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ORIGINAL ARTICLE

Gastric Electric Stimulation for Refractory Gastroparesis: A Prospective Analysis of 151 Patients at a Single Center

Jason Heckert[1] · Abhinav Sankineni[1] · William B. Hughes[2] · Sean Harbison[2] · Henry Parkman[1]

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Abstract
Background Gastric electric stimulation (GES) is used to treat patients with refractory gastroparesis symptoms. However, the effectiveness of GES in clinical practice and the effect of GES on specific symptoms of gastroparesis are not well delineated.
Aims To determine the effectiveness of GES for treatment for refractory symptoms of gastroparesis, the improvement in specific symptoms of gastroparesis, and clinical factors impacting on outcome.
Methods Enterra GES was used to treat refractory gastroparesis symptoms. Patients filled out a symptom severity questionnaire (PAGI-SYM) prior to insertion. At each follow-up visit, the patient filled out PAGI-SYM and assessed their therapeutic response using the Clinical Patient Grading Assessment Scale (CPGAS).
Results One hundred and fifty-one patients (120 females) with refractory gastroparesis (72 diabetic, 73 idiopathic, 6 other) underwent GES. Of the 138 with follow-up (1.4 ± 1.0 years), the average CPGAS was 2.4 ± 0.3 (SEM): 104 patients (75 %) improved (CPGAS > 0) and 34 (25 %) did not (CPGAS ≤ 0). Sixty patients (43 %) were at least moderately improved (CPGAS score ≥ 4). Clinical improvement was seen in both diabetic and idiopathic patients with the CPGAS in diabetic patients (3.5 ± 0.3) higher in idiopathic patients (1.5 ± 0.5; $p < 0.05$). Symptoms significantly improving the most included nausea, loss of appetite, and early satiety. Vomiting improved in both diabetic and idiopathic patients although the diabetic subgroup experienced a significantly greater reduction in vomiting than the idiopathic subgroup.
Conclusions In this cohort of patients with refractory gastroparesis, GES improved symptoms in 75 % of patients with 43 % being at least moderately improved. Response in diabetics was better than in nondiabetic patients. Nausea, loss of appetite, and early satiety responded the best.

Keywords Gastroparesis · Enterra · Diabetes · Idiopathic gastroparesis

Introduction

Gastroparesis is a chronic disorder often with persistent symptoms despite medical treatment. Gastric electric stimulation (GES) has been investigated as a treatment for patients with symptoms of gastroparesis who do not improve with conventional prokinetic and antiemetic agents [1–5]. Prospective studies in large series of patients are few and from few centers [5, 6]. Furthermore, the effectiveness of this treatment in clinical practice is not well delineated with reported response rates varying from 50 to 80 % [2, 3]. Several studies report a better therapeutic outcome in patients with diabetic gastroparesis than patients with idiopathic gastroparesis [1, 4, 5]. However, a recent study reported there was no difference in response between these two subgroups [3]. Regarding other prognostic factors, patients whose main symptoms are nausea/vomiting have been reported to respond better than patients whose main

✉ Henry Parkman
henry.parkman@temple.edu

[1] Gastroenterology Section, Department of Medicine, Temple University School of Medicine, Parkinson Pavilion, 8th Floor, 3401 North Broad Street, Philadelphia, PA 19140, USA

[2] Department of Surgery, Temple University School of Medicine, Philadelphia, PA, USA

symptom is abdominal pain [4]. These prognostic factors have not been well delineated in large series of patients.

The aim of this study was to determine the effectiveness of GES when used for clinical care for refractory symptoms of gastroparesis. We also wished to determine the improvement of specific symptoms of gastroparesis and to determine clinical factors and patient-related factors impacting on outcome.

Methods

This clinical protocol was conducted prospectively at Temple University Hospital in patients undergoing GES (Medtronic, Inc.) for refractory gastroparesis under the FDA's Humanitarian Device Exemption program, which has been approved at our institution by our Institutional Review Board.

Patients

This study included 151 consecutive patients with refractory gastroparesis who were implanted at our institution under the HDE program over a 42-month period from July 2010 to December 2013. All patients had delayed gastric emptying [7, 8] and had continued symptoms despite therapy with prokinetic agents and antiemetic agents.

