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ORIGINAL ARTICLE

Surgical Treatment for Refractory Gastroparesis: Stimulator, Pyloric Surgery, or Both?

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Abstract

Background Several surgical options exist for refractory gastroparesis (Gp) including gastric electric stimulation (GES) and pyloric surgery (PS) such as pyloromyotomy or pyloroplasty. Few studies exist comparing the outcomes of these surgeries.

Aim Compare the clinical outcomes of GES, PS, and simultaneous GES+PS for refractory Gp.

Methods Patients undergoing surgical intervention at our medical center from January 2016 to April 2019 were given pre- and post-surgery questionnaires to assess their response to intervention: Patient Assessment of Upper Gastrointestinal Symptoms (PAGI-SYM) grading symptoms and Clinical Patient Grading Assessment Scale (CPGAS) grading response to treatment. Results are expressed as mean ± SE.

Results One hundred thirty-two patients underwent surgical intervention; 12 were excluded. Mean CPGAS improvement overall was 2.8 ± 0.2 ($p < 0.01$): GES+PS had CPGAS score at 3.6 ± 0.5, pyloric interventions 3.1 ± 0.5, and GES 2.5 ± 0.4 ($p > 0.05$). Mean improvement in Gastroparesis Cardinal Symptom Index (GCSI) total score was 1.0 ± 0.1 ($p < 0.01$), with improvement of 1.1 ± 0.2 for GES + PS, 0.9 ± 0.2 for GES, and 0.9 ± 0.2 for PS ($p > 0.05$). GES and GES + PS, but not PS only, significantly improved symptoms of nausea and vomiting ($p < 0.01$). Among gastroparesis subtypes, patients with diabetic gastroparesis had more improvement on nausea/vomiting subscale compared with idiopathic gastroparesis ($p = 0.028$).

Conclusions Patients with refractory symptoms of Gp undergoing GES, PS, or combined GES+PS each had significant improvement of their GCSI total score. GES and combined GES+PS significantly improved nausea/vomiting. These results suggest GES or combined GES+PS appears better for nausea/vomiting predominant refractory Gp.

Keywords Gastroparesis · Gastric electric stimulation · Pyloroplasty · Pyloromyotomy

Introduction

Gastroparesis (Gp) is a chronic gastrointestinal motility disorder of delayed gastric emptying with associated symptoms of nausea, vomiting, early satiety, postprandial fullness, and abdominal pain.[1] Gp is divided into three main subcategories: diabetic, idiopathic, and post-surgical. The frequently intractable symptoms of gastroparesis make it a difficult disease to treat. Many patients do not respond to conventional medical treatments including dietary modifications, adequate glucose control in diabetics, prokinetic or antiemetic medications, and symptom modulators. Those who do not respond (refractory Gp) account for high healthcare utilization, as close to 50% of Gp hospital expenditures result from a minority of Gp patients.[2]

Various surgical interventions can be offered and may help reduce symptom burden for patients with medically refractory Gp. These procedures include gastric electric stimulation (GES), pyloric surgeries (PS) including pyloromyotomy and pyloroplasty, and gastrectomy. Of these, GES and PS are the most commonly performed, as gastrectomy is more invasive and often considered last resort. Pyloromyotomy has gained

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popularity due to the advent of gastric per oral endoscopic pyloromyotomy (G-POEM), an endoscopic option.[3] GES, in part, entails neurostimulation to decrease nausea and vomiting, whereas pyloromyotomy primarily facilitates gastric emptying. Recently, some patients are receiving both GES+PS as a combined surgical intervention and others might receive a second surgery for subtherapeutic response to an initial surgery.[4, 5]

The outcomes of these surgeries are characterized individually; however, few studies exist comparing the outcomes of surgical patients. Thus, it may not be clear which specific surgical procedure to offer patients. A single center retrospective analysis conducted by Arthur et al. analyzed 33 stimulator, 7 pyloroplasty, 2 gastrectomy, and 16 combined stimulator and pyloroplasty patients.[6] Pyloroplasty patients demonstrated the least symptom improvement, combination GES and pyloroplasty patients demonstrated increased improvements, and GES alone demonstrated the greatest improvement. However, none of the combined surgeries were simultaneous, with the second surgical intervention performed after failure of the first procedure. As such, the decision of whether to proceed with simultaneous GES+PS compared with GES or PS individually remains unclear.

Therefore, the aim of this study is to compare the outcomes of the different surgeries to characterize and compare improvements after GES, PS, or simultaneous GES+PS. By doing so, we hope to demonstrate that (1) these surgical interventions for refractory gastroparesis are effective; and (2) elucidate which surgery, or combination of surgeries, may best reduce overall and specific symptom burden in patients with refractory Gp.

