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ORIGINAL ARTICLE

Laparoscopic Gastric Electrical Stimulation for Medically Refractory Diabetic and Idiopathic Gastroparesis

P. Timratana · K. El-Hayek · H. Shimizu · M. Kroh · B. Chand

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Abstract
Background Gastric electrical stimulator (GES) implantation is effective in certain patients with gastroparesis; however, laparotomy is often employed for placement. The aim of this study is to review outcomes of patients who underwent laparoscopic GES therapy for diabetic and idiopathic gastroparesis at a large referral center.
Methods Patients who underwent GES (Enterra Therapy System; Medtronic, Minneapolis, MN) implantation with subsequent interrogation and programming between March 2001 and November 2011 were analyzed.
Results A total of 113 patients underwent GES placement or revision during the study period. One hundred eleven patients underwent primary GES at our institution, while two patients underwent GES generator revision at our institution. Primary operations were completed laparoscopically in 110 of 111 cases, with one conversion to laparotomy due to severe adhesions. At a mean follow-up of 27 months (1–113), symptom improvement was achieved in 91 patients (80 %) and was similar for both the diabetic and idiopathic subgroups. Need for supplemental nutrition (enteral and/or parental) decreased in both groups.
Conclusions GES placement is feasible using a laparoscopic approach. Medical refractory gastroparesis in the diabetic and idiopathic groups had significant symptom improvement with no difference between the two groups. Need for supplemental nutrition is decreased following GES.

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P. Timratana · K. El-Hayek · H. Shimizu · M. Kroh
Cleveland Clinic, Bariatric and Metabolic Institute, Cleveland, Ohio 44195, USA

P. Timratana
e-mail: timratp@ccf.org

K. El-Hayek
e-mail: elhayek@ccf.org

H. Shimizu
e-mail: shimizh@ccf.org

M. Kroh
e-mail: krohm@ccf.org

B. Chand
Division of Gastrointestinal and Minimally Invasive Surgery, Loyola University Medical Center, Maywood, IL 60153, USA

B. Chand (✉)
Stritch School of Medicine, Loyola University Medical Center, 2160 South First Avenue, Bldg. 110-Room 3291, Maywood, IL 60153, USA
e-mail: bchand@lumc.edu

Keywords Laparoscopy · Gastric stimulation · Gastroparesis

Introduction

Gastroparesis reportedly occurs in up to five million patients in the USA and typically affects the younger population. Diagnosis is more often made in females than males with a 4:1 ratio.[1] General symptoms and signs include abdominal pain, bloating, nausea, emesis, anorexia, and weight loss. Etiology is believed to be multifactorial, with the main categories being defined as medication induced, diabetic, postsurgical, and idiopathic.[2] Of these categories, the most commonly identified etiologies are diabetic and idiopathic, which occur in greater than 60 % of all patients with this condition.[2–4]

Postsurgical and medication induced causes are likely related to vagal nerve disruption or interference.[4,5] The pathophysiology of diabetic gastroparesis has been linked to autonomic neuropathy of vagal innervation of the stomach

in up to 40 % of cases.[6–8] Furthermore, various metabolic and hormonal disturbances related to diabetes can also contribute to impaired gastric tonicity and antral contractions.[9] Patients with idiopathic gastroparesis are less well understood with possibly an inflammatory component involved.[10]

The diagnosis of gastroparesis is made when the above constellation of symptoms are combined with no evidence of mechanical obstruction and an abnormal gastric emptying study. Most clinicians prefer that abnormal gastric emptying be confirmed when a patient has been off medications both known to be associated with gastroparesis, such as opioids, as well as pro-motility agents known to improve symptoms.[11] Medications aimed at improving gastric motility, such as metoclopramide and erythromycin are often used as first line treatments of gastroparesis. Metoclopramide acts on the central nervous system to stimulate an increase in gut motility, while erythromycin is an agonist to the motilin receptor within the stomach. While these agents have relatively good effectiveness at improving gastric motility, metoclopramide has been associated with irreversible tardive dyskinesia in 1–15 % of patients, which led to a Food and Drug Administration (FDA) black box warning in 2010.[3,12–14] Other classes of medications, such as anti-emetics are also used to treat the principle symptoms of gastroparesis, all with varying improvement rates. When opioids are used for pain related to gastroparesis, the unwanted side effect of decreased gut motility may be experienced.[15]