Gastric Electric Stimulator Placement

Enterra gastric electric stimulator was placed surgically under general anesthesia, via laparotomy by one of two surgeons (SH and WBH). The Enterra GES system consists of a pair of electrodes connected to a pulse generator. The two stimulation leads were inserted into the gastric muscularis propria 1 cm apart along the greater curvature 9.5 and 10.5 cm proximal to the pylorus. An upper endoscopy was performed to ensure that there was no penetration of the wires through the mucosa into the stomach lumen. A horizontal incision through the skin in the right lower quadrant was performed, and the distal ends of the stimulating wires were tunneled through the abdominal wall and connected to the neurostimulator. The impedance (resistance) between the wires was measured to ensure it was in the appropriate range (400–800 Ω). The neurostimulator with the distal ends of the stimulating wires was then placed into the RLQ subcutaneous pocket. Both the RLQ incision and the laparotomy incision were closed, followed by repeat interrogation of the stimulator to determine the impedance of the stimulating system. Patients were hospitalized with a median recovery time of approximately 3 days, for intravenous fluids, controlling any postoperative ileus, advancing diet and decreasing analgesic pain medications. The day after surgery, the stimulator was turned on. The pulse generator delivers low energy, 0.1-s train of pulses at a frequency of 12 cycles per minute. Within each pulse train, individual pulses oscillate at a frequency of 14 cycles per second. The voltage of the stimulations is set so that the current is 5 mA.

After hospital discharge, patients were seen 2 weeks later for assessment of the incision. Then patients were followed at 6 weeks, 3, 6, 9 and 12 months after stimulator placement. Patients also continued with their usual medical care including visits with their internist and/or endocrinologist who managed the patient's other medical problems including diabetes. At follow-up visits to the gastroenterologists, medications were reviewed and new treatments could be added if appropriate. The gastric stimulator was interrogated to see if changes in resistance occurred; if so readjustments were made to keep the current at desired levels (5 mA). For severe refractory symptoms, the stimulator parameters could be adjusted at or after the 3-month follow-up visit, typically first increasing the current from 5 to 10 mA, then increasing the frequency from 14 to 28 Hz. Rarely, the on duration was increased from 0.1 to 1 s.

Questionnaires

Patients completed questionnaires to acquire data prior to Enterra implantation (at baseline) and at subsequent visits. Baseline was defined as the 2-week period before the surgical implantation of the device. The Patient Assessment of GI Symptoms (PAGI-SYM) questionnaires include the Gastroparesis Cardinal Symptom Index (GCSI) scores as well as additional questions concerning abdominal pain, constipation, and diarrhea [9]. The GCSI evaluates the severity of nine symptoms over the past 2 weeks using a Likert scale from 0 (none) to 5 (very severe) [10]. The symptoms include nausea, retching, vomiting stomach fullness, inability to finish a normal meal, feeling excessively full after meals, loss of appetite, bloating and stomach visibly larger. Questions were also asked about the presence of upper abdominal pain, upper abdominal discomfort, constipation, and diarrhea with similar scoring to the GCSI symptoms.

Patient-related factors have been associated with treatment outcomes in chronic disorders. The Patient Activation Measure questionnaire quantifies patients' knowledge, skill, and confidence for self-management of their health and chronic conditions [11]. It has been previously shown to predict outcomes in chronic diseases such as diabetes [12]. Patient's activation, that is, knowledge/confidence in treatment, has not been examined in patients with refractory gastroparesis, and particularly, those undergoing GES. The 13-item Patient Activation Measure (PAM) was

assessed in the patients before undergoing GES. This study also assessed if employment status, income, and support network influenced therapeutic outcome.

For assessment of global clinical response, the following question was utilized. "In thinking about the last 2 weeks, how would you say your stomach/gastroparesis-related problems/symptoms have been compared to the period before you started Enterra gastric electric stimulation?" Responses were improved, no change, worsened. Patients were then asked to quantify their therapeutic response using the Clinical Patient Grading Assessment Scale (CPGAS) [4]. Patients could pick a number over a range ($+7$ = completely better; 0 = no change; -7 = very much worse) that best answered the question. A score of 4 indicates the patient being moderately better, which this study considered as being "at least moderately improved." This response scale has been used in other studies assessing outcomes in gastroparesis [13, 14].