Methods

The clinical protocol was conducted at Temple University Hospital evaluating the response of patients undergoing Enterra GES (Medtronic, Inc), PS (pyloromyotomy [either laparoscopic or G-POEM], pyloroplasty), or simultaneous GES+PS combination surgery (laparoscopic pyloroplasty or pyloromyotomy or robotic-assisted pyloroplasty).

Subjects

Patients undergoing surgical intervention for refractory gastroparesis at our academic medical center from January 2016 to April 2019 were considered for this study. Patients had an established diagnosis of gastroparesis, confirmed by pre-operative delayed gastric emptying on 4-h gastric emptying test to solids (gastric retention > 60% at 2 h and/or > 10% at 4 h) in the absence of mechanical obstruction.[7] Patients were excluded if they were the following: (1) less than 18 years old; (2) unable to consent; (3) lost to follow-up; (4) had previously failed a prior surgical intervention for refractory Gp (for these patients, only the first procedure performed within the study period was used). Patients were only included in the GES+PS group if the surgeries were performed simultaneously.

Procedures

The choice of surgery was decided by the patient with discussions with the surgeon and gastroenterologist. All surgical options were discussed with the patients. Surgical recommendations were often suggested to patients based on symptoms, gastric emptying, and other treatment responses. Patients who had shown response to Botox pyloric injection treatment (indicating that they may be amenable to pyloric surgical intervention) were often recommended pyloric surgeries. Patients who had either no response to Botox pyloric injection, or who had nausea/vomiting symptom predominance, were recommended a gastric stimulator or combination gastric stimulator with pyloric surgery. Patients with severely delayed gastric emptying (> 35% retention at 4 h were often suggested to have a pyloromyotomy or pyloroplasty.

Gastric Electric Stimulator Placement Enterra gastric electric stimulator (GES) for refractory gastroparesis is approved under the FDA humanitarian device exemption program and approved at our institution by our Institutional Review Board. Enterra GES is placed surgically under general anesthesia. The procedure is performed either with laparotomy, conventional laparoscopy, or robotic-assisted laparoscopy. The Enterra system consists of two stimulation leads and a pulse generator. The two stimulation leads are placed 10 cm proximal to the pylorus in the muscularis propria 1 cm apart along the greater curvature of the stomach. An upper endoscopy is performed to ensure that there is no penetration of the leads through the mucosa into the stomach lumen. Outer ends of the stimulator wires are tunneled through the abdominal wall and connected to the pulse generator, positioned in the subcutaneous pocket. The resistance between the wires is measured to ensure it is in the appropriate range of 200–800 Ohms.

Pyloroplasty Pyloroplasty is performed surgically under general anesthesia. It can be done either open, robotically, or laparoscopically. The pylorus is first identified. Stay sutures are placed in the corners of the anterior pylorus, and a longitudinal anterior gastroduodenotomy is performed with cautery, extending onto the stomach and the duodenum. The gastroduodenotomy is then closed transversely with sutured in Heineke-Miculikz fashion. Frequently, an omental patch is placed and secured across the pyloroplasty.

Pyloromyotomy Pyloromyotomy is performed either surgically or endoscopically (G-POEM) under general anesthesia. Endoscopically, the procedure is performed with an endoscope with a transparent distal cap attachment. A submucosal tunnel is created 5 cm proximal to the pylorus to allow submucosal entry. Subsequently, a 2–3 cm selective circular myotomy is performed at the pyloric muscular ring. Mucosotomy is then closed using endoscopic clips or overstitch device. Surgically, similar to pyloroplasty, pyloric muscle is divided, keeping the mucosal lining intact. Mucosal integrity can be checked with insufflation of air into the stomach with either nasogastric tube or endoscope.

Questionnaires

Patients scheduled for surgery filled out Patient Assessment of Upper Gastrointestinal Symptoms (PAGI-SYM) pre-surgery. Patients also filled out the PAGI-SYM and Clinical Patient Grading Assessment Scale (CPGAS) questionnaires during postoperative follow-up appointments. Questionnaires used for data analysis included the pre-surgery questionnaire and the last (most recent) follow-up-questionnaire. In some patients ($n = 12$), the follow-up questionnaire was obtained by telephone interview.

PAGI-SYM This questionnaire is a commonly used, validated instrument for assessing symptom severity in patients with gastroparesis.[8] The patient is asked to reflect on the past 2 weeks and then grade various symptom severities on a scale of 0 (none), 1 (very mild), 2 (mild), 3 (moderate), 4 (severe), and 5 (very severe). The symptoms are grouped into subscales, which are heartburn/regurgitation, nausea/vomiting, postprandial fullness/early satiety, bloating, upper abdominal pain, and lower abdominal pain. Average of the nausea/vomiting, fullness/early satiety, and bloating subscales provides the Gastroparesis Cardinal Symptom Index (GCSI) total score.

