

Gastric Electrical Stimulation

An Alternative Surgical Therapy for Patients With Gastroparesis

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Hypothesis: Gastric electrical stimulation is an alternative to gastrectomy in patients with refractory gastroparesis.

Design: Retrospective case series with a median follow-up of 20 months.

Settings: A tertiary care university hospital and a university-affiliated community hospital.

Patients: Twenty-nine patients (22 women, 7 men; median age, 39 years; age range, 20-87 years) with debilitating gastroparesis who were referred for gastrectomy from December 10, 2001, through October 1, 2004. Twenty-four patients had type 1 diabetic gastroparesis and 5 patients had idiopathic gastroparesis.

Interventions: Placement of a gastric stimulator device laparoscopically in 24 patients and by laparotomy in 5 patients.

Main Outcome Measures: Morbidity and mortality of the procedure, symptom control, hospital readmissions, need for supplemental nutritional support, body mass index (calculated as weight in kilograms divided by the square of height in meters), and gastric emptying.

Results: Follow-up results were available in 27 patients. There was no 30-day mortality or morbidity in 4 patients. The median hospital stay was 3 days. All of the patients tolerated an oral diet at discharge. Symptom control was excellent to good in 19 patients. Nutritional support was discontinued in the 19 patients who were dependent on supplemental feeding before the procedure ($P < .001$). The median body mass index improved significantly (22.9 preoperatively vs 25.1 postoperatively; $P = .006$). The median gastric emptying rate (percentage per minute) was measured in 15 of the 27 patients postoperatively and showed significant improvement (0.17% per minute preoperatively vs 0.38% per minute postoperatively; $P < .001$). Additional procedures were required in 4 patients (owing to poor outcome in 3 patients).

Conclusions: Gastric electrical stimulation ameliorated symptoms, returned patients to normal oral nutritional intake, increased body mass index, improved gastric emptying rates, and is an alternative to gastrectomy in patients with end-stage gastric disease.

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GASTRIC DYSFUNCTION in the absence of a structural or mechanical obstruction usually causes minor symptoms that are easily controlled with medications and is a self-limiting condition of short duration.^{1,2} There is a subset of patients, however, who have a chronic debilitating problem that is uncontrolled by antiemetic or prokinetic medications, is associated with severe epigastric pain³ often resulting in narcotic dependence, and is manifested by the inability to eat, nutritional compromise, and weight loss. These patients have frequent hospital admissions, are socially restricted by their symptoms, and require enteral or paren-

teral feedings to maintain their nutrition. This end-stage gastric dysfunction results most commonly from insulin-dependent diabetes mellitus^{3,4} but can also result from viral gastritis⁵ and surgical vagal nerve injury.⁶

The magnitude of the gastric dysfunction in these patients often leads to gastric resection. More recently, an alternative therapy, gastric electrical stimulation (GES) using an implantable neurostimulator (Enterra Therapy Itriel 3 model 7425G; Medtronic Inc, Minneapolis, Minn), received a humanitarian device exemption for the management of these patients.⁷⁻¹⁰ The basis for this was a single case report by FAMILONI et al¹⁰ and 2 reports from a multinational, multi-

Table 1. Patient Demographics

Demographic	Patients With Type 1 Diabetic Gastroparesis	Patients With Idiopathic Gastroparesis
Patients, no.	24	5
Age, median (range), y	39 (22-60)	34 (20-87)
Sex, men/women	5/19	2/3
Duration of symptoms, median (range), mo	24 (12-240)	30 (12-84)
Patients with narcotic dependence, No.	11	2
Duration of diabetes mellitus, median (range), mo	192 (24-564)	NA
Patients with renal failure, No.	5	NA
Patients with coronary artery disease, No.	13	NA
Patients with diabetic retinopathy, No.	12	NA
Patients with peripheral neuropathy, No.	19	NA

Abbreviation: NA, not applicable.

center trial^{7,8} that showed improvement in symptoms following GES. These studies were based on animal experiments that showed that gastric stimulations induced antegrade and retrograde conduction of gastric slow waves and increased gastric emptying in dogs with vagotomy.¹¹⁻¹³ The purpose of this study was to retrospectively review the benefits of GES in a group of patients with chronic intractable (drug refractory) nausea and vomiting secondary to gastroparesis who were referred for gastrectomy.