Statistical Analysis

Data were compiled in a Microsoft Excel database. Results are expressed as percentage of patients, or mean ± SD or mean ± SEM where appropriate. Analyses were performed using paired Student's t test, ANOVA, Pearson correlation coefficient, and Chi-squared where appropriate.

Results

Baseline Demographics

One hundred and fifty-one patients with refractory gastroparesis were implanted with Enterra GES at our institution over a 42-month period under the HDE guidelines, that is, refractory symptoms of nausea and vomiting from diabetic or idiopathic gastroparesis. The patients consisted of 120 females and 31 males with a mean age of 38.2 years (range 18–69). Two patients, both diabetic, ultimately had the stimulator removed for infection (one at 6 months, the other at 7 months post-implantation). One diabetic patient died due to unrelated causes. Ten patients were lost to follow-up and never completed any follow-up questionnaire. Follow-up data were available for 138 of the 151 patients. The mean follow-up for the 138 patients was 520 ± 350 (SD) days. Table 1 shows the baseline demographic information of the 151 patients undergoing GES therapy and 138 patients who have follow-up information.

Of the 138 patients, 65 had diabetic gastroparesis and 68 were classified as idiopathic. The remaining 5 were classified as other (one CIIP, one post-infection, two post-surgery, 1 borderline diabetic). Of the 138 patients, all had documented delayed gastric emptying.

Global Response

The data from the completed questionnaire during the last follow-up were used as the outcome data. 59 % of patients completed at least 12 months of follow-up, 22 % completed between 6 months and 12 months of follow-up, and 19 % completed less than 6 months of follow-up. More specifically, 1 patient had follow-up at 26 days, 7 patients had follow-up between 1 to 3 months days, and 19 patients had follow-up between 3 to 6 months. The remaining 111 patients had follow-up greater than 6 months, with 80 patients having follow-up greater than 1 year. In response to the CPGAS question, 104 patients (75 %) felt their symptoms had improved, and 34 (25 %) felt that their symptoms were the same or had worsened (Fig. 1). The response in diabetics was greater than in idiopathic patients ($p < 0.05$). Of the 65 diabetic patients, 55 (85 %) felt their symptoms had improved, while 10 (15 %) felt their symptoms had remained the same or worsened. Of the 68 idiopathic patients, 46 (68 %) felt their symptoms had improved, while 22 (32 %) felt that their symptoms remained the same or worsened.

Of the 138 with follow-up (1.4 ± 1.0 years), the average CPGAS was 2.4 ± 0.3 (SEM), which is significantly different from zero or no change in CPGAS ($p < 0.001$). Both the diabetic patients and the idiopathic patients had a significant improvement by the CPGAS scores (3.4 ± 0.4 for diabetic patients ($p < 0.001$) and 1.7 ± 0.4 in idiopathic patients ($p < 0.001$).

CPGAS scores $\geq$4 were considered at least moderately improved. 36 of 65 diabetic patients (55 %) had at least moderately improved, whereas 24 of 68 idiopathic patients (35 %; Chi-square = 4.6; $p < 0.05$) had marked improvement.

The most common adverse effect was pain or sensation at the stimulator site, which was experienced in 15 of the 138 patients (11 %).

Predictive Factors

Table 2 shows the mean CPGAS for patients based on various factors assessed. The only factor that was shown to have predictive value on CPGAS was etiology. Although both the diabetic patients and the idiopathic patients had a significant improvement by the CPGAS scores, diabetic patients had a mean CPGAS of 3.4 ± 0.4 which was significantly greater than the mean CPGAS of 1.7 ± 0.4 in idiopathic patients ($p < 0.01$). Sex, age, major symptom, speed of symptom onset, and use of nutritional support were not found to be significant predictive factors. Patients had similar responses if they were taking oral nutrition (CPGAS = 2.50 ± 0.3; $n = 109$), compared to jejunostomy tube (CPGAS = 1.94 ± 0.7; $n = 17$, or were on

Table 1 Demographic information of patients undergoing gastric electric stimulation

Demographics	Stimulator placement	Available for follow-up
N	151	138
Mean age	38.2 ± 11.8	38.7 ± 11.7 years
Females	120	110
Diabetic	72	65
Idiopathic	73	68
Other	6	5
Duration of follow-up after implantation		17 ± 11 months

