Safety and Feasibility of Per-Oral Pyloromyotomy as Augmentative Therapy after Prior Gastric Electrical Stimulation for Gastroparesis

Andrew T Strong, MD, John Rodriguez, MD, FACS, Matthew Kroh, MD, FACS, FASGE, FASMBS, Jeffrey Ponsky, MD, FACS, Michael Cline, DO, Kevin El-Hayek, MD, FACS

BACKGROUND: For medically refractory diabetic or idiopathic gastroparesis, gastric electrical stimulation (GES) is an excellent option for symptom control; however, a small subset of patients may develop recurrent or persistent symptoms. Per-oral pyloromyotomy (POP, also described by some authors as gastric per-oral endoscopic myotomy or G-POEM) is an emerging therapy for medically refractory gastroparesis. This study investigated the safety and feasibility of POP after previous GES for recurrent or persistent gastroparesis.

STUDY DESIGN: We retrospectively identified all patients undergoing POP between January 2016 and December 2017, with GES in situ. Patient characteristics, gastroparesis etiology, and procedural data were collected. Symptoms were assessed with the Gastroparesis Cardinal Symptom Index (GCSI) both before and 30 to 90 days after POP. Standard pre- and post-procedure 4-hour gastric emptying tests were obtained when available.

RESULTS: There were 22 patients who met inclusion criteria (81.8% female, mean age 42.3 ± 12.4 years). Causes of gastroparesis were diabetes in 38.1%, and idiopathic in 61.9%. The average time since GES insertion was 3.45 years. Mean preoperative 4-hour gastric retention was 50.1%. Most POP procedures were performed in the operating room (90.9%), with mean operative time of 40 minutes and a 1.4-day length of stay. There were 4 readmissions within 30 days, but no POP-related complications. Overall, GCSI improved by an absolute reduction of 1.63 points ($p = 0.002$), with significant improvements in all sub-scores. Of 11 patients with post-procedural motility or emptying studies available, 7 were normal.

CONCLUSIONS: Per-oral pyloromyotomy appears to be safe and feasible for patients with recurrent gastroparesis symptoms after GES. Both symptoms and motility significantly improved in the short-term. These data replicate similar data suggesting laparoscopic pyloroplasty as an effective augmentative therapy after GES, but may provide a less invasive option for patients. (J Am Coll Surg 2019;229:589−595. © 2019 by the American College of Surgeons. Published by Elsevier Inc. All rights reserved.)

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From the Departments of General Surgery, (Strong, Rodriguez, Kroh, Ponsky, El-Hayek) and Gastroenterology and Hepatology (Cline), Cleveland Clinic and the Cleveland Clinic Lerner College of Medicine of Case Western Reserve University (Strong, Rodriguez, Kroh, Ponsky, Cline, El-Hayek), Cleveland, OH; and Cleveland Clinic Abu Dhabi, Abu Dhabi, United Arab Emirates (Kroh).

Correspondence address: Andrew T Strong, MD, Desk A100, 9500 Euclid Ave, Cleveland, OH 44195. email: stronga@ccf.org

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Abbreviations and Acronyms

BMI = body mass index
GCSI = Gastroparesis Cardinal Symptom Index
GES = gastric electrical stimulator/stimulation
POP = per-oral pyloromyotomy

In the past 2 decades, there has been a dramatic increase in health care use related to gastroparesis, which includes increases in emergency department visits and inpatient hospital stays.[1-3] Recent estimates suggest that up to 4% of the adult population in the United States may be affected, a figure that is suspected to rise as diabetes rates continue to increase.[1,3,4] Symptoms of gastroparesis include nausea, vomiting, bloating, early satiety, and abdominal pain. Diagnosis is confirmed by objective evidence of delayed gastric emptying using scintigraphy in the absence of mechanical obstruction.[5] Conventionally, causes are divided into idiopathic, diabetic, and postsurgical (classically after vagotomy). While the mechanisms that underlie gastroparesis likely differ by etiologic cause, histologic examinations have revealed a general loss of interstitial cells of Cajal.[4,6]