METHODS

STUDY POPULATION

The study was approved by the institutional review board of the University of Southern California Keck School of Medicine and the Western Institutional Review Board, Olympia, Wash.

The study population comprised 29 patients with refractory gastroparesis who were referred for gastrectomy but agreed to enter a protocol-driven GES study. They all fulfilled the criteria for the use of GES, which included the following: (1) vomiting more than 7 times per week, (2) duration of vomiting greater than 12 months, (3) refractoriness or intolerance of antiemetic and prokinetic drugs, and (4) delayed gastric emptying as documented by radionuclide studies. There were 22 female and 7 male patients with a median age of 39 years (range, 20-87 years). Five patients did not have an identifiable underlying disease and 24 patients had insulin-dependent diabetes mellitus. Patient demographics are shown in **Table 1**. The criteria for discharge were the ability to tolerate oral intake, independence from narcotics, and adequate glucose control. Follow-up was complete in 27 (93%) of the 29 patients. The median follow-up was 20 months (range, 4-37 months). Two patients were lost to follow-up. Three patients died of unrelated causes during the follow-up period: 2 died of complications related to renal failure at 12 and 18 months following implantation of the gastric stimulator and 1 died of a myocardial infarction at 17 months following implantation of the gastric stimulator.

ASSESSMENT OF SYMPTOMS AND OBJECTIVE MEASURES OF OUTCOME

Symptomatic outcome was assessed during a face-to-face encounter or via telephone interview for those patients out of the geographic area of the clinic. The severity and clinical impact of the symptoms that are typical of gastroparesis (ie, nausea, vomiting, epigastric pain) were assessed using 4 dichotomous variables. These variables documented whether the symptoms required (1) prokinetic agents, (2) narcotic analgesia, (3) further repeat hospitalizations, and (4) additional procedures. The patient's outcome was assessed by judging how many of the 4 variables were necessary to control the symptoms.

The postoperative clinical outcome was graded as excellent if there was relief of foregut symptoms without the use of narcotics, prokinetic agents, repeat hospitalizations for gastroparesis, and additional procedures. Outcome was graded as good if the patient responded affirmatively to 1 of the 4 variables, fair if the patient responded affirmatively to 2 of the 4 variables, and poor if the patient responded affirmatively to 3 or all 4 of the variables.

Objective measures of outcome included the need for supplemental nutrition postoperatively, changes in body mass index (calculated as weight in kilograms divided by the square of height in meters), and gastric emptying as assessed by a technetium Tc 99m gastric emptying scan.

TECHNETIUM TC 99M GASTRIC EMPTYING SCAN

Gastric emptying was measured in all of the patients preoperatively and in 15 (52%) of the 29 patients postoperatively. A standardized radiolabeled test meal¹⁴ consisting of a scrambled egg substitute (120 g of Egg Beaters [ConAgra Foods Inc, Omaha, Neb]; 60 kcal), 2 slices of bread (120 kcal), strawberry jam (30 g; 75 kcal), and water (120 mL) was used. The meal had a caloric value of 255 kcal (nutritional composition: 72% carbohydrate, 25% protein, 2% fat, and 2% fiber). The Egg Beaters were cooked with 1 mCi (37 MBq) of technetium Tc 99m sulfur colloid as a marker. After an overnight fast, the meal was given to the patients, who were encouraged to ingest the meal in 20 minutes. One-minute anterior and posterior images were obtained in the technetium Tc 99m window (140 keV \pm 10%) with the patient sitting in a 90° upright position. The first image was taken immediately following the meal, with subsequent images taken at 120 and 240 minutes. Other images were taken according to the discretion of the radiologist. The patients were allowed to leave the camera between having images taken. The study was considered abnormal if there was gastric retention of greater than 10% at 240 minutes, or if there was retention greater than 60% at 120 minutes if the patient was unable to complete the 4-hour study because of vomiting. The gastric emptying rate was calculated as the percentage emptying per minute.