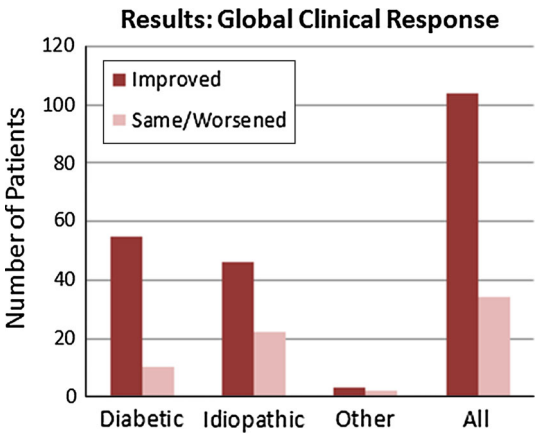

Fig. 1 Effect of Enterra gastric electric stimulation on patient's global clinical response. Of the 138 patients, 104 patients felt their symptoms had improved, while 34 felt that their symptoms were the same or had worsened. Of the 65 diabetic patients, 55 felt their symptoms had improved, while 10 felt their symptoms had remained the same or worsened. Of the 68 idiopathic patients, 46 felt their symptoms had improved, while 22 felt that their symptoms remained the same or worsened. More diabetics reported improvement than idiopathic patients ($p < 0.05$)

TPN (CPGAS = 2.25 ± 1.2; $n = 12$) ($p = 0.83$). Patients had similar responses if their symptom onset was slow (2.42 ± 0.4; $n = 50$), or sudden (2.34 ± 0.5; $n = 61$).

Effect on Symptom Severity

Individual symptom scores were assessed by comparing PAGI-SYM scores obtained during the last follow-up with those obtained prior to GES therapy. For all of those undergoing Enterra therapy (Fig. 2), symptom improvement was seen in all symptoms ($p < 0.05$). Symptoms that improved the most included nausea, early satiety, and loss of appetite. Each of these symptoms showed a mean reduction in symptom score by more than 1 point. Constipation, diarrhea, and abdominal distension were found to improve the least. These symptoms showed a mean reduction in symptom score by less than ½ point. When the symptom scores were analyzed in the diabetic and idiopathic subgroups, each subgroup saw significant reductions in all symptoms except for abdominal distension, constipation, and diarrhea. When comparing diabetic and idiopathic subgroups (Fig. 3), patients with diabetic gastroparesis reported greater reductions in most

Table 2 Effect of certain factors on global response to GES therapy

Factor	Mean CPGAS	*p* values
Etiology		
Diabetic ($N = 65$)	3.4 ± 0.4	<0.01
Idiopathic ($N = 68$)	1.7 ± 0.4	
Sex		
Male ($N = 28$)	2.9 ± 0.7	0.4
Female ($N = 110$)	2.3 ± 0.3	
Age		
<40 ($N = 72$)	1.9 ± 0.4	0.1
>40 ($N = 66$)	2.9 ± 0.4	
Major symptom		
N/V ($N = 109$)	2.4 ± 0.3	0.7
Abd pain ($N = 15$)	2.0 ± 1.0	
Nutritional support		
Oral ($N = 109$)	2.50 ± 0.3	0.83
J-tube ($N = 17$)	1.94 ± 0.7	
TPN ($N = 12$)	2.25 ± 1.2	
Symptom onset		
Slow ($N = 50$)	2.42 ± 0.4	0.6
Sudden ($N = 61$)	2.34 ± 0.5	
Support network		
Strong ($N = 98$)	2.42 ± 0.4	1.0
Weak (24)	2.42 ± 0.7	
Employed		
Yes ($N = 47$)	2.94 ± 0.5	0.5
No (83)	2.29 ± 0.4	
Income (in thousands)		
<$15 ($N = 10$)	3.40 ± 1.0	0.74
$15–$30 ($N = 15$)	2.53 ± 0.7	
$30–$50 ($N = 20$)	1.95 ± 0.9	
>$50 ($N = 69$)	2.52 ± 0.4	