Treatment of gastroparesis is a multimodal endeavor, involving a range of treatments, from lifestyle modification to surgical resection. In many cases, multiple therapeutic modalities are used simultaneously. First-line therapies include dietary modification including ingestion of smaller, more frequent meals.[4,7] Numerous antiemetic, antibloating, and prokinetic medications may be used for symptom management, often in combination.[4,7] Currently, metoclopramide is the only medication that has been evaluated and approved by the United States Food and Drug Administration to treat gastroparesis; most other medications have been adapted from study of chemotherapy-induced and/or postoperative nausea and vomiting.[8,9] For some patients, medical therapy fails, and surgical options are entertained for symptom relief. Often the first-line surgical treatment is placement of an enteral access tube to provide supplemental nutrition and a route for medication administration. Gastric electrical stimulation (GES) holds a conditional recommendation from the Food and Drug Administration for medically refractory idiopathic and diabetic gastroparesis, as a compassionate use device.[7,10] Implantable GES involves surgical placement of 1-cm long electrodes along the greater curvature of the stomach, roughly 10 cm proximal to the pylorus. Leads from the electrodes are connected to an implanted generator that provides high frequency/low energy electrical impulses to the stomach.[10] Therapeutic effect is suspected to be mediated not by "pacing," but rather by decreased sensitivity to gastric sensitive medication by vagus nerve afferents, resulting in augmentation of gastric accommodation function.[11] Both open and minimally invasive approaches for GES placement have been described in large single-center series.[10,12]

Typical response to GES is a 60% to 70% improvement in symptom scores, but without a concomitant increase in objective measures of gastric emptying.[10] This observation has led clinicians to seek methods to augment gastric emptying. Pyloric disruption, in the form of pyloroplasty, was proposed as an adjunctive therapy for GES by Sarosiek and colleagues.[13] Separate single-center studies have demonstrated that the addition of laparoscopic pyloroplasty improves gastric emptying when performed either before or simultaneously with GES.[13,14] This effect may be prolonged to as many as 38 months.[15] Endoscopic per-oral pyloromyotomy (POP) has recently been introduced as a therapeutic option for pyloric disruption.[16] We sought to evaluate our experience using POP as a salvage therapy for patients who had previously undergone GES placement and developed recurrent symptoms.

METHODS

Both GES and POP are prospectively tracked in databases approved by the Institutional Review Board. Gastric electrical stimulation has been a treatment option since 2001, and patients undergoing stimulator placements have been tracked since that point to maintain regulatory compliance. Per-oral pyloromyotomy was introduced as a therapeutic

option in January 2016 at our institution, and all patients have been prospectively tracked. All patients undergoing POP who had previously undergone GES placement were retrospectively identified from both databases, which included POP procedures performed up to December 31, 2017. Inclusion criteria were diabetic or idiopathic gastroparesis in patients older than age 18 at the time of POP. These patients were reviewed to verify that all had an initial response to GES therapy and had recurrence of symptoms. In addition, we verified that all devices were functional at the time symptoms recurred. Exclusion criteria included patients with postsurgical gastroparesis, and patients under the age of 18 at the time of POP. We also excluded patients who had undergone GES therapy, but had devices removed before performance of POP procedures. Not all patients identified as meeting inclusion criteria had undergone GES at our institution, though all POP procedures were completed at our institution.

Patient demographics, 30-day outcomes, and 90-day outcomes were collected for all patients. Demographic information included age at time of POP, sex, body mass index (BMI), comorbid illnesses, etiology of gastroparesis, and previous interventions related to gastroparesis, including medications used at the time of POP procedure. Symptoms were evaluated pre- and post-POP using the Gastroparesis Cardinal Symptom Index (GCSI).[17,18] Gastric emptying was evaluated using 4-hour solid phase scintigraphic gastric emptying studies according to standard protocols, and is reported as percent retention.[5] Perioperative details included intraoperative complications, estimated blood loss, operative time, and length of stay. Outcomes evaluated at 30 days included procedure-related complications, repeat operations or endoscopic evaluations, and unplanned readmissions. Outcomes evaluated at 90 days included BMI, GCSI, and gastric emptying.

Surgical techniques

Surgical techniques for both GES placement[12] and POP[19] have been previously detailed. A brief description follows.

Gastric electrical stimulation insertion

Patients are positioned supine under general anesthesia. A 4-port approach is typically used, with the surgeon standing on the patient's right side, and the assistant on the patient's left. Electrical leads are positioned 10 to 12 cm proximal to the pylorus along the greater curvature, just anterior to the origin of the greater omentum and the gastroepipoloic artery. Intraoperative endoscopy is used to verify that leads do not violate the gastric mucosa. The generator is placed in a subcutaneous pocket in the abdominal wall and secured with suture.

Per-oral pyloromyotomy

Patients are positioned supine under general anesthesia, and the procedure is performed using a standard gastroscope with an affixed, beveled, silicone-based cap. After diagnostic upper endoscopy, a mucosal lift is performed along the lesser curve of the stomach. A 1.5-cm transverse mucostomy is made using an endoscopic knife. The endoscopic knife is then used to develop a tunnel in the submucosal plane. Once the pylorus is identified, it is divided completely. The mucostomy is then closed using multiple endoscopic clips.