BODY MASS INDEX

Body mass index was calculated as kilograms of body weight divided by the square of height in meters.

PREOPERATIVE PREPARATION

All of the patients underwent a preoperative period of optimization and counseling before placement of the gastric stimulator. During this period, the patients were weaned off of any narcotic analgesics, unnecessary medications were discontinued, and their preexisting medical conditions were optimized. They were given directions concerning the expected manage-

ment of their pain postoperatively, the proposed postoperative feeding regimen, and general expectations of life following placement of the stimulator.

GASTRIC STIMULATOR PLACEMENT TECHNIQUE

Gastric stimulation was achieved through 2 intramuscular leads (Medtronic model 4301) anchored into the stomach wall and connected to a neurostimulator (Medtronic model 7425G). The technique involved 2 steps: (1) placement of the stimulating leads in the muscularis propria of the stomach and (2) placement of the neurostimulator in a subcutaneous pocket on the anterior abdominal wall.

Any preexisting gastrostomy tubes were removed before preparing the abdomen. Placement of the electrodes was done preferentially laparoscopically or through an upper midline incision. The placement technique of the device for the open procedure was identical to that used for the laparoscopic approach. A pneumoperitoneum was created in a standard fashion. A 5-mm trocar was placed in the midline below the umbilicus for a 30° laparoscope. A 12-mm trocar was centered over the lateral border of the patient's left rectus muscle at the level of the umbilicus. This incision was later enlarged to approximately 4 to 5 cm to create the subcutaneous pocket for the neurostimulator. Another 5-mm trocar was placed through the patient's right rectus muscle lateral to the umbilicus (**Figure 1**). If the patient needed a feeding jejunostomy, an additional 5-mm trocar was placed in the midline supraperitoneally. A feeding jejunostomy was placed in 5 patients. The pylorus was located by identifying the vein of Mayo with the laparoscope and its location was confirmed intraluminally by a gastroscope. Two stimulating electrodes were placed 1 cm apart along the greater curvature 10 cm proximal to the pylorus. The stimulating electrodes were placed in the muscularis propria of the stomach wall, aided by endoscopic visualization to ensure that the gastric mucosa was not breached. Correct intramuscular placement was confirmed by measuring the impedance between the 2 electrodes (approximately 500 Ω). The electrodes were anchored to the stomach wall with sutures. The stimulating leads were brought out through the left rectus muscle and attached to the neurostimulator. This was placed in a subcutaneous pocket. The impedance was rechecked, the subcutaneous pocket was irrigated with antibiotic solution, and the skin was closed. The patients were routinely given prophylactic intravenous antibiotics preoperatively and oral antibiotics for 5 days postoperatively. A baseline abdominal radiograph was obtained in the recovery room to document correct placement of the device.

PROGRAMMING TECHNIQUE

Gastric electrical stimulation was initiated in the operating room with the neurostimulator initially programmed to the following parameters: pulse width, 330 microseconds; current (amplitude), 5 mA; frequency, 14 Hz; cycle on for 0.1 second and cycle off for 5.0 seconds. The impedance was measured daily during the hospital stay. It was noted that in some patients, the impedance fluctuated with the healing process. In these patients, the voltage was adjusted to maintain the initial baseline stimulating current of 5 mA. Follow-up was weekly for the first 2 weeks following discharge and thereafter at 6 weeks, 3 months, and then every 6 months. If it was noted at follow-up that the patient's symptoms were not relieved, the stimulating current was then incrementally increased by 1 mA per day until the

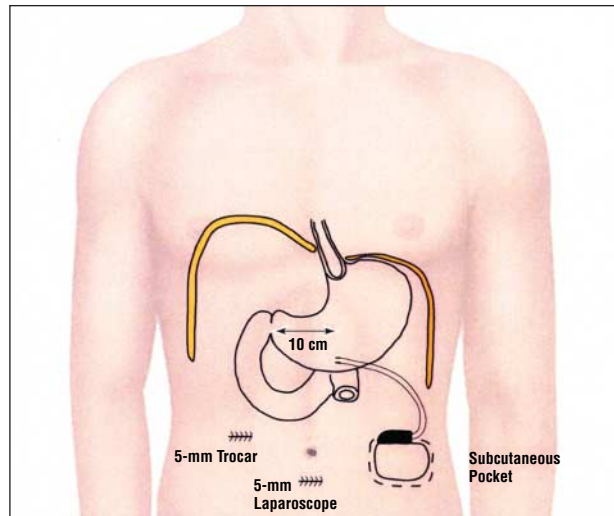


Figure 1. Diagrammatic representation of the laparoscopic placement technique showing trocar placement, lead placement in the stomach wall, and position of the subcutaneous pocket for the neurostimulator.