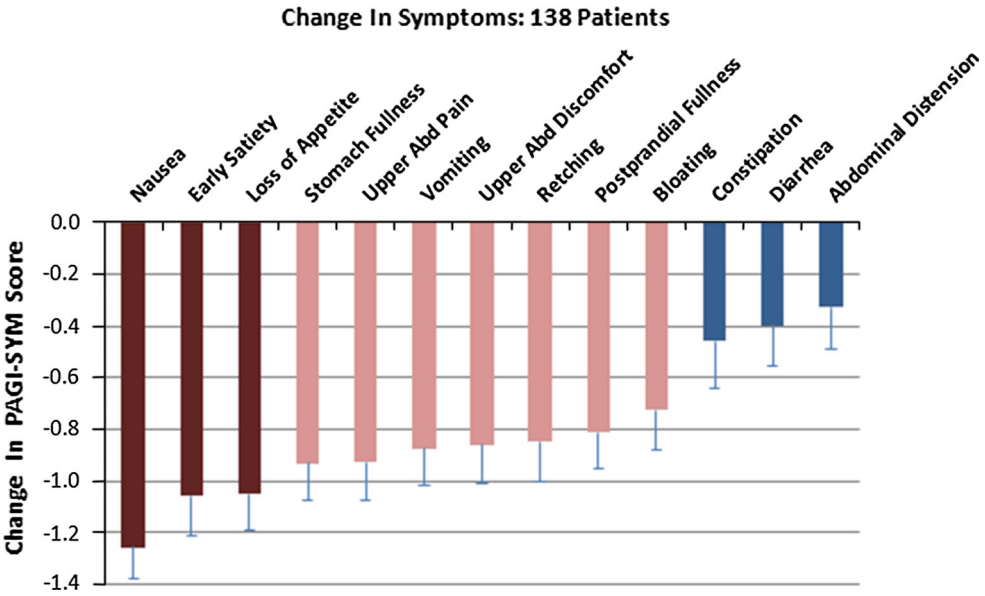

Fig. 2 Change in symptom scores from baseline to the last follow-up. Significant symptom improvement was seen in all symptoms ($p < 0.05$). Symptoms that improved the most included nausea, early satiety, and loss of appetite. Each of these symptoms showed a mean reduction in symptom score by more than 1 point (burgundy). Constipation, diarrhea, and abdominal distension were found to improve the least. These symptoms showed a mean reduction in symptom score by less than ½ point (*blue*). All other symptoms improved between ½ point to 1 point (*pink*)

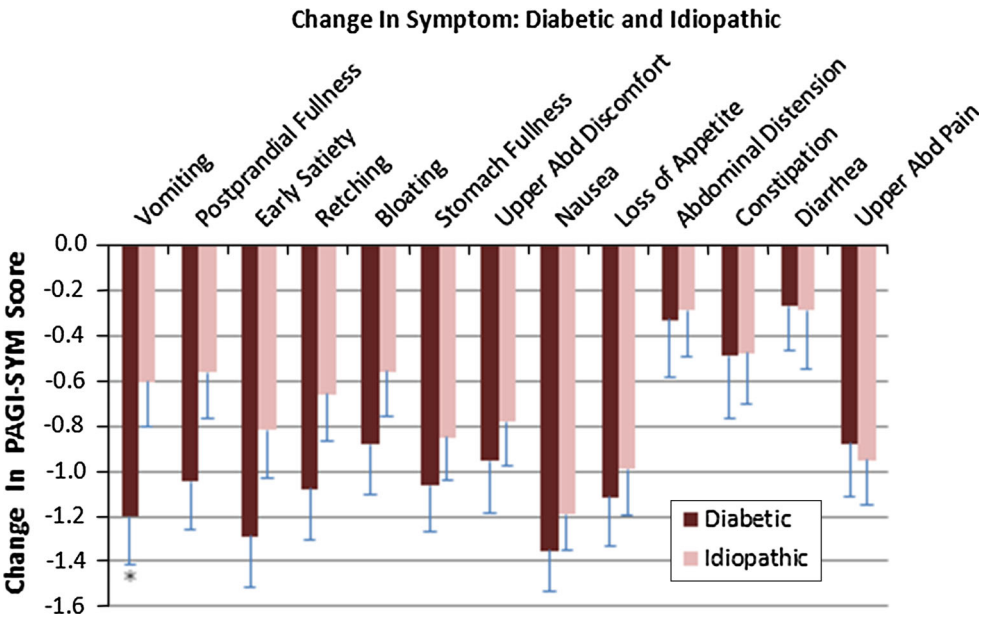

Fig. 3 Change in symptom scores from baseline to last follow-up for diabetic and idiopathic patients. Each subgroup saw significant reductions in all symptoms ($p < 0.05$) except for abdominal distension, constipation, and diarrhea. When comparing diabetic and idiopathic subgroups, diabetic patients experienced a greater reduction in vomiting than idiopathic patients ($p < 0.05$, denoted by *)