CPGAS This questionnaire asks patients about the therapeutic response of their gastroparesis to an intervention. This is also asked in reflection of the previous 2 weeks of symptom severity. It is ranked on a 15-point Likert scale of − 7 (very much worsened), 0 (no change) to + 7 (completely better) as compared with before the surgical intervention.

Follow-up Visits

Patients were typically seen in follow-up at 1 month, 3 month, 6 months, 12 months after surgery, and then every 6–12 months. Patients could also be seen if needed for worsening symptoms. Adjustments of the GES settings were started at the 3 month visit if needed for persistently severe symptoms of gastroparesis, typically by increasing the current from 5 to 10 milliamp, then if needed, the frequency from 14 to 28 to 55 Hz; on occasion, the ON time was increased from 0.1 to 1 s ON.[9]

For this data analysis, the last follow-up visit was used for the symptomatic outcome. If patients had a subsequent additional surgical procedure (1 GES patient had a subsequent PS and 1 PS patient had a subsequent GES placed), then the last follow-up visit prior to the second surgical intervention was used.

Data Analysis

Data were compiled in Microsoft Excel and analyzed using SPSS statistical software. Chi-squared test was used for categorical data. Paired two-tailed Student's t tests were used to compare the differences in pre-and post-symptomatology across each surgical intervention and two-sample t tests were used to compare improvements in symptomatology between different surgical treatments. Analysis of variance was used to compare multiple groups, with p value for subsequent students t tests adjusted with Bonferroni correction.

Results

Baseline Demographics

There were 132 patients who underwent surgical intervention between January 2016 and April 2019. Of these 132 patients, 12 were excluded, 7 had pervious histories of stimulator or pyloric surgeries, 3 did not have follow-up, and 2 had gastric stimulators removed for severe pain or infection. Therefore, 120 patients had adequate follow-up and were included in our analysis, including 74 gastric electric stimulators, 25 pyloric interventions (17G-POEM, 4 laparoscopic pyloromyotomy, and 4 laparoscopic pyloroplasty), and 21 GES+PS (5 pyloromyotomy and 16 pyloroplasty). The etiology of the gastroparesis included diabetic ($n = 47$), idiopathic ($n = 67$), post-surgical ($n = 6$; post fundoplication). For GES, there were 29 diabetic (22 type 1, 7 type 2), 42 idiopathic, and 3 post-surgical. For PS, there were 7 diabetic (4 type 1, 3 type 2), 17 idiopathic, and 1 post-surgical. For GES+PS, there were 11 diabetic (9 type 1, 2 type 2), 8 idiopathic, and 2 post-surgical. The average age at surgical intervention was 39.9 ± 1.2 years of age with 104 (86.7%) patients female.

There was no difference in the age, gender, BMI, or diabetes status of patients undergoing GES, PS, or GES+PS (Table 1). The baseline GCSI total scores among the three treatment groups (GES 3.8 ± 0.1, PS 3.3 ± 0.2, and GES+PS 3.7 ± 0.1), were not statistical different (ANOVA, $p = 0.11$) (Table 2). There was a higher severity of the nausea/vomiting subscore for GES patients (3.6 ± 0.2) and GES+PS (3.5 ± 0.3) compared with patients receiving PS alone (2.5 ±

Table 1 Background demographic data of patients undergoing treatments for refractory gastroparesis stratified by surgical intervention

Background demographics			
	GES	PS	GES+PS
Average age	39.9 ± 1.5	39.8 ± 2.6	40.0 ± 2.8
Gender	64 female, 10 male	22 female, 3 male	18 female, 3 male
BMI	26.3	27	26.2
Type of Gp	29 diabetic, 42 idiopathic, 3 post-surgical	7 diabetic, 17 idiopathic, 1 post-surgical	11 diabetic, 8 idiopathic, 2 post-surgical
Diabetes type	22 type 1, 7 type 2	4 type 1, 3 type 2	9 type 1, 2 type 2

0.3). There was no difference in the PPF/ES or bloating subscores among the patients undergoing the different treatments. The duration of follow-up averaged 12.7 ± 0.1 months, 16.6 ± 1.6 months for GES, 7.1 ± 1.1 months for pyloric interventions, and 9.1 ± 2.2 months for GES+PS.

