (0-5)			
GCSI total score	3.5 (±1.0)	2.8 (±1.0)	<0.001
Nausea/vomiting subscale	3.2 (±1.5)	2.1 (±1.4)	<0.001
Nausea	3.9 (±1.3)	3.1 (±1.5)	<0.001
Retching	2.8 (±1.8)	1.6 (±1.7)	<0.001
Vomiting	2.7 (±2.0)	1.6 (±1.8)	<0.001
Postprandial fullness subscale	3.8 (±1.1)	3.3 (±1.1)	<0.001
Stomach fullness	3.9 (±1.2)	3.4 (±1.3)	0.003
Unable to finish meal	3.8 (±1.4)	3.3 (±1.5)	0.006
Feel full after meals	4.0 (±1.2)	3.7 (±1.3)	0.06
Loss of appetite	3.6 (±1.5)	2.8 (±1.6)	<0.001
Subscale for bloating	3.5 (±1.4)	2.9 (±1.6)	0.001
Bloating	3.7 (±1.3)	3.0 (±1.6)	<0.001
Stomach visibly larger	3.3 (±1.7)	2.7 (±1.8)	0.009
Subscale for upper abdominal pain	3.5 (±1.4)	2.9 (±1.6)	<0.001
Upper abdominal pain	3.5 (±1.5)	2.7 (±1.7)	<0.001
Upper abdominal discomfort	3.6 (±1.5)	3.0 (±1.6)	0.007
Propensity score (%)			
Used for GCSI total score	0.39 (±20)	0.21 (±16)	<0.001
Used for nausea/vomiting subscale	0.37 (±19)	0.21 (±15)	<0.001
%Follow-up time with exposure# (follow-up weeks with exposure/maximum possible follow-up weeks)	63% (2,456/3,888)	100% (11,424/11,424)	

GCSI, Gastroparesis Cardinal Symptom Index

* *P*-values from *t*-test for continuous variables and Fisher's exact test for categorical variables.

† Counted the following 11 classes of medication: antidiabetic; antihyperlipidemic; anticoagulant; systemic corticosteroids; cardiovascular/antihypertensive; proton pump inhibitors/histamine H2 receptor antagonists; prokinetic; antiemetic; pain relieving/analgesics/non-steroidal anti-inflammatory/aspirin; narcotic (opioid) pain medications; and neuropathic pain medications.

‡ Patient Assessment of Upper Gastrointestinal Disorders-Quality of Life.

§ Defined as the gastric emptying test of >60% at 2 hours or >10% at 4 hours.

¶ Patient Assessment of Gastrointestinal Disorders Symptom Severity Index.

‖ Two clinics provided the GES system implantation at a rate of ≥ 50%; other clinics provided at 15-25%.

\# Follow-up weeks with exposure is defined as: weeks with the GES system implanted in GES patients, and weeks without the GES system in non-GES patients. Maximum possible follow-up weeks are defined as follow-up weeks we would expect if patients had been exposed to the exposure at the enrollment.

Table 2 Effectiveness of the gastric electrical stimulation (GES) for reduction of gastroparesis symptoms over 48 weeks: observed and propensity score adjusted model ($N = 319$)

Measurement of 48-week improvements in PAGI-SYM score (48-week vs. enrollment)	Observed data				Propensity score-adjusted model*	
	N (% improved) or Mean difference (± SD)		Unadjusted model			
	GES ($N = 81$)	Non-GES ($N = 238$)	Relative risk or difference in changes (GES vs. non-GES) (95% CI)	*P*†	Relative risk or difference in changes (GES vs. non-GES) (95% CI)	*P*
Improvement in GCSI total score						
Improved GCSI (yes vs. no)	63 (78%)	139 (58%)	1.33 (1.14, 1.56)	0.002	1.16 (0.98, 1.38)	0.11
Improved GCSI by ≥ 1-point (yes vs. no)	31 (38%)	56 (24%)	1.63 (1.14, 2.33)	0.01	1.29 (0.88, 1.90)	0.20
Net change in GCSI	-0.8 (± 1.3)	-0.3 (± 1.0)	-0.5 (-0.8, -0.3)	<0.001	-0.3 (-0.6, 0.0)	0.07
Improvement in nausea/vomiting subscale						
Improved subscale (yes vs. no)	59 (73%)	117 (49%)	1.48 (1.23, 1.78)	<0.001	1.21 (1.00, 1.47)	0.06
Improved subscale by ≥ 1-point (yes vs. no)	38 (47%)	69 (29%)	1.62 (1.19, 2.20)	0.003	1.11 (0.82, 1.50)	0.52
Net change in subscale	-0.9 (± 1.5)	-0.3 (± 1.4)	-0.6 (-1.0, -0.3)	<0.001	-0.2 (-0.5, 0.2)	0.41