symptoms were relieved. The maximum stimulating current was, however, arbitrarily set at 10 mA. The median stimulating current for the patients was 7.75 mA (range, 4.30-10.00 mA).

STATISTICS

All of the data are expressed as medians \pm interquartile ranges unless otherwise stated. Paired data were analyzed using Wilcoxon signed rank test, and unmatched data were analyzed using the Wilcoxon rank sum test. Categorical data were analyzed using a χ^2 test.

RESULTS

The characteristics of the study population are shown in Table 1. The gastric stimulator leads were placed laparoscopically in 24 (83%) of the 29 patients and by laparotomy in 5 (17%). There were no conversions from laparoscopy to laparotomy. All of the patients in the laparotomy group had prior abdominal procedures, including 2 patients who had received abdominal aortic procedures, 1 patient who had received a pancreatic and kidney transplant, 1 patient with a large incisional hernia, and 1 patient who had received an open feeding jejunostomy tube. The median hospital stay was 3 days (range, 1-11 days). The median length of stay of 2 days (range, 1-10 days) in the laparoscopy group was significantly shorter than the median length of stay of 7 days (range, 3-11 days) in the laparotomy group ($P=.02$).

HOSPITAL MORBIDITY AND MORTALITY

There was no 30-day mortality. Postoperative morbidity occurred in 4 patients and comprised postoperative aspiration pneumonia requiring intubation and ventilatory support for 1 week in 1 patient, postoperative atrial fibrillation in 1 patient, a subcutaneous abscess around a feeding jejunostomy tube site requiring removal of the feeding tube in 1 patient, and postoperative hypoglycemia in 1 patient. There were no wound infections or complications related to the subcutaneous pocket.

Table 2. Use of Supplemental Nutrition During Follow-up Period

Nutrition Type	Patients With Type 1 Diabetic Gastroparesis, No. (%) (n = 24)		Patients With Idiopathic Gastroparesis, No. (%) (n = 5)	
	Preoperatively	Postoperatively	Preoperatively	Postoperatively
Total parenteral nutrition	9 (38)	0 (0)	3 (60)	0 (0)
Enteral nutrition	3 (13)	0 (0)	0 (0)	0 (0)
Both enteral and total parenteral nutrition	3 (13)	0 (0)	1 (20)	0 (0)

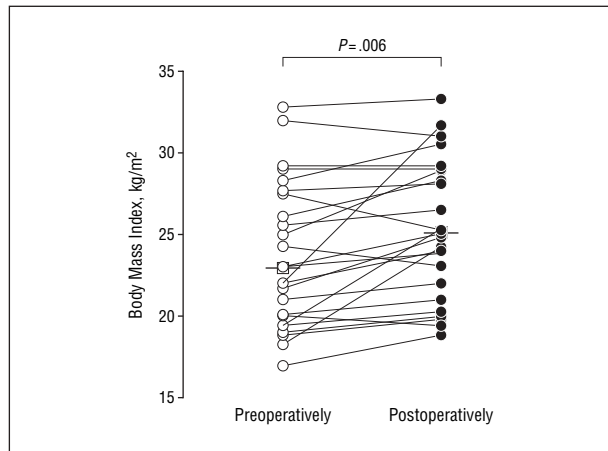


Figure 2. Scatterplot of body mass index preoperatively and postoperatively after a median follow-up of 19.9 months. There was a significant increase in the body mass index postoperatively ($P = .006$).