CPGAS Response

There were 120 patients for which follow-up CPGAS score were obtained. The mean CPGAS improvement score across all patients was 2.8 ± 0.2 ($p < 0.01$ versus no improvement [CPGAS score of 0]). On the CPGAS scale, a score of "3" corresponds to "somewhat better". Patients with diabetic Gp had a trend for higher CPGAS scores than patients with idiopathic Gp (3.3 ± 0.4 vs 2.5 ± 0.3 respectively, $p = 0.13$). GES+PS had the highest CPGAS score at 3.6 ± 0.5 followed by pyloric interventions at 3.1 ± 0.5 and GES at 2.5 ± 0.4 (Fig. 1). The difference in CPGAS values did not reach statistical significance ($P = 0.485$ by ANOVA).

Symptom Improvement Compared to Baseline

For all patients who received surgical intervention for refractory Gp, there was a significant reduction in all individual symptoms (Table 2). The GCSI subscales and GCSI total score were improved significantly as well ($p < 0.001$). Patients with diabetic Gp reported more significant improvement of symptoms on nausea/vomiting subscale ($p = 0.028$), including individual symptoms of retching and vomiting, compared with patients with idiopathic Gp (Table 3).

Patients undergoing gastric electric stimulator placement had significant improvement of all individual symptoms, GCSI subscales, and GCSI total score (Table 2).

Table 2 Symptom improvement in patients who underwent gastric electric stimulator placement, pyloric interventions, or both gastric electric stimulator with pyloric intervention. "All" refers to all surgical categories combines

	All			Gastric electric stimulator (GES)			Pyloric interventions (PS)			Simultaneous GES+PS		
Individual symptom	Pre-op	Post-op	*p* value	Pre-op	Post-op	*p* value	Pre-op	Post-op	*p* value	Pre-op	Post-op	*p* value
Nausea	4.1 ± 0.1	3.0 ± 0.2	< 0.001	4.4 ± 0.1	3.3 ± 0.3	< 0.001	3.5 ± 0.4	2.7 ± 0.4	0.066	4.1 ± 0.3	2.6 ± 0.2	< 0.001
Retching	3.9 ± 0.2	2.3 ± 0.2	< 0.001	3.3 ± 0.3	2.4 ± 0.3	0.012	2.3 ± 0.5	2.3 ± 0.5	0.909	2.8 ± 0.4	2.1 ± 0.4	0.103
Vomiting	3.0 ± 0.2	1.9 ± 0.2	< 0.001	3.3 ± 0.2	2.3 ± 0.3	0.004	1.8 ± 0.5	1.3 ± 0.4	0.234	3.5 ± 0.4	1.8 ± 0.5	0.003
Stomach fullness	4.2 ± 0.1	2.8 ± 0.2	< 0.001	4.0 ± 0.3	2.5 ± 0.3	< 0.001	4.3 ± 0.2	2.8 ± 0.3	< 0.001	4.2 ± 0.2	3.1 ± 0.3	0.007
Early satiety	4.20.1	3.1 ± 0.2	< 0.001	4.2110.2	3.3 ± 0.3	0.011	4.0 ± 0.2	2.9 ± 0.4	< 0.001	4.4 ± 0.3	3.1 ± 0.4	0.004
Post- prandial fullness	4.2 ± 0.1	3.3 ± 0.2	< 0.001	4.1 ± 0.2	3.4 ± 0.3	0.041	4.3 ± 0.2	3.1 ± 0.4	0.001	4.2 ± 0.2	3.1 ± 0.3	0.009
Loss of appetite	3.7 ± 0.1	2.6 ± 0.2	< 0.001	3.6 ± 0.2	2.8 ± 0.3	0.02	3.6 ± 0.3	2.1 ± 0.3	< 0.001	3.9 ± 0.3	2.6 ± 0.4	0.006
Bloating	3.7 ± 0.2	2.7 ± 0.2	< 0.001	3.8 ± 0.2	2.9 ± 0.2	0.013	3.7 ± 0.4	2.8 ± 0.4	0.003	3.5 ± 0.4	2.4 ± 0.4	0.006
Stomach distension	3.3 ± 0.2	2.4 ± 0.2	< 0.001	3.4 ± 0.3	2.5 ± 0.3	0.045	2.9 ± 0.5	2.1 ± 0.5	0.003	3.7 ± 0.3	2.5 ± 0.4	0.003
Upper abdominal	3.3 ± 0.2	2.6 ± 0.2	0.003	3.2 ± 0.3	2.6 ± 0.3	0.006	3.6 ± 0.5	2.6 ± 0.4	0.034	2.8 ± 0.4	2.2 ± 0.4	0.272
NN subscale	3.3 ± 0.1	2.4 ± 0.2	< 0.001	3.6 ± 0.2	2.7 ± 0.3	0.001	2.5 ± 0.3	2.1 ± 0.3	0.223	3.5 ± 0.3	2.2 ± 0.3	0.001
PPF1ES subscale	4.1 ± 0.1	3.0 ± 0.2	< 0.001	4.0 ± 0.2	3.1 ± 0.3	0.001	4.0 ± 0.2	2.7 ± 0.3	< 0.001	4.1 ± 0.2	3.0 ± 0.3	0.001
Bloating subscale	3.5 ± 0.2	2.6 ± 0.2	< 0.001	3.6 ± 0.2	2.7 ± 0.3	0.021	3.3 ± 0.4	2.410.4	< 0.001	3.6 ± 0.4	2.4 ± 0.4	0.002
GCSI total score	3.6 ± 0.1	2.6 ± 0.1	< 0.001	3.8 ± 0.1	2.8 ± 0.2	0.001	3.3 ± 0.2	2.5 ± 0.3	0.001	3.7 ± 0.1	2.5 ± 0.3	< 0.001