* Propensity scores were calculated using logistic regression with the binary indicator for the GES implantation as an outcome. Included covariates were baseline values of GCSI total score or nausea/vomiting subscale, gender (female vs. male), age (two spline terms with a breakpoint at 35 years), race (white vs. non-white), education (post high school education or more vs. less), annual household income ($50,000+ vs. less), BMI, delay in gastric emptying (present vs. absent), etiology of gastroparesis (diabetic, idiopathic, or other), duration

with gastroparesis symptoms (as two spline terms with a breakpoint at 12 years), use of narcotic pain medications (yes vs. no), and total number of classes of medications.

The patients were stratified into 3 subclasses so that subclasses have an equal number of GES patients. The average GES effect was calculated as the Mantel-Haenszel relative risk for the binary outcomes (any improvement in score and improvement in score by ≥ 1point) and the inverse-variance weighted average for the continuous outcome (change in score).

† *P*-values from chi-squared test for the binary outcomes and *t*-test for the continuous outcome.

Table 3. Effectiveness of the gastric electrical stimulation (GES) for reduction of 3 item scores that constitute the nausea/vomiting subscale over 48 weeks: observed and propensity score adjusted model ($N = 319$)

Measurement of 48-week improvements in PAGI-SYM score (48-week vs. enrollment)	Observed data				Propensity score-adjusted model*	
	N (% improved) or Mean difference (± SD)		Unadjusted model			
	GES ($N = 81$)†	Non-GES ($N = 238$)†	Relative risk or difference in changes (GES vs. non-GES) (95% CI)	*P*‡	Relative risk or difference in changes (GES vs. non-GES) (95% CI)	*P*
N**ausea** item score						
Improvement by ≥ 1-point (yes vs. no)	50 (62%)	100 (42%)	1.47 (1.17, 1.84)	0.002	1.31 (1.03, 1.67)	0.04
Net change in item score	-0.9 (±1.6)	-0.5 (±1.7)	-0.4 (-0.9, 0.0)	0.04	-0.1 (-0.6, 0.3)	0.52
Retching item score						
Improvement by ≥ 1-point (yes vs. no)	46 (58%)	76 (32%)	1.79 (1.38, 2.34)	<0.001	1.23 (0.97, 1.58)	0.10
Net change in item score	-1.0 (±1.8)	-0.1 (±1.7)	-0.9 (-1.3, -0.5)	<0.001	-0.3 (-0.8, 0.1)	0.13
Vomiting item score						
Improvement by ≥ 1-point (yes vs. no)	39 (48%)	75 (32%)	1.53 (1.14, 2.05)	0.007	1.06 (0.80, 1.40)	0.70
Net change in item score	-0.7 (±1.9)	-0.3 (±1.6)	-0.5 (-0.9, 0.0)	0.04	0.0 (-0.4, 0.4)	0.93

* Propensity scores were calculated using logistic regression with the binary indicator for the GES implantation as an outcome. Included covariates were baseline values of corresponding item score, gender (female vs. male), age (two spline terms with a breakpoint at 35 years), race (white vs. non-white), education (post high school education or more vs. less), annual household income ($50,000+ vs. less), BMI, delay in gastric emptying (present vs. absent), etiology of gastroparesis (diabetic, idiopathic, or other), duration with gastroparesis symptoms (as two spline terms with a breakpoint at 12 years), use of narcotic pain medications (yes vs. no), and total number of classes of medications.

The patients were stratified into 3 subclasses so that subclasses have an equal number of GES patients. The average GES effect was calculated as the Mantel-Haenszel relative risk for the binary outcomes (any improvement in score and improvement in score by ≥ 1point) and the inverse-variance weighted average for the continuous outcome (change in score).