symptoms as assessed with the PAGI-SYM; however, only the reduction in vomiting was significantly reduced more in the diabetic patients than the idiopathic patients ($p < 0.05$).

We correlated the CPGAS score obtained at last follow-up visit with improvement in specific symptoms of gastroparesis (Table 3). There were significant correlations between CPGAS and all symptoms except for constipation. The strongest correlations between CPGAS and symptom improvement occurred with nausea ($r = 0.44$; $p < 0.01$), vomiting ($r = 0.39$; $p < 0.01$), and loss of appetite ($r = 0.38$; $p < 0.01$).

Patient-Related Factors

One hundred and twenty-seven patients had follow-up and completed the PAM survey appropriately (59 diabetic, 64 idiopathic, 4 other). Three patients were not used who had "perfect scores" on the survey, as suggested by the supplier of the questionnaire. Seventy-eight of 127 (61 %) patients with refractory gastroparesis were characterized as having a high PAM indicating that they are either beginning to take action in their healthcare management or have played an active role for some time. Forty-nine (39 %) patients were characterized as having low PAM indicating

Table 3 Correlation of CPGAS score with improvement in individual symptoms

	Nausea	Upper abdominal pain	Stomach fullness	Loss of appetite
R	0.44	0.29	0.28	0.38
P	<0.01	<0.01	<0.01	<0.01

	Upper abdominal discomfort	Bloating	Retching	Stomach visibly larger
R	0.23	0.28	0.25	0.18
P	<0.01	<0.01	<0.01	0.03

	Vomiting	Not able to finish meal	Feeling excessively full	Constipation	Diarrhea
R	0.39	0.26	0.15	0.02	0.21
P	<0.01	<0.01	<0.01	0.78	0.01

Table 4 Patient activation measure (PAM) subgroups for gastroparesis patients

	Lower Activation PAM level 1 (disengaged and overwhelmed) (%)	Activation PAM level 2 (becoming aware but still struggling)	Higher Activation PAM level 3 (taking action)	Activation PAM level 4 (maintaining behaviors and pushing further)
Diabetic ($N = 59$)[a]	7 (11.9)	16 (27.1 %)	19 (32.2 %)	17 (28.8 %)
Idiopathic ($N = 64$)[a]	11 (17.2)	13 (20.3 %)	23 (35.9 %)	17 (26.6 %)
Other ($N = 4$)	2 (50.0)	0	2 (50.0 %)	0

[a] No significant difference in the % of patients in each PAM subgroup when comparing these etiologies ($p = 0.71$)

they are less active in their healthcare management, either because they feel overwhelmed or struggle to initiate action. The PAM score was correlated with the CPGAS outcome score of the 127 total patients ($r = 0.18$; $p = 0.04$) and in the subset of diabetic patients ($r = 0.26$; $p = 0.05$), but not in the idiopathic patients ($r = 0.11$; $p = 0.39$). All 17 of the diabetic patients who fell into the highest PAM level reported a CPGAS > 0. When comparing diabetics and idiopathics, there was no significant difference in the percent of patients in each PAM subgroup ($p = 0.71$) (Table 4). There was no significant correlation between PAM and individual symptom improvement as measured by the PAGI-SYM.

Other patient-related factors such as strength of support network, economic status, and employment status had no significant effect on the outcome of GES therapy (Table 2).

Discussion

This study shows that in our cohort of patients with refractory gastroparesis in need of further therapy, GES was beneficial to the majority of patients. In this study, 75 % improved with 43 % having at least moderate clinical improvement. The response in diabetics was better than in nondiabetic patients. Importantly, this study evaluated the improvement in individual symptoms of gastroparesis. Symptoms especially improving with GES included nausea, early satiety, and loss of appetite.