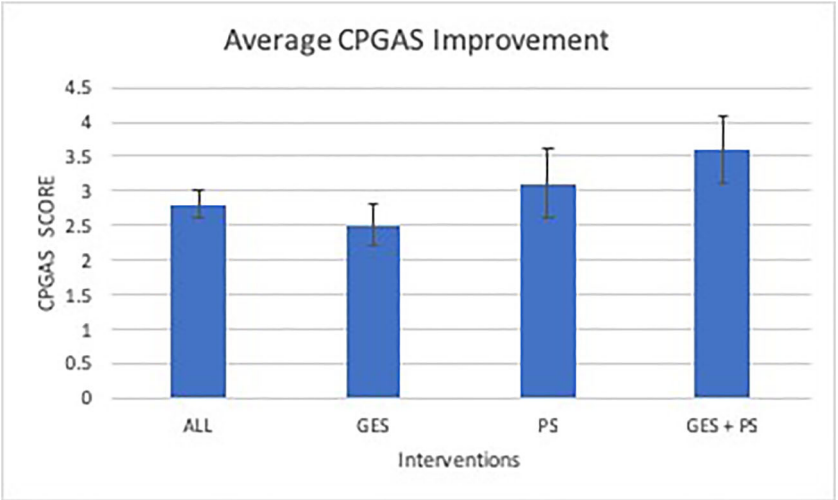

Fig. 1 Average CPGAS improvement per surgical intervention. All are expressed average ± standard error of the mean. Each procedure resulted in a significant improvement by the CPGAS score ($p < 0.05$). The trend of higher CPGAS score GES+PI > PS > GES was not significant ($p = 0.485$ by ANOVA)

Amongst patients who were undergoing pyloric interventions for refractory Gp, all symptoms improved significantly except for nausea ($p = 0.066$), retching ($p = 0.909$), and vomiting ($p = 0.234$). The GCSI total score and GCSI subscales were all significantly improved post-surgery except for the nausea/vomiting subscale (Table 2).

Patients who underwent both GES and PS for refractory Gp, most of the symptoms were improved post-surgically, including nausea and vomiting. The GSCI subscales and GCSI total score were all significantly improved post-surgically as well (Table 2).

Table 3 Improvement of symptom severity measured by PAGI-SYM amongst patients with idiopathic and diabetic gastroparesis undergoing surgical treatments for refractory symptoms

Individual symptom	Idiopathic Gp ($n = 66$)	Diabetic Gp ($n = 50$)	p value
Nausea	0.9 ± 0.3	1.4 ± 0.3	0.186
Retching	0.5 ± 0.4	1.2 ± 0.3	0.043
Vomiting	0.3 ± 0.3	1.6 ± 0.4	0.011
Stomach fullness	1.0 ± 0.3	1.4 ± 0.3	0.417
Early satiety	0.7 ± 0.3	1.3 ± 0.3	0.201
Post-prandial fullness	0.8 ± 0.3	1.1 ± 0.3	0.439
Loss of appetite	1.0 ± 0.4	1.3 ± 0.3	0.381
Bloating	0.9 ± 0.4	0.8 ± 0.4	0.874
Stomach distension	0.7 ± 0.4	0.8 ± 0.4	0.942
Upper abdominal pain	0.6 ± 0.4	1.1 ± 0.4	0.170
Symptom subscales			
N/V subscale	0.7 ± 0.3	1.4 ± 0.3	0.028
PPF/ES subscale	1.1 ± 0.2	1.2 ± 0.3	0.539
Bloating subscale	1.0 ± 0.3	0.6 ± 0.4	0.444
GCSI total score	1.0 ± 0.2	1.1 ± 0.2	0.518