Endoscopic therapies, such as Botulinum toxin injection of the pylorus have been used with some efficacy, though long-term results are limited and patients require repeat injections for ongoing relief.[16] Surgical options include gastric electrical stimulator (GES) or some form of gastric resection or bypass. GES has been reported to give adequate relief in select patients, with a better reported result in patients with diabetes.[17] Currently, there is an FDA approval for humanitarian use device (HUD) in patients with medical refractory diabetic or idiopathic gastroparesis.[18] GES is not indicated in patients with postsurgical or medication-induced gastroparesis; however, some reports demonstrate improvement in symptoms in patients with postsurgical gastroparesis.[5,19]

The predominant surgical approach for GES placement since its approval for use has been laparotomy. The principle aim of our study is to review laparoscopic GES for patients with either diabetic or idiopathic medical refractory gastroparesis at a large quaternary referral center.

Materials and Methods

Patients

An Institutional Review Board approved, prospectively managed surgical database including all patients who underwent GES (Enterra Therapy System; Medtronic, Minneapolis, MN) placement or evaluation was analyzed. The study period ranged from March 2001 to November 2011. Data collected included preoperative characteristics, comorbidities, BMI, preoperative work-up, nutritional support, operative technique, complications, and postoperative results. Both short- and long-term outcomes were analyzed. Laparoscopic placement was the principal surgical approach in all cases.

Patient Selection

Patient selection is determined following the algorithm highlighted in Fig. 1. When a patient is referred for GES evaluation, the patient's chart is reviewed prior to the outpatient visit. Patients over the age of 18 with typical symptoms of gastroparesis who have either failed medical management or who are unable to tolerate medications are evaluated. At evaluation, a thorough history and physical exam is obtained. Patients with prior gastric surgery are evaluated for revisional gastric surgery and are not considered candidates for GES. Those patients with no prior gastric surgery are evaluated for medical causes for their upper gastrointestinal symptoms, such as scleroderma, chronic narcotic use, global bowel dismotility, psychogenic vomiting or other eating disorders, and swallowing disorders such as achalasia. Patients suspected to have any such cause are evaluated for the enteral access and are referred to the appropriate specialist(s) for treatment.

The remaining patients who have either diabetic or idiopathic causes undergo a solid 4-h gastric emptying study and must be off all narcotics and pro-motility agents for 2 weeks prior to the study. Further testing, such as upper endoscopy and contrast studies (upper GI, computed tomography) are also performed to rule out any mechanical or anatomic abnormalities.

Once candidacy is confirmed, patients must sign informed consent to proceed with an Institutional Review Board approved study for HUD through the FDA.

Operative Technique

Operative set-up involves a four trocar technique (three 5-mm trocars and one 10-mm trocar) in the lower abdomen, with placement of the device battery at the site of the 10-mm trocar. Upper endoscopy is used intraoperatively to assure pacer leads are placed within the seromuscular layer of the stomach without mucosal transgression. Pacer leads are seated 10–12 cm proximal to the pylorus in close proximity to the greater curvature to maximize the charge potential delivered to the antral pump (Fig. 2). Following implantation, the pacer is interrogated and set to 3 V and 0.1-s on cycle. Subsequent interrogation and adjustments occur at 3,