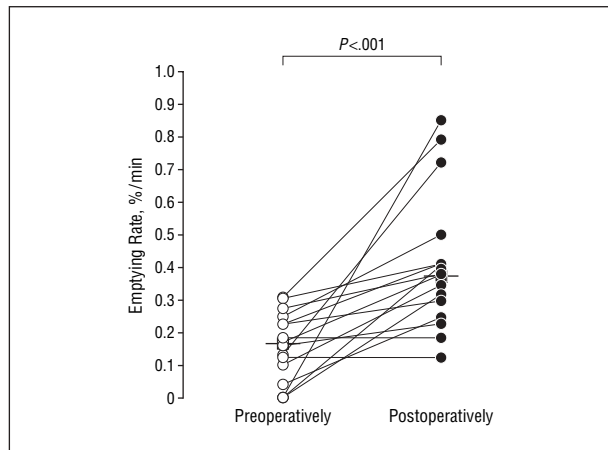


Figure 3. Scatterplot of the gastric emptying rate (percentage per minute) preoperatively and postoperatively ($n = 15$). There was a significant increase in the emptying rate postoperatively ($P < .001$).

OUTCOME OF GASTRIC STIMULATOR PLACEMENT

Clinical Outcome

Good to excellent outcomes were found in 19 (70%) of the 27 patients who were followed up for a median of 20 months or until death. Eight (30%) of the 27 patients had a fair to poor outcome. In the 3 patients who died, the outcome was graded as fair in 2 patients and poor in 1 patient. This lat-

ter patient required a pyloroplasty 7 months following placement of her GES device and succumbed 10 months later to a myocardial infarction. Additional procedures were required in 3 other patients. One had erosion of the gastric stimulator leads through the gastric mucosa at 6 months postoperatively. This required reoperation and replacement of the leads in the stomach wall. One patient requested removal of the GES device owing to pain at the subcutaneous pocket site, and the other patient had a total gastrectomy for failure to improve with GES.

Nutritional Outcome

A greater-than-10-pound (>4.5 kg) weight loss was reported by 13 (45%) of the 29 patients in the year preceding placement of the gastric stimulator. Nineteen (66%) of the 29 patients were dependent on total or supplemental nutritional support preoperatively, and none of these patients (significant at $P < .001$) were dependent during the follow-up period (**Table 2**). All of the patients tolerated an oral diet at discharge. Six patients had a feeding jejunostomy tube placed in the postoperative period that was subsequently removed in all of the patients by 6 weeks. The median \pm SD body mass index of the patients preoperatively was 22.9 ± 7.5 , and this increased significantly ($P = .006$) to 25.1 ± 7.45 at a median follow-up of 20 months (**Figure 2**).

GASTRIC EMPTYING

Seven (46%) of 15 patients normalized their gastric emptying postoperatively. Eight (66%) of the 15 patients continued to show abnormal gastric emptying. Emptying was improved in 6 patients and remained unchanged in 2 patients postoperatively. The median \pm interquartile range preoperative gastric emptying rate of $0.17\% \pm 0.54\%$ per minute was significantly increased to $0.38\% \pm 0.26\%$ per minute postoperatively ($P < .001$; **Figure 3**).

COMMENT

This study shows that GES can ameliorate the debilitating symptoms of end-stage gastric disease, can return patients to normal oral nutritional intake, can increase body mass index, and can improve gastric emptying in those patients refractory to medical treatment.

The patients in this study had failed long-term medical therapy with prokinetic and antiemetic agents,

which has a reported median success of approximately 50%.¹⁵ Although the symptoms of gastroparesis can fluctuate, all of the patients in this study had persistent symptoms of severe gastroparesis for a duration of more than 1 year. Thus, the patients with transient or self-limiting gastroparesis were excluded. The underlying pathophysiological etiology associated with end-stage gastric disease is unclear, but reports have shown a disturbance in the gastric myoelectrical activity. This results in a gastric dysarrhythmia that most commonly is nonspecific, though bradygastria and tachygastria have been reported.¹⁶⁻¹⁸ The underlying arrhythmia causes a loss of the normal fundic-pyloric-duodenal pressure gradient and flow with resultant gastric stasis. Furthermore, the gastric arrhythmias in these patients are associated with severe and constant nausea and, in many patients, are also associated with severe epigastric pain that is often only controlled by narcotic analgesia that further perpetuates the problem of delayed gastric emptying.^{3,19} Although the mechanism of action of GES is unclear, evidence does support the hypothesis that GES alters the gastric myoenteric neural network (both efferent and afferent) and interrupts the gastric arrhythmias causing their symptoms.²⁰⁻²⁴