In this study, etiology of the gastroparesis was the primary factor that was associated with a favorable outcome to GES. Although both patients groups of diabetic and idiopathic gastroparesis improved, patients with diabetic gastroparesis had better response with a mean CPGAS of 3.4 compared to 1.7 in patients with idiopathic gastroparesis. Patients with diabetic gastroparesis also reported greater reductions in most symptoms as assessed with the PAGI-SYM; however, only the reduction in vomiting was significantly reduced more so than in idiopathic gastroparesis. This finding that patients with diabetic gastroparesis had better therapeutic outcomes than patients with idiopathic gastroparesis support the double-blind study reported by Abell [1] and the previous study carried out at our center by Maranki [4]. It is of interest that the prior double-blind studies have used vomiting frequency as the primary response endpoint; this study suggests global response or nausea might be a better endpoint.

This study shows that symptoms especially improving included nausea, early satiety, and loss of appetite. The symptoms were also significantly correlated with the patient's perception of their overall improvement with GES. This information is helpful to physicians considering

the use of GES in patients. In a prior study from our center, we found that symptoms of nausea and vomiting were significantly improved with GES, but not abdominal pain [4]. In this study reported by Maranki et al. [4], patients who reported nausea and vomiting as their primary symptoms had significantly better outcomes than patients who reported abdominal pain as their major symptom; this was not found in this present study.

Patient motivation in regard to understanding their disorder and involvement in their treatment as assessed with PAM appear to have a favorable impact on the clinical outcome of GES in patients with refractory gastroparesis. PAM was correlated with the therapeutic outcome of GES, primarily for the subgroup of diabetic patients. PAM has not been previously assessed in patients with refractory gastroparesis. It was hypothesized by the authors that patients who are activated, meaning that they are heavily involved in the management of their own healthcare and work hard to maintain the appropriate behaviors to benefit their health, would have a better response to GES therapy than patients who were less activated. The correlation between PAM and CPGAS was present albeit weak ($r = 0.18$) for the entire subject group and slightly stronger in the diabetic subgroup ($r = 0.26$). Thus, this study shows that PAM may have value as a prognostic factor for GES outcome, especially when combined with etiology. All 17 of the diabetic patients who fell into the highest PAM level reported a CPGAS > 0. This may be due to patients with diabetic gastroparesis receiving education regarding the management of their diabetes, in addition to the guidance offered for their gastroparesis. This association of PAM to efficacy suggests that motivated patients were likely to benefit with GES treatment.

The advantages of the study are that it evaluates the effect of GES in clinical practice, rather than in a research study. This study not only looks at improvement in overall improvement using the CPGAS, but also on specific symptoms using the PAGI-SYM. Nausea, early satiety, and loss of appetite respond best to treatment with GES. This information on specific symptoms is of benefit to physicians as well as patients. The weaknesses of this study include the non-controlled, open treatment design from a single center. In any open-label study, a placebo effect may affect some of the findings; however, patients in this study were persistently symptomatic despite aggressive attempts to treat symptoms medically.

In conclusion, this study has shown that in selected patients with refractory gastroparesis, GES is beneficial to the majority of patients. In this study, 75 % of patients improved with 43 % were at least moderately improved. Clinical improvement was seen in both diabetic and idiopathic patients, although the response in diabetics was better than in nondiabetic patients. Symptoms especially improving included nausea, early satiety, and loss of appetite. This study provides helpful prognostic information to both physicians and patients contemplating use of GES—the type of patient and the type of symptoms that improve with this treatment.

Authors Contributions Jason Heckert, BS: study concept and design; data entry; analysis and interpretation of data; statistical analysis, drafting of manuscript. Abhinav Sankineni, MD, MPH: study concept and design; data entry; analysis and interpretation of data; statistical analysis, drafting of manuscript. William B. Hughes, MD: inserting gastric stimulator, interpretation of data; reviewing manuscript. Sean Harbison, MD: inserting gastric stimulator, interpretation of data; reviewing manuscript. Henry P. Parkman, MD: study concept and design; analysis and interpretation of data; critical revision of the manuscript for important intellectual content; study supervision.

Compliance with ethical standards

Conflict of interest None.

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