† When the outcome is about retching, the sample size was: 80 GES patients and 237 non-GES patients.

‡ *P*-values from chi-squared test for the binary outcomes and *t*-test for the continuous outcome.

Table 4 Effectiveness of the gastric electrical stimulation (GES) for reduction of gastroparesis symptoms over 48 weeks: observed and adjusted effects stratified by severity of gastroparesis symptoms at baseline

GCSI total score	Mean change during the 48-week follow-up Estimate (± SD)		Observed difference in changes* GES vs. non-GES		Adjusted difference in changes† GES vs. non-GES	
	GES	Non-GES	Estimate (95% CI)	*P* for difference	Estimate (95% CI)	*P* for difference
<3.0 (N = 159‡)	0.0 (±1.1)	-0.1 (±1.0)	0.1 (-0.3, 0.6)	0.009	0.1 (-0.3, 0.6)	0.02
≥3.0 (N = 160§)	-1.2 (±1.2)	-0.5 (±0.9)	-0.6 (-1.0, -0.3)		-0.5 (-0.8, -0.2)	

* Linear regression was used with the change in GCSI total score as an outcome. Included covariates were indicator variables for GES implantation (yes vs. no) and severity of gastroparesis (GCSI total score ≥3.0 vs. <3.0) and their interaction term. Results of 1-*df* Wald test for the interaction term were reported as *P*-values for difference in differences in changes in GCSI total score by gastroparesis severity (GCSI total score ≥3.0 vs. <3.0).

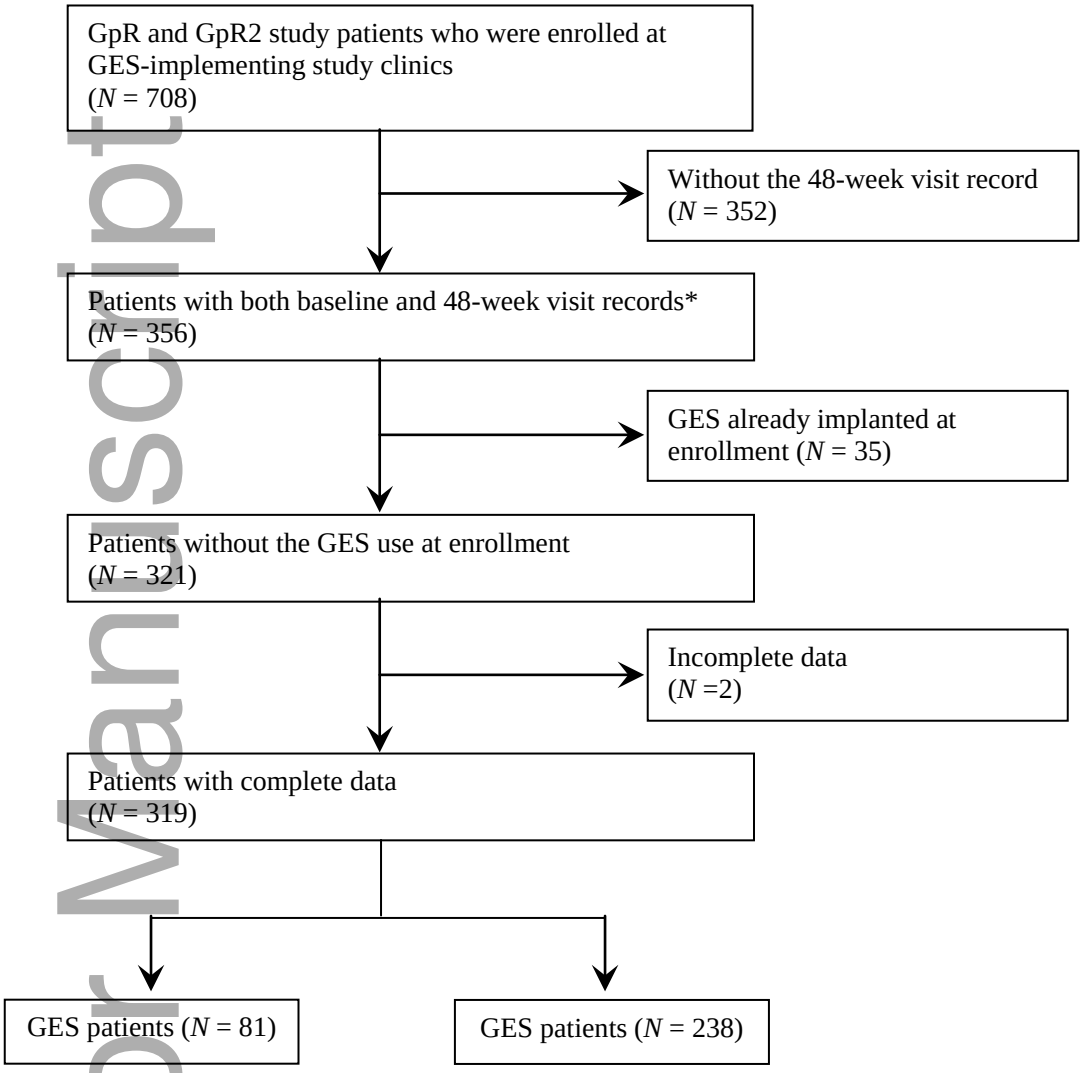
† Adjusted for patient characteristics using linear regression with the change in GCSI total score as an outcome. Included additional covariates were the same as those used to construct a propensity score model, which are: baseline GCSI total score, gender, age, race,