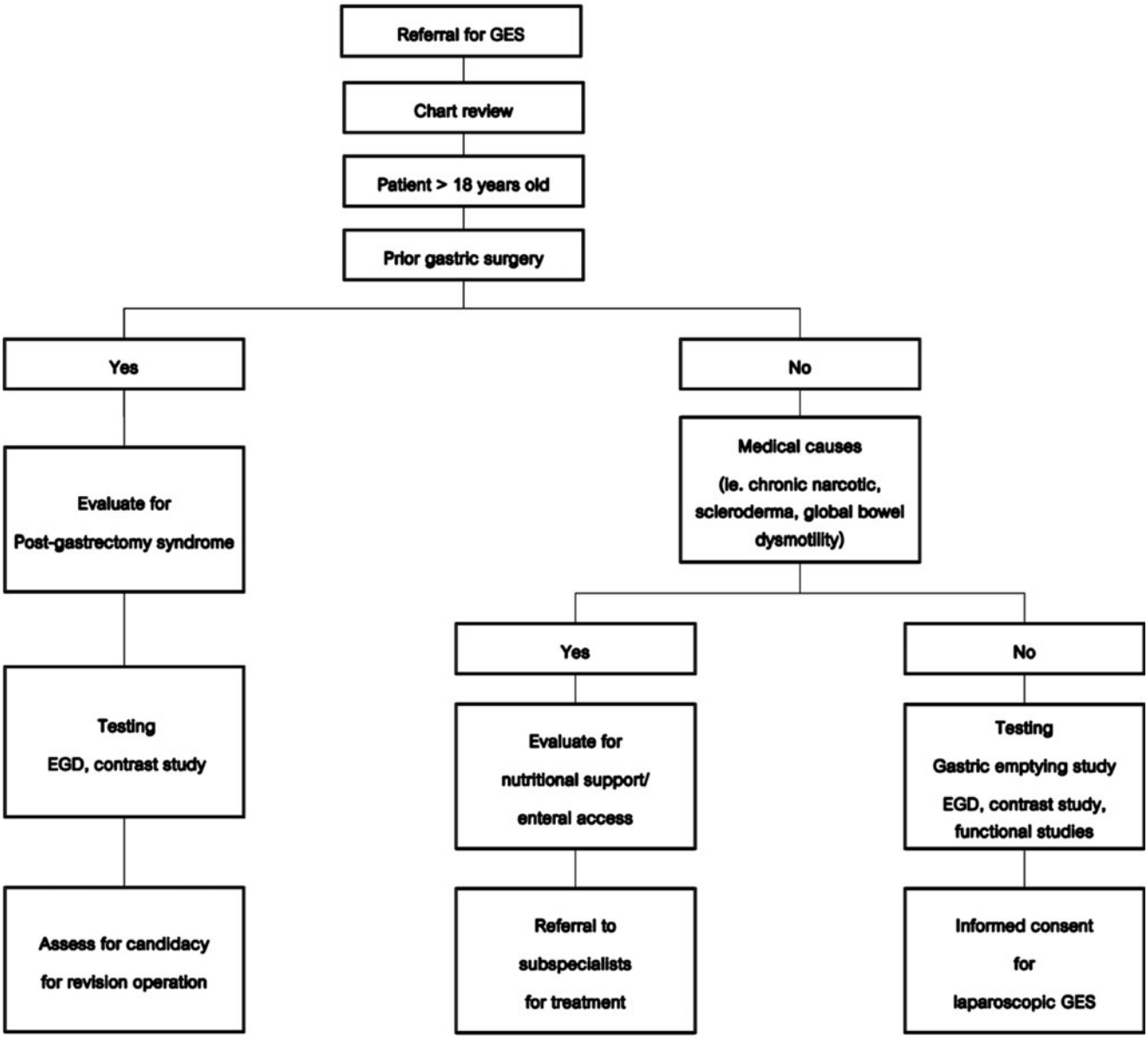

Fig. 1 Patient selection algorithm for laparoscopic GES placement

6, and 9 months and annually postoperatively, as well as sooner if needed. Patients are followed-up annually after their initial pacemaker adjustments. In select cases, a laparoscopic jejunostomy tube is placed for enteral access either preoperatively, concomitantly during laparoscopic pacemaker placement, or postoperatively in patients with failure to thrive. Total parenteral nutrition is offered to patients who cannot tolerate enteral nutrition.

Statistical Analysis

Data are presented as mean ± standard deviation for continuous variables. The distribution of the data was checked for normality using the Shapiro–Wilk test. These characteristics were analyzed using unpaired Student's t test (or Mann–Whitney U test) for continuous variables and Chi-square test (or Fisher's exact test) for categorical variables. All tests were two tailed, and the results with a $p<0.05$ were considered statistically significant. Statistical analyses were performed using the software package PASW, version 18.0, for Windows (SAS Institute, Cary, NC).

Results

A total of 113 patients had GES placement and were available for analysis. One hundred eleven patients had primary laparoscopic GES at our institution, while two had generator