ES Early satiety, *Gp* Gastroparesis, *N* Nausea, *PPF* Post-prandial fullness, *V* Vomiting

Comparison of Symptom Improvements Across Surgeries

Further comparison of the difference between pre-and post-symptomatology, there was no significant difference in the mean improvement of symptom severities between patients undergoing GES, PS, and GES+PS (Table 4). In comparing subscale scores, patients reported significant improvement in nausea/vomiting subscale in both GES+PS (1.2 ± 0.3; $p < 0.05$) and GES (1.0 ± 0.3; $p < 0.05$), compared with PS alone (0.4 ± 0.3) which had no significant improvement of nausea/vomiting (Fig. 2). There was a trend for the PS group to have greater improvement in the PPF/ES subscore (1.3 ± 0.2) compared with GES (1.0 ± 0.3) or GES+PS (1.0 ± 0.3). There was also a trend for the GES+PS group to have greater improvement in the bloating subscore (1.2 ± 0.3) compared with GES (0.8 ± 0.2) or GES (0.8 ± 0.2). Although there was a trend for GES+PS having a higher numerical improvement for GCSI total score (1.1 ± 0.2) than GES (0.9 ± 0.2) or PS alone (0.9 ± 0.2), this was not statistically significant ($P > 0.05$).

We further focused on the symptoms of nausea/vomiting, which for many patients was the primary symptom. We set a value for "significant improvement" at a reduction of > 1 point on the GCSI symptom questionnaire (Table 2). In this manner, nausea demonstrated mean improvements in GES and GES + PS of > 1 but not PS. For vomiting, only GES+PS decreased symptom severity scores by > 1.

Discussion

The aim of this study was to compare the effectiveness of the various surgical interventions, individually or in combination, that can be offered to patients with refractory gastroparesis to help determine which treatment may best reduce symptom burden. We compared results of prospectively collected

Table 4 Comparison of mean symptom severity improvement by PAGI-SYM amongst patients undergoing gastric stimulator placement, pyloric interventions, and both gastric stimulator placements and pyloric interventions for gastroparesis

Symptom	All patients ($n = 120$)	Gastric stimulators ($n = 74$)	Pyloric interventions ($n = 25$)	Stimulators and pyloric interventions ($n = 21$)
Nausea	1.1 ± 0.2	1.1 ± 0.3	0.8 ± 0.4	1.4 ± 0.2
Retching	0.6 ± 0.2	0.8 ± 0.3	0.1 ± 0.5	0.6 ± 0.4
Vomiting	1.0 ± 0.2	1.0 ± 0.3	0.4 ± 0.4	1.6 ± 0.5
Stomach fullness	1.4 ± 0.2	1.5 ± 0.3	1.5 ± 0.2	0.9 ± 0.3
Early satiety	1.0 ± 0.2	0.9 ± 0.3	1.1 ± 0.2	1.1 ± 0.4
Post-prandial fullness	0.9 ± 0.2	0.7 ± 0.3	1.3 ± 0.3	0.9 ± 0.3
Loss of appetite	1.1 ± 0.2	0.8 ± 0.3	1.5 ± 0.4	1.1 ± 0.4
Bloating	1.0 ± 0.2	0.9 ± 0.3	0.9 ± 0.3	1.1 ± 0.4
Stomach distension	0.9 ± 0.2	0.9 ± 0.4	0.8 ± 0.2	1.1 ± 0.3
Upper abdominal pain	0.7 ± 0.2	1.0 ± 0.3	1.0 ± 0.4	0.4 ± 0.5
Symptom subscales				
N/V subscale	0.9 ± 0.2	1.0 ± 0.3	0.4 ± 0.3	1.2 ± 0.3
PPF/ES subscale	1.1 ± 0.2	1.0 ± 0.3	1.3 ± 0.2	1.0 ± 0.3
Bloating subscale	1.0 ± 0.2	0.8 ± 0.2	0.8 ± 0.2	1.2 ± 0.3
GCSI total score	1.0 ± 0.1	0.9 ± 0.2	0.9 ± 0.2	1.1 ± 0.2

No statistically significant difference in symptom improvement between patients undergoing gastric stimulator placement, pyloric interventions, and both gastric stimulator placements and pyloric interventions for gastroparesis (all $p > 0.05$)

symptom questionnaires (both CGPAS and PAGI-SYM) for patients undergoing GES, PS, or simultaneous GES+PS at our institution. Each of the surgical procedures resulted in significant clinical improvement as assessed by the CPGAS with grading by the patients on the response to treatment during follow-up surveys, with a trend that the combined GES with PS had greatest CPGAS score. Additionally, we compared individual symptom improvements through symptom severity using the PAGI-SYM questionnaire. Each of the surgical procedures resulted in improvement in the overall GCSI total score, with the combined GES+PS resulting in a quantitatively higher improvement in GCSI total score. Of the sub-scores, nausea/vomiting was improved significantly by GES and GES+PS.