education, annual household income, BMI, delay in gastric emptying, etiology of gastroparesis, duration with gastroparesis symptoms, use of narcotic pain medication, and total number of classes of medications. Note that we applied linear regression adjusted for these baseline patient characteristics as covariate, different from propensity score analysis that was used in the main analysis.

‡ *N* = 159; GES = 24 vs. non-GES = 135.

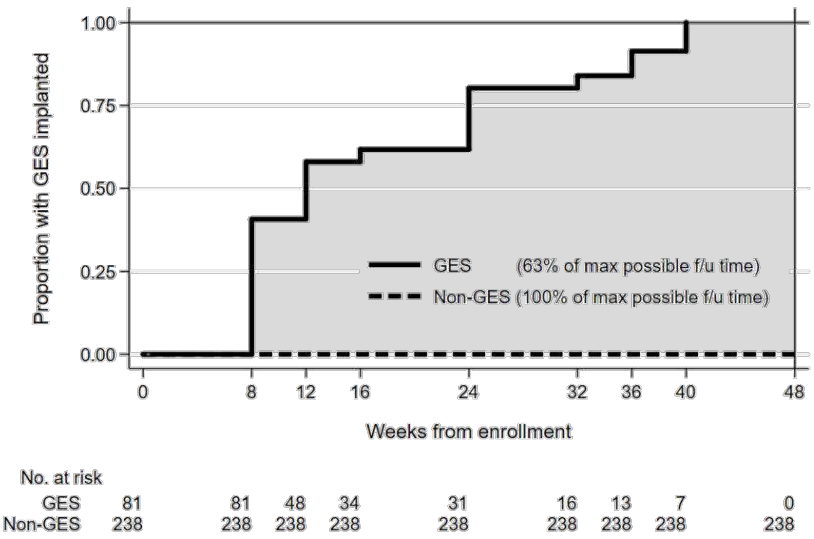
§ *N* = 160; GES = 57 vs. non-GES = 103.

Figure 1 Selection of study population from Consort Diagram



* Six (6) patients participated in both study, and their records of the GpR study were used if they had never had the GES. If the GES was implanted during the follow-up, records of the first study when the GES was implanted were used.

Figure 2 Time from enrollment to GES implantation (*N* = 319; 81 GES patients, 238 non-GES patients)