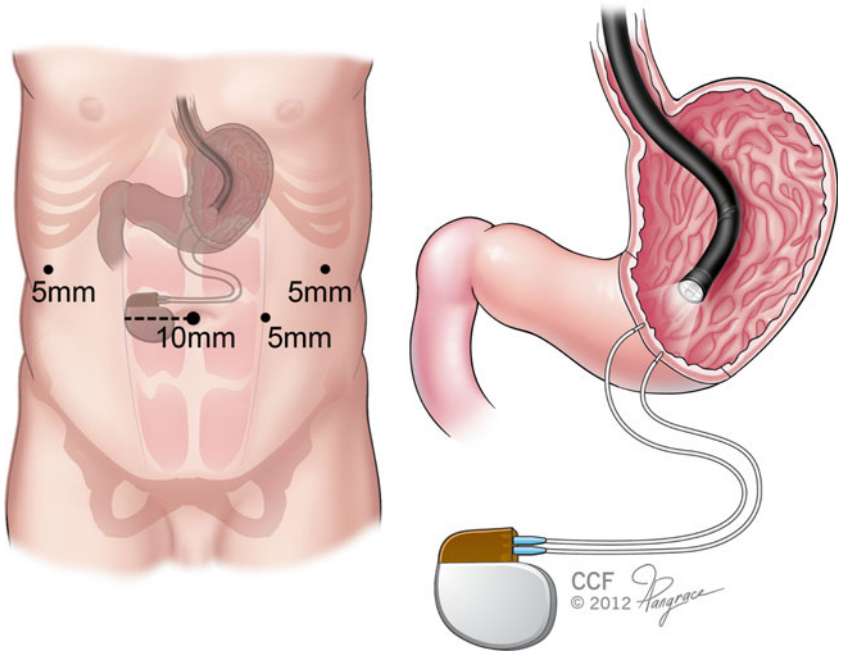

Fig. 2 Depiction of laparoscopic gastric electrical stimulation placement with trocar placement and intraoperative endoscopy

revision. One hundred ten of 111 (99 %) of all primary GES placements were completed laparoscopically, with one conversion to laparotomy due to severe adhesions. Our cohort included 55 patients with diabetic gastroparesis and 58 with idiopathic gastroparesis. Other details of patient characteristics are highlighted in Table 1. There was no difference between the groups when evaluating age at operation. There was a significantly higher percentage of females in the idiopathic group ($p<0.01$), a significantly longer duration of gastroparesis symptoms in the diabetic group ($p=0.03$), and a significantly higher rate of cardiac comorbidities, such as hypertension and coronary artery disease found in the diabetic cohort ($p<0.01$ and 0.011, respectively). In patients with diabetes, insulin was required in 48of 55 (87 %) and two underwent prior pancreatic transplantation. At least one manifestation of end-organ dysfunction, such as retinopathy, neuropathy, and nephropathy was evident in 26 of 55 (47 %) of diabetic patients.

Nutritional Status

Nutritional status as characterized by need for supplemental nutrition (enteral or parenteral) was examined in all patients (Tables 2 and 3). Use of enteral nutrition was required in 20 patients preoperatively, 6 of whom remained on enteral nutrition at last follow-up. Fourteen patients had enteral access placed either concomitantly with GES or postoperatively, 5 of whom had use at last follow-up. Total parental nutrition was used in four patients prior to gastric pacemaker placement, and none of these patients required parenteral nutrition at final follow-up.

Table 1 Patient characteristics

	Diabetic GP	Idiopathic GP	*p* value
Number of patients	55	58	N/A
Age at operation	41.3±12.3	38.6±13.7	0.3
Gender (F/M)	38/17	56/2	<0.01
Mean duration of GP (years)[a]	6.4±3.5 (1–20)	3.5±3.0 (1–12)	0.03
Mean duration of DM (years)[b]	18 (1–40)	N/A	N/A
Hypertension	20	1	<0.01
Coronary artery disease	6	0	0.011
Treatment of DM			
Noninsulin medications	5	N/A	N/A
Insulin	48	N/A	N/A
Pancreatic transplantation	2	N/A	N/A

[a]From 68 cases (diabetic, 30 cases; idiopathic, 38 cases)

[b]From 41 cases

Table 2 Nutrition supplementation prior to or concomitantly during GES

Nutritional route	Preoperative GES	Use at F/U	*p* value	No improvement of symptom
Enteral	20	6	0.003	1
Enteral and parenteral	2	1		–
Parenteral	4	0		–

There was no statistical significance between preoperative and postoperative BMI in both diabetic and idiopathic subgroups after GES implantation; however, there was a small trend toward increased BMI in each group (Table 4). Figures 3 and 4 depict the pre- and postoperative weight changes of both the diabetic and idiopathic cohorts.

Patient Symptoms

Patient symptoms were closely monitored at follow-up and subjective improvement or failure of treatment documented. Objective measures of symptom improvement included reduction or cessation of pro-motility, anti-emetic, or pain medications. The principle parameters adjusted on the pacemaker interrogations included voltage and on cycle, which was slowly titrated up over the course of the first year and later if necessary.

Figures 5 and 6 show changes of the most common symptoms associated with gastroparesis (nausea, vomiting, pain, and bloating) after GES. On follow-up, a nonstandardized assessment of patient symptoms was determined by clinician interview with comparison to prior visits and baseline symptoms. There was a statistically significant reduction in patients' nausea, vomiting, and pain following GES, while bloating improved in a nonstatistically significant fashion.