For refractory symptoms, after failure of medical management of Gp, surgical intervention is often considered. Gastric electric stimulation has been used for the past two decades. The mechanism of improvement is not completely understood, and although initially thought to improve gastric emptying, not all patients that have symptom improvement have improvement in gastric emptying. The high frequency, low energy stimulation has suggested a reduction in gastric tone as well as potential afferent modulatory mechanism.[10] Two large multicenter trials—the Gastric Electrical Mechanical Stimulation Study (GEMS) and the Worldwide Anti-Vomiting Electrical Stimulation Study (WAVES)—demonstrated significant symptom reduction primarily for vomiting frequency for patients with refractory gastroparesis, particularly those with diabetic

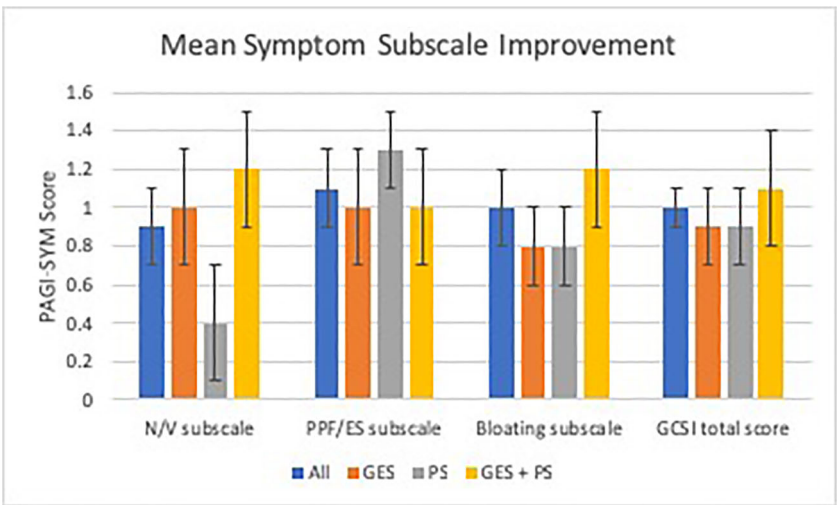

Fig. 2 Mean GCSI symptom subscale improvement per surgical intervention. Data are expressed average ± standard error. Comparisons were performed using student *t* test with Bonferroni correction. Combined GES+PS and GES alone improved the N/V subscales than PS alone ($p = 0.028$)

gastroparesis.[11, 12] Because of these studies, GES was granted a humanitarian use device (HUD) exemption from the US Food and Drug Administration in 2000. Subsequent studies, primarily open label studies, have shown an improvement in symptoms; however, double blind cross over studies have not.

More recently, pyloric interventions have also been used extensively for refractory gastroparesis. Botox injections, pyloroplasty, and pyloromyotomy have all been used to reduce the pyloric barrier in order to facilitate gastric emptying. Recently, the advent of endoscopic approaches to pyloromyotomy (gastric per oral pyloromyotomy, G-POEM) has been attractive for its ability to maintain surgical intervention through a less invasive technique. A recent systematic review of 14 studies using G-POEM demonstrated pooled clinical symptom improvement rate of 88.2% with an intraoperative complication rate of 3.2%, thus demonstrating high efficacy with marginal risk.[13]

Recently, the combination of GES with pyloric intervention therapy (intraoperative pyloromyotomy or pyloroplasty) has been used for refractory gastroparesis. Combination GES with pyloroplasty has been reported to result in improvement in total symptom score, and also improved gastric emptying time by 64% at 4 h; the symptom improvement was similar to GES alone which only improved GES by 7%.[4] Longer-term efficacy of GES+PS has been reported with a 71% improvement in total symptom score at follow-up between 3 and 38 months (mean 17 months).[5]

Several symptom questionnaires have been developed and validated to monitor the symptom severity and potential improvement of patients with gastroparesis. The Gastroparesis Cardinal Symptom Index (GCSI), a subset of the Patient Assessment of Upper Gastrointestinal Symptoms (PAGI-SYM), is one of the most common questionnaires used.[14] This validated questionnaire assesses patients' assessments of their individual symptoms over the past 2 weeks, with scores rated from 0 (none) to 5 (very severe). Clinical Patient Grading Assessment Scale (CPGAS) is another commonly used clinical measurement and qualitatively measures overall patient improvement from a + 7 (completely better), 0 (no change, − 7 (very much worsened).[15] The CPGAS score is commonly used clinical symptomatology score; however, there have been no official validation studies for this scoring subscale.