STATISTICAL ANALYSIS

Summary statistics for demographic variables and operative variables are expressed as mean and standard deviation for continuous variables or count and percent for categorical variables. Tests of significance comparing pre- and post-procedure outcomes of interest were performed using 2 sample *t*-tests for continuous variables. All tests were 2-tailed and performed at a significance level of $\alpha = 0.05$. R (v3.3.1, 2016-06-21) software was used for all analyses.

RESULTS

During the study period, there were 161 patients who underwent POP therapy at our center, 22 of whom had previously undergone placement of GES and had the device

Table 1. Patient Demographics

Factor	Data
Age, y, mean ± SD	42.3 ± 12.4
Female sex, n (%)	18 (81.8)
Medical comorbidity, n (%)	
Hypertension requiring medication	11 (50.0)
Fibromyalgia	3 (13.6)
Hyperlipidemia	8 (36.4)
COPD	1 (4.5)
Diabetes mellitus	10 (45.4)
Noninsulin dependent	3 (13.6)
Insulin dependent	7 (31.8)
POTS	2 (9.1)
Other dysautonomia	4 (18.1)
Gastrointestinal comorbidity, n (%)	
Irritable bowel syndrome	6 (27.2)
GERD	3 (13.6)
Slow transit constipation/colonic inertia	2 (9.1)
Psychiatric comorbidity, n (%)	
Depression	4 (18.1)
PTSD	1 (4.5)

GERD, gastroesophageal reflux disease; POTS, postural orthostatic hypotension syndrome; PTSD, post-traumatic stress disorder.

Table 2. Gastroparesis Characteristics

Factor	Data
Cause of gastroparesis	
Idiopathic	13 (61.9)
Diabetes	9 (39.1)
Previous intervention for gastroparesis (apart from GES)	
Gastrostomy tube	4 (18.1)
Jejunostomy tube	9 (39.1)
Intrapyloric botulinum toxin injection	8 (36.1)
Previous need for parenteral nutrition	5 (22.7)
Time since GES inserted, mo, median (IQR)	36.3 (23.0–51.4)

GES, gastric electrical stimulator/stimulation; IQR, interquartile range.

in situ (13.7%) at the time of POP procedure. The study sample was predominantly female (81.8%) and had a mean age of 42.3 years (Table 1). In terms of comorbidities, hypertension was common (50%), as was hyperlipidemia (36.4%). The known association between gastroparesis and autonomic dysfunction was represented with the study sample including 2 subjects with postural orthostatic tachycardia syndrome (9.1%) and 4 with other dysautonomic disorders (18.1%). There were 6 individuals who carried diagnoses of irritable bowel syndrome (27.2%) in addition to gastroparesis, and 2 patients with concomitant slow transit constipation (9.1%) (Table 1).

In terms of gastroparesis etiology, the study population was divided between idiopathic causes (61.9%) and diabetes-associated causes (39.1%); there were no patients with post-surgical gastroparesis, as GES therapy is not approved for that indication (Table 2). The median time of GES therapy was 36.3 months (interquartile range [IQR] 23.0 to 51.4 months). In addition to previously undergoing GES implantation, a subset of the study population had undergone previous surgical intervention for gastroparesis. These interventions included gastrostomy tube (18.1%), jejunostomy tube (39.1%), and previous pyloric injection of botulinum toxin (36.1%). There were 5 patients who had become malnourished to the degree that they had previously required parenteral nutrition (Table 2).

The majority of the POP procedures were performed in the operating room (90.9%), as this was our preferred practice for the majority of the study period. The median procedure time was 33.5 minutes (mean 40 minutes, range 16 to 85 minutes) (Table 3). One patient underwent simultaneous placement of a nasojejunal feeding tube, and another underwent replacement of a GES generator that was nearing the end of its battery life. There were no intraprocedural complications. The mean length of stay after the procedure was 1.4 days. Within 30 days, there were 3 patients readmitted to the hospital (13.6%). One patient underwent a diagnostic laparoscopy for nonresolving abdominal pain, which was determined to be from unresolved capnoperitoneum and intestinal adhesive disease. There were no infections noted of the generators or electrode leads, and there were no mortalities noted in this series.