Diabetic Control

The mean preoperative glycated hemoglobin level was 7.6±1.3 % (N=37), while the mean postoperative glycated hemoglobin level was 8.7±1.8 % (N=17; p= 0.015). When comparing patients with glycated hemoglobin levels both pre- and postoperatively (N=11), all patients without symptom improvement (5 of 11) had preoperative levels of >6.0 % and subsequent worsening of this value postoperatively.

Device-Related Adverse Events

Device-related complications occurred in eight patients (7 %). Battery depletion requiring replacement occurred at a mean time after operation of 75 months (49–101). Stimulator malfunction occurred in two cases: one secondary to electrical malfunction and one from lead fracture. Postsurgical complications occurred in nine patients, four in the idiopathic group, and five in the diabetic group. These complications included pacer malposition and repositioning in five, wire erosion with subsequent replacement in one of three, and skin necrosis requiring removal in one.

Mortality

Death occurred in four patients at a mean follow-up of 14.5 months (1–26), with symptom improvement in all. All mortalities were in the diabetic group with three patients having class II obesity. All causes were deemed to be related to underlying disease and not directly related to GES placement.

Gastroparesis in Morbid Obesity

Fourteen of 112 (12 %) patients had class II obesity (BMI> 35), 13 of whom (93 %) remained morbidly obese postoperatively. Of this group, ten (71 %) had improvement of symptoms; however, three ultimately died from non-GES-related causes. Four patients with BMI>30 preoperatively converted to class II obesity post-laparoscopic GES placement. Of these patients, three had no improvement of symptoms. Stimulator removal and laparoscopic Roux-en-Y gastric bypass was offered to 8 of 18 patients with morbid obesity and failure of therapy, four of whom underwent conversion to Roux-en-Y gastric bypass with concomitant device removal. Review of these four patients demonstrated improvement of symptoms in two patients and persistence of symptoms in the other two.

Table 3 Nutritional supplementation after GES

Nutritional route	Postoperative GES	Use at F/U	*p* value	No improvement of symptom
Enteral	14	5	0.037	2
Enteral and parenteral	4	3		1
Parenteral	–	–		

Table 4 BMI in diabetic and idiopathic cohorts

	Diabetic GP	Idiopathic GP
Preoperative BMI	27.2±5.9	25.1±7.7
Postoperative BMI	27.6±6.7	26.1±7.8
BMI change	0.2±3.8	0.8±3.8
Follow-up period (m)	22.7±22.5	29.2±28.1
P value	0.7	0.1

Discussion

Diagnosing Gastroparesis

Despite advancements in our understanding of gastroenterological disorders, gastroparesis remains a challenging clinical entity on many levels. First, the diagnosis remains difficult to make given the broad spectrum of etiologies, pathophysiology, and differing severity. A patient's gender, underlying past medical and surgical history, and medication usage all play a role in diagnosing gastroparesis. As in former studies, a large percentage of our gastroparetic patients are female, with an even higher percentage in the idiopathic subgroup. It is unclear why females constitute the bulk of these patients, though an autoimmune source may be involved due to loss of the interstitial cells of Cajal and abnormal immune infiltrates.[20] Half of our patients are diabetic, again supporting the literature that another end-organ affect of diabetes is neuropathy of the stomach nervous system leading to gastroparesis. Finally, while our cohort excluded medication and postsurgical gastroparesis, our practice receives referrals for many of these patients as well; therefore, a rigorous preoperative assessment must ensue prior to GES implantation. The gold standard for diagnosis remains a solid-phase gastric emptying study, but this needs to be combined with an absence of medication or surgically induced causes. Once the diagnosis is made, challenges for treatment continue.

Treatment Options for Gastroparesis

Various medications have been used with limited success, while others have been either taken off the market or received FDA black box warnings for persistent use (cisapride and metoclopramide).[3] These warnings have thus dissuaded clinicians from using these medications long term. Endoscopic therapies, such as Botulinum toxin injection of the pylorus have been used with some success in the past; however, this therapy requires multiple procedures and repeat injections for ongoing relieve.