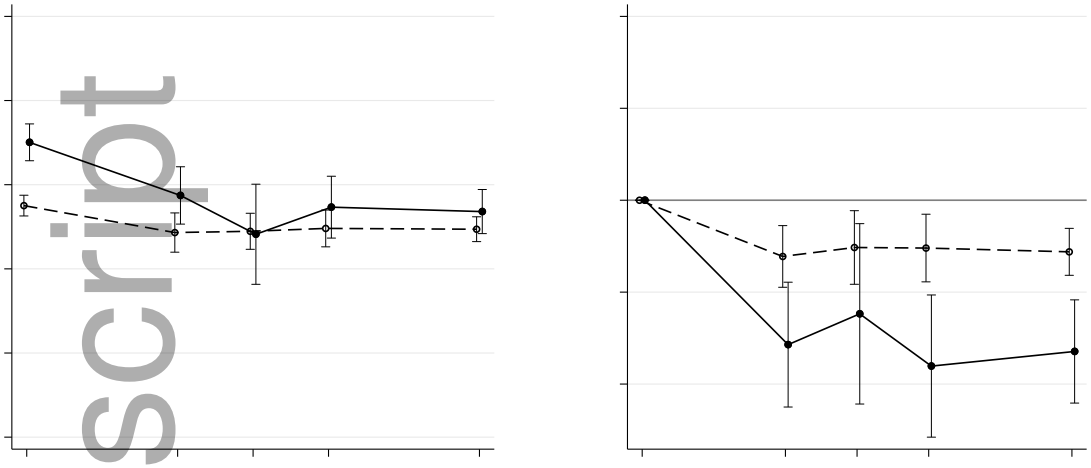


Notes:
Time of GES implantation was interpolated as the midpoint between two visits.

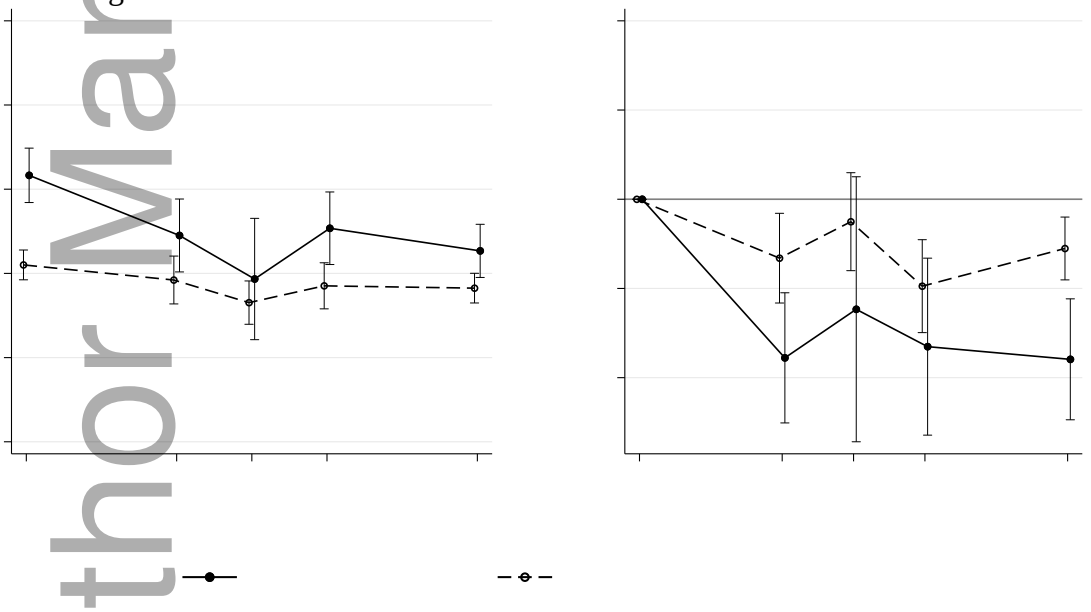
The follow-up time in GES patients with the GES system was 63% of the maximum possible follow-up time if the GES system had been implanted at enrollment. Among GES patients, 58%, 62% and 84% had the GES system implanted by 16, 24, 36 weeks, respectively; median and mean weeks to the GES implantation were 12 weeks and 17.7 weeks, respectively.

Figure 3 Change of PAGI-SYM scores from study enrollment to 48 weeks, GES vs. non-GES patients (*N* = 319; 81 GES patients, 238 non-GES patients)

GCSI total score



Nausea/vomiting subscale



Notes:

The vertical bars are 95% confidence intervals.

The 4-*df* test for the difference in change in GCSI Total Score between GES and non-GES patients was *P* = 0.005, and the test for nausea/vomiting subscale was *P* = 0.01. The significance was computed from generalized estimating equations (GEE) linear regression with robust variance estimation, modeling change in GCSI total score as a function of GES implantation, visit indicator (16-, 24-, 32-, or 48-week), and GES implantation by visit indicator interaction.