At 90 days post-procedure, follow-up clinical assessment was available for 16 patients (72.7%); 13 patients had undergone repeat objective evaluation of gastric emptying (59.1%). Although there was an absolute increase in mean BMI from pre-POP to 90 days post-POP, this failed to reach statistical significance. (25.4 kg/m^2 vs 26.8 kg/m^2; $p = 0.27$) (Table 4). Mean gastric emptying also improved, as measured by 4-hour scintigraphic gastric retention (50.1% vs 4%, $p = 0.0011$), though these data are available only for a subset of patients. Among those with gastric emptying studies available, 6 had normal emptying with solid phase scintigraphic emptying studies, and 1 additional had normal emptying by wireless motility capsule. In terms of symptoms related to gastroparesis, improvement was noted in all domains of the GCSI. The overall average GCSI improved from a mean of 3.70 to 2.07 points (absolute reduction of 1.63 points; $p = 0.002$). Fullness and early satiety were the predominant symptoms pre-POP, and they improved to a mean of 2.57 ($p = 0.0012$).

DISCUSSION

This is the first study to evaluate POP as a salvage therapy for patients who have previously undergone GES implantation, but have developed symptom recurrence. All included patients had previously undergone GES implantation for either medically refractory diabetic (39.1%) or idiopathic gastroparesis (61.9%) with initial symptom improvement and subsequent symptom recurrence. All patients had functional GES systems at the time they were evaluated for POP, and did not have exhausted batteries as a cause for their symptom recurrence. After successful pyloric disruption, both gastric emptying and gastroparesis symptoms improved, with a response durable to at least 90 days.

Gastric electrical stimulation has been performed in the United States for nearly 2 decades, including more than 12 years at our institution. At many centers across the country, this has represented one of the most effective surgical interventions that did not involve resection as an option for symptomatic relief among patients with diabetic or idiopathic gastroparesis. Although the original stimulation patterns conceived were meant to promulgate gastric slow

Table 3. Per-Oral Pyloromyotomy Procedure Characteristics

Factor	Data
Operative time, min, mean ± SD	40.0 ± 18
Length of hospital stay, d, mean ± SD	1.4 ± 1.4
POP procedure location, n (%)	
Operating room	20 (90.9)
Endoscopy suite	2 (9.1)
Concurrent procedure performed*, n (%)	2 (9.1)
Intraoperative complication, n (%)	0 (0)
Post procedure complication, n (%)	3 (13.6)
Operative intervention	1 (4.5)
Readmission related to POP	3 (13.6)
Repeat esophagogastroduodenoscopy	1 (4.5)

*Concurrent procedures included: nasojejunal feeding tube placement, replacement of GES generator.
GES, gastric electrical stimulation; POP, per-oral pyloromyotomy.

wave activity, subsequent studies demonstrated that higher frequency with very short pulse duration, on the order of milliseconds, was the most effective in improving gastroparesis symptoms.[20,21] This pulse pattern is insufficient to produce myoelectrical capture in the stomach, and does not appear to reliably augment gastric emptying.[20,22,23] Instead, GES appears to produce symptom relief by altering signaling pathways within the central nervous system conveyed by afferent vagal nerve fibers.[11] The dependence on afferent vagal nerve signaling may explain why GES tends to have poor efficacy for patients with gastroparesis resulting from vagal nerve injury.

Since GES was approved as a therapeutic option, additional data have been produced by several centers, including our own, highlighting the importance of the altered physiologic function of the pylorus for patients with gastroparesis. Impaired pyloric relaxation and hypertonicity have been objectively demonstrated among patients with various subtypes of gastroparesis; the pylorus itself serves as a mechanical barrier to movement of chyme from the antrum to the duodenum.[24,25] As such, pyloric disruption has been demonstrated to be efficacious in improving gastric emptying, allowing antral contractions to push gastric contents into the duodenum, while also avoiding the need for coordinated pyloric relaxation.[24,25] The best accumulated evidence for pyloric disruption has been shown in patients who underwent surgical pyloroplasty.[14,26]

Based on evidence of improved gastric emptying with pyloric disruption, one center performed a small nonrandomized pilot trial comparing GES with pyloroplasty to GES alone. There were 26 patients in each arm, all undergoing GES placement for medically refractory gastroparesis. The study group additionally underwent laparoscopic pyloroplasty at the time of GES placement.[13] Patients were evaluated at 3, 6, and 12 months. Those patients undergoing GES with pyloroplasty had greater improvements noted in total symptom severity score (35% vs 45% relative improvement; groups not compared statistically) and gastric emptying (7% improvement vs 64% improvement; groups not compared statistically).[13] Interestingly, the addition of pyloroplasty also reduced annual hospital days. Enhanced symptomatic relief afforded by the pyloroplasty persisted even at 38 months post-procedure in a follow-up study.[15] To our knowledge, there are no other published reports of simultaneous pyloromyotomy and GES insertion. We have recently demonstrated substantially similar results in terms of symptom improvement after laparoscopic pyloroplasty and POP.[27] Although there was no comparison arm in this study to GES with pyloroplasty, our results with POP appear similar to those from previous studies with pyloroplasty.