Gastric Electrical Stimulation Use

Early use of gastric electrical stimulation use for medically refractory gastroparesis was reported by Lin et al. and McCallum et al. in 1998.[21,22] The findings of two randomized trials showing good results prompted FDA approval for usage in diabetic or idiopathic gastroparesis. Approach for GES placement was initially performed via a laparotomy, which subjected patients to the associated morbidity such as wound complications (infection and hernia), increased pain, and long recovery periods. Al-Juburi et al. showed comparable symptom outcomes with decreased length of stay for those undergoing laparoscopy versus laparotomy.[23] Several more authors have since reported on laparoscopic GES placement with comparable results to studies using laparotomy.[24–26]

To our knowledge, the current study represents the largest series of laparoscopic GES. Our institution begin GES placement during the era of advanced laparoscopy and all patients were considered who qualified for GES therapy were considered candidates for laparoscopic approach. Our conversion rate was less than 1 %, despite having many patients with prior abdominal operations. There were minimal perioperative complications and no immediate wound complications, such as infection or dehiscence. Table 5 compares outcomes from the current laparoscopic series to

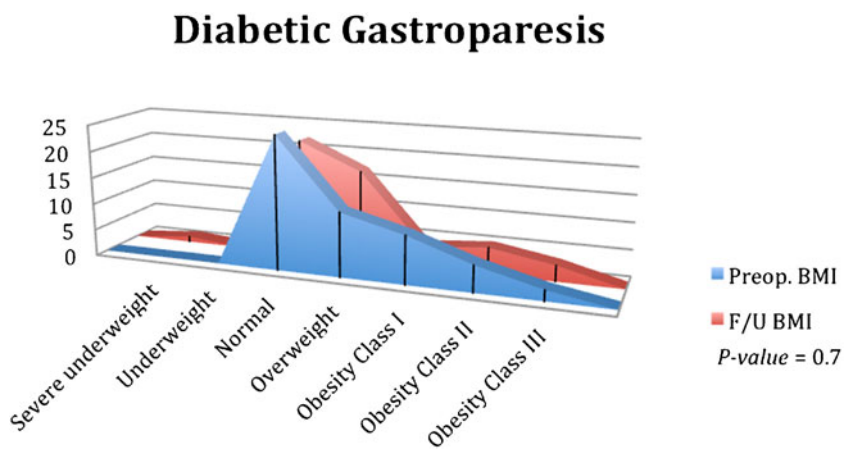

Fig. 3 BMI change following gastric pacemaker implantation in diabetic gastroparesis

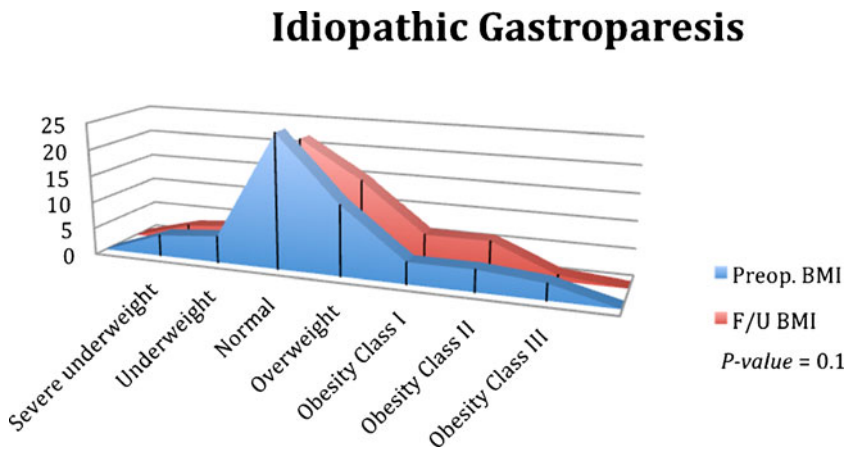

Fig. 4 BMI change following gastric pacemaker implantation in idiopathic gastroparesis

the open series by McCallum et al.[19] We note a statistically significant decrease in perioperative mortality within the laparoscopic series, while device migration occurred at a significantly higher rate in the laparoscopic series. Given the preponderance of evidence in favor of the application of laparoscopy to improve pain, length of stay, and wound morbidity, we believe that laparoscopic GES is superior to open GES and should be considered the standard of care.