Various studies demonstrate symptom improvements with individual surgical interventions, yet few comparison studies exist. A recent retrospective systematic review analyzed the data of various manuscripts publishing the outcomes of GES and pyloric interventions. A therapeutic effect was established in each intervention, with pyloric surgery demonstrating greater response to intervention than GES. However, attempts to analyze combination interventions were limited due to lack of power.[16] Additionally, a single center retrospective analysis compared the outcomes of 33 GES, 7 pyloroplasty, 2 gastrectomy, and 16 combined GES and pyloroplasty patients. Pyloroplasty demonstrated the least symptom improvement, combination of GES and pyloroplasty demonstrated greater improvements, and GES alone demonstrated the most improvement. However, this study is limited given its single center design, small pyloroplasty size, and the bias against the combined surgical interventions as they were all salvage surgeries and not performed simultaneously.[8]

In our study, we compared the three types of surgeries that are commonly performed in patients with refractory symptoms. We assessed the improvement in severity post-surgery for three surgical interventions, notably GES, PS, and simultaneous GES+PS. We demonstrate qualitative improvements via the CPGAS score and GCSI score for all surgical interventions compared with baseline. Combined surgical GES+PS had the highest CPGAS score compared with GES or PS alone; however, this did not reach statistical significance. This might be due to relatively small sample size, as there were only 21 patients with simultaneous combined surgeries.

Individual symptoms as registered by the GCSI questionnaires also improved markedly compared to baseline for all three surgical interventions. When comparing individual symptoms, the GCSI nausea and vomiting subscale was significantly improved in patients undergoing GES or GES+PS compared with PS alone, which had no significant improvement. This effect may be due to the GES neurostimulation function, as compared with the functional mechanism of PS. However, one bias of our study was that patients with appreciable nausea and vomiting were often offered GES or GES with PS, since studies have suggested improvements in vomiting with GES. As such, the nausea/vomiting severity scores were higher in our patients undergoing GES or GES+PS than those undergoing PS alone.

This study reporting our results of the three types of surgical treatments generally performed for patients with refractory gastroparesis symptoms has some limitations. This study reports on the response to surgical treatments performed clinically for patients; it was not a prospective randomized clinical trial. Surgical choice, due to non-randomization, may have introduced selection bias, notably patients who received GES or GES+PS had baseline higher nausea/vomiting subscales than did those with PS. This study looked at patients operated at our center over the last 2.5 years. Longer follow-up was available with GES procedures, as pyloromyotomy and pyloroplasty were introduced more recently. Recently, pyloric compliance is being measured with EndoFLIP; low pyloric compliance suggests more favorable improvement with G-POEM. We did not use EndoFLIP to assess pyloric diameter and compliance to assist in choosing treatments. Additionally, we made the determination that patients who had a second salvage surgical therapy for gastroparesis would only be counted for their first surgical intervention, as our GES+PS intervention arm was exclusive for simultaneous surgeries. Thus, salvage surgery was not assessed in this

manuscript. For patients undergoing surgery at two different times, only the first procedure was assessed. Lastly, in analyzing the data, despite the fact that most symptoms improved individually compared with baseline, there was not a single symptom that significantly improved greater in one surgery than another. This might suggest that all surgeries are effective at reducing symptom burden, reflect the relatively small sample size, or reflect a placebo effect.

In summary, the results of our study demonstrate that the surgical interventions GES, PS, and GES+PS are beneficial in improving the symptom burden in patients with gastroparesis. For patients with nausea and vomiting predominant symptoms, GES or GES+PS appear more favorable than PS alone. From this study, our current working hypothesis is that nausea and vomiting improve better with GES, whereas early satiety and postprandial fullness improve better with pyloric surgery. Selection of appropriate intervention for patients with refractory symptoms of gastroparesis may encompass patient's symptoms, results of physiologic testing of gastric motility, and response to prior treatments. More research on surgical interventions, specifically prospectively randomized studies comparing the efficacy of the combined surgery versus individual surgeries (as well as placebo intervention), are needed to gain understanding of different treatment options for patients with refractory Gp.

There was no difference in the age, gender, BMI, or diabetes status of patients undergoing GES, PS, or GES+PS

Authors Contributions Bryan Zoll, MD, MBA: data acquisition, data interpretation, drafting and revising manuscript.

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Compliance with Ethical Standards

Enterra gastric electric stimulator (GES) for refractory gastroparesis is approved under the FDA humanitarian device exemption program and approved at our institution by our Institutional Review Board

Conflicts of Interest The authors declare that they have no conflict of interest.

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