Although the availability of GES was initially met with zeal, it was not the panacea that was hoped for gastroparesis. Subsequent studies have demonstrated that stimulators introduce a number of challenges and opportunity for complications. These includes small bowel obstruction from electrode leads, lead erosion, and device infection.[28] Generators also have a fixed battery capacity and must be changed at regular intervals, obliging patients to repeat surgical intervention. Unfortunately, there are no clear guidelines regarding when or how to intervene for a

Table 4. Ninety-Day Outcomes for Gastric Emptying and Gastroparesis Symptoms

Factor	Pre-POP	Post-POP	p Value
Mean BMI, kg/m^2	25.4	26.8	0.27
Mean 4-hour scintigraphic retention, %*	50.1	4	0.0011
GCSI, mean ± SD			
Fullness/early satiety sub-score	4.06 ± 0.95	2.57 ± 1.74	0.0012
Nausea/vomiting sub-score	3.44 ± 1.24	1.72 ± 1.71	0.0003
Bloating sub-score	3.61 ± 1.69	2.18 ± 1.87	0.024
Overall GSCI score	3.70 ± 0.90	2.07 ± 1.61	0.002

BMI, body mass index; GCSI, Gastroparesis Cardinal Symptom Index; POP, per-oral pyloromyotomy.
*Comparison is for 7 patients with equivalent studies of gastric motility performed pre-POP and post-POP.

patient that no longer is responding to GES therapy. One center proposed placement of a new generator with new leads in a second area of the stomach.[13] Some would also entertain device removal and concomitant subtotal or total gastrectomy. The patient with no response to GES therapy is another challenge. Although all patients included in this series had initial symptom improvement post-GES, for some that effect was relatively minimal and/or short lived. There are insufficient patients included to identify predictive factors for response to GES or POP.

When performing an invasive procedure for a patient with an implanted medical device, the risk of infection must always be a considered. There were no device infections noted in this series of patients. This is further substantiated by previous data from our own institution suggesting that generator infections are rare, even in the event of simultaneous insertion of jejunostomy, which then classifies the surgical wound class as clean contaminated, rather than clean.[12] Other centers have reported safely inserting jejunostomy tubes at the time of GES insertion as well, at least in terms of no increased risk of generator infection.[28]

There are several limitations to this study. First we based this study on the idea of failure of GES therapy, for which there is no consistent definition in the literature. Previous publications have used recurrence of symptoms, despite appropriate increase in voltage and frequency of stimulation, to define therapeutic failure, but have used inconsistent tools to assess for symptoms recurrence. Developing such an assessment tool is outside the scope of this study. The definition we used was similar in this study: patients with symptom recurrence after GES or symptoms have failed to improve after GES. Of note, the patients included in this study had a mean pre-POP GCSI of 3.70, indicating that gastroparesis symptoms were severe at the time of POP. Due to the retrospective nature of this study we were not able to assess response to GES therapy at the time of implantation, nor track how symptoms worsened over time. Given that both POP and GES may act to improve gastroparesis symptoms, it is impossible to ascertain which intervention was the greater contributor, or if this effect was truly additive. Gastric electrical stimulation therapy has previously been studied in a crossover design study,[29] which could be replicated to answer this question. The intervention would then be a simultaneous pyloromyotomy and GES insertion, with a crossover period of GES on or off. We additionally did not control or adjust for medications being used at the time of POP or post-procedure assessments, including antiemetics and pro-motility agents. A future controlled prospective study may be helpful in mitigating these limitations.

CONCLUSIONS

Per-oral pyloromyotomy appears to be a safe and effective minimally invasive strategy to augment gastroparesis symptom relief after response to GES wanes. For some patients, the combination of POP and GES may also improve objective measures of gastric motility, even when POP is not performed at the time of GES implantation. In short-term follow-up, the effects of delayed pyloric disruption with GES in situ, appear to be similar to simultaneous GES insertion and pyloric disruption.

Author Contributions

Study conception and design: Strong, Rodriguez, Kroh, Ponsky, Cline, El-Hayek

Acquisition of data: Strong, Rodriguez, Kroh, Ponsky, Cline, El-Hayek

Analysis and interpretation of data: Strong, El-Hayek

Drafting of manuscript: Strong, El-Hayek

Critical revision: Strong, Rodriguez, Kroh, Ponsky, Cline, El-Hayek

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