Symptom Improvement with GES

Symptom improvement with GES has been well documented both with open and laparoscopic approach. A recent study with more than 200 patients with GES showed a total improvement of greater than 50 % for idiopathic, diabetic, and postsurgical gastroparesis.[19] Many similar studies showed that response rates were better with the diabetic subgroups when compared with the idiopathic subgroups.[9,19,27,28] While we did not measure pre- and postoperative total symptom severity scores, there appeared to be a similar improvement rate in both the diabetic and idiopathic subgroups in our series. Furthermore, there was a high rate of partial or complete resolution of symptoms (80 %) in both groups, which is higher than most reported response rates. This has been attributed to a stringent preoperative selection process that often involves multidisciplinary evaluations with our Gastroenterology, Pain Management, and Gastrointestinal Surgery departments. For every 80–100 charts reviewed, 10 patients are evaluated and considered candidates for GES with 1 patient ultimately undergoing GES placement.

Nutrition Improvement with GES

Several authors have evaluated nutritional improvement following GES placement.[29] McCallum et al. noted that 89 % of 221 patients undergoing GES placement were able to have jejunostomy tubes removed following placement.[19] Likewise, in our series we observed considerable improvement regarding patient's nutritional status when evaluating supplemental nutritional needs via either enteral or parenteral routes. Furthermore, there was a slight increase in overall BMI, though this was not statistically significant. Results of the current study support the use of GES in patients using supplemental nutritional needs secondary to medically refractory diabetic or idiopathic gastroparesis.

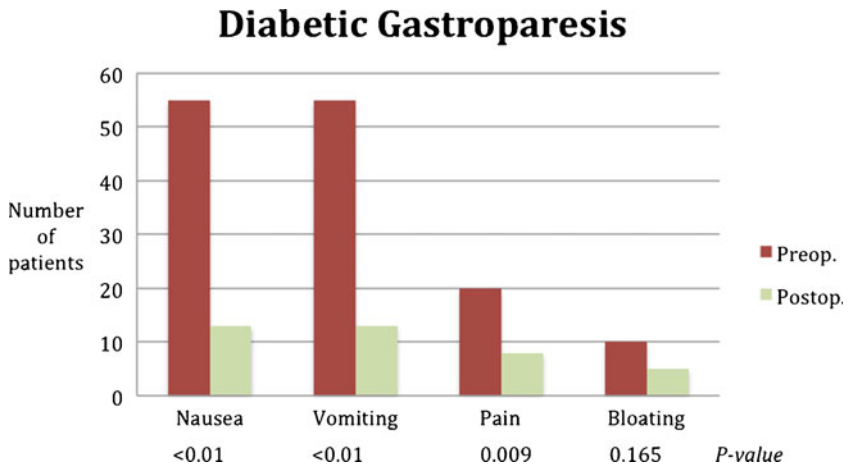

Fig. 5 Pre- and postoperative symptoms in diabetic cohort

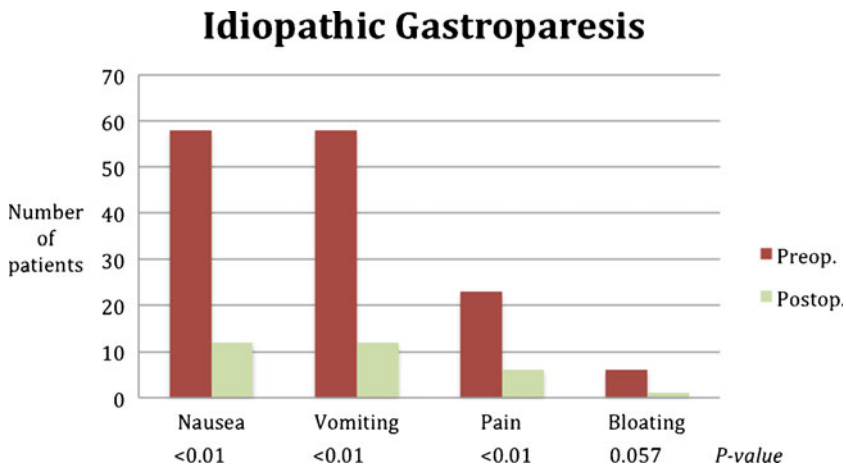

Fig. 6 Pre- and postoperative symptoms in idiopathic cohort

Failure of Symptom or Nutritional Improvement with GES

While there was a low failure rate of symptom control, several theories may explain this phenomenon. First, despite a rigorous selection process, some patients who qualify for GES may actually have undiagnosed disorders (such as chronic narcotic use and global bowel dysmotility) which are known to respond poorly to GES therapy. Furthermore, those patients in the diabetic cohort with long-standing diabetes may have such poorly controlled diabetes and end-organ damage as to not have adequate nerve function remaining to the stomach. In terms of failure of nutritional improvement, of all patients who needed supplemental nutrition at some point during their GES therapy (N=44), only 15 required supplemental nutrition at last follow-up (Tables 2 and 3). Four out of these 15 patients had no improvement of symptoms which led to persistent need for enteral access. The other 11 patients had improvement of symptoms but required ongoing nutritional supplementation due to the severity of their malnutrition or symptom constellation. These findings confirm the idea that gastroparesis is a disorder with a broad spectrum of symptom duration and severity, and long-term follow-up with a multimodality approach is required.

Improvement of Glycemic Control with GES

Diabetes improvement as measured by improved glycated hemoglobin was reported by McCallum et al.[19] Due to the retrospective nature of our analysis and the number of patients referred from outside institutions, we did not have baseline and follow-up glycated hemoglobin levels in all patients. The current IRB protocol did not include retrieving all glycated hemoglobin levels, which is an obvious limitation in our study. Further follow-up should include monitoring these levels to determine the relationship between GES and diabetic control. In the 11 patients who did have values measured both pre- and postoperatively, the only patients who did not have improvement of symptoms (five) also showed worsening glycated hemoglobin levels. This finding confirms the value of glycemic control as a method of improving gastroparetic symptoms. More rigorous follow-up of diabetes control is therefore recommended when

Table 5 Comparison of current study to largest series of open GES in the literature

	Laparoscopic (current study) (n=113)	Open[19] (n=221)	p value
Mean time F/U (years)			
Diabetic	2.0±1.85	8.7±6.04	N/A
Idiopathic	2.4±2.3	9.7±6.2	N/A
LOS (days)	3.5 (2–17)	5 (2–9)	N/A
Death (nonrelated to GES)	4 (4 %)	26 (12 %)	0.013
Pacer removal	7 (6 %)	24 (11 %)	0.164
Pacer infection	3 (3 %)	13 (6 %)	0.191
Battery depletion	6 (5 %)	4 (2 %)	0.0769
Device migration (malposition)	6 (5 %)	2 (1 %)	0.020
Device, lead, or wire malfunction	2 (2 %)	5 (2 %)	0.559

evaluating gastroparesis symptoms. Also, enteral access may be beneficial in helping to minimize blood sugar fluctuations.

Complications with GES

Overall morbidity was divided into device-related problems such as battery depletion and device malfunction or surgical-related complications, such as skin infection and pacer malposition. Total morbidity occurred in 16 patients (14 %). No immediate surgical site infections or hernias were noted in this predominantly population of predominantly laparoscopic cases. Mortality occurred in four patients (3.5 %), all in the diabetic gastroparesis group, during the study period. This finding is not surprising given the significantly higher rate of cardiovascular co-morbidities in the diabetic versus idiopathic groups. There was also evidence of end-organ dysfunction in roughly 50 % of these patients, making them higher risk patients.

Gastroparesis in Morbid Obesity

A particular challenge arises when addressing patients with both medically refractory gastroparesis and class I or II obesity. Those with class II obesity remained obese following GES placement, and several patients with class I obesity converted to class II obesity during the study period. The symptom response rate in this subgroup was lower than the overall cohort, suggesting that alternative therapies such as gastric bypass or gastric resection may be better tolerated after initial evaluation. In those patients who went on to Roux-en-Y gastric bypass or gastric resection, several patients ultimately had resolution of symptoms as well as associated weight loss. Given the results of the current study and the dearth of information regarding GES use in the morbidly obese, the authors currently recommend laparoscopic GES for patients with class I obesity. For patients with class II obesity, the authors recommend obesity and comorbidity control with either medical or surgical (i.e., gastric bypass) means. Further research in this patient subgroup is warranted.

Study Limitations

The study limitations include its retrospective nature and incomplete data for all patients. Furthermore, a symptom severity score was not used; rather, symptom improvement was documented via outpatient follow-up and documentation of decrease in medical therapy. Mean follow-up was only 22.7 and 29.2 months, respectively for the diabetic and idiopathic groups, therefore, longer-term follow-up is necessary.

Conclusions

This study demonstrates that with careful selection, the majority of patients with medically refractory diabetic or idiopathic gastroparesis respond to GES therapy. Laparoscopy should be the gold-standard approach in placement of GES with conversion rate of around 1 %. Supplemental nutrition in the form of enteral and parenteral means decreases with ongoing GES therapy over time. Treatment of morbidly obese gastroparetic patients remains a challenge, and clinicians should consider Roux-en-Y gastric bypass for these patients. Morbidity and mortality for this procedure is less than 15 %.

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