The patients who should be considered for GES fall into 3 categories. The first category includes those patients who are refractory to medications and have daily nausea and vomiting with an inability to maintain nutrition. These patients are categorized by frequent admissions to the hospital and by severe weight loss. Sixty-six percent of our patients were dependent on total parenteral nutrition or enteral nutrition preoperatively. Early in our experience, a feeding jejunostomy tube was placed because of concerns about postoperative nutrition. Importantly, however, none of the patients required any supplemental nutritional support postoperatively, and this was maintained throughout the duration of follow-up. The feeding tube was removed by 6 weeks postoperatively in all of the patients, and we no longer recommend routine placement of a feeding jejunostomy tube. The main reason for the inability of the patient to tolerate oral intake preoperatively is severe nausea. We believe that the commencement of early feeding is probably most related to the instantaneous relief of nausea by the gastric stimulator combined with the preoperative counseling and optimization that the patients received. Overall, the patients have shown significant weight gain, to such an extent that a weight-restricting diet has had to be instituted in 2 patients.

In this study, clinical outcome was assessed using an objective scoring system that considered 4 dichotomous variables of symptom control. Other comparable studies have subjectively evaluated symptoms, which may reflect other factors associated with the underlying disease of the patients rather than symptoms specifically caused by gastroparesis. Symptom control was favorable in 19 (70%) of the patients, which is similar to the specific symptom relief reported by others.^{7,8,20,25-30} The philosophy and programming technique for GES in this study is different from the other reported series.^{7,8,20,25-30} A more active approach was used and the stimulating current was titrated to control nausea, vomiting, and epigastric pain. This policy is

based on the observation that other medical disciplines using neuromodulation for conditions such as urinary and fecal incontinence, neurological seizure, and tremor control titrate and adjust stimulating current to control the patients' symptoms. The median stimulating current in this series, 7.75 mA, is higher than the fixed current of 5 mA used in other series.^{7,8,25,27,28}

Twenty-four (86%) of the patients in this study had implantation of the leads laparoscopically as opposed to the other larger studies in which a laparoscopic approach was used in only 0%,^{27,28} 18%,⁷ and 42%⁸ of patients. Stimulation began in the operating room in this study whereas stimulation began after a postoperative recovery period ranging from 48 hours to 1 month in other studies. Early activation of the stimulator helps with postoperative recovery by reducing ileus and aiding glucose control. Oral intake began on postoperative day 1 in the laparoscopic patients, and all of the patients were successfully discharged home relying totally on oral nutrition. As opposed to Forster et al,²⁷ who believe that all patients should be implanted via an open technique and list the factors that support this in their article, we believe that all patients should be implanted by a laparoscopic technique for the following reasons: (1) postoperative pain can be controlled more easily without narcotics; (2) postoperative ileus is minimal and the patient can commence receiving food orally on postoperative day 1, which aids in glucose control and results in a shorter hospital stay; (3) the pylorus and lead implantation site are easy to determine using the technique described; (4) wound infection occurs less often with a laparoscopic approach; (5) a feeding jejunostomy tube can easily be placed laparoscopically and was done in 5 of our patients; and (6) as this is an upper abdominal procedure, adhesions from previous abdominal procedures can be dissected laparoscopically. Eight (28%) of the 29 patients in this study had received previous abdominal procedures and, in our opinion, the adhesions encountered could have been managed laparoscopically.

The second category of patients who should be considered for GES includes those who continue to have gastric motor dysfunction and arrhythmias causing severe stasis of food and chronic epigastric pain. Of the 29 patients involved in this study, 15 (52%) had gastric emptying studies before and after placement of the gastric stimulator. Seven (46%) of these 15 patients normalized their gastric emptying postoperatively. This incidence is comparable with other studies.^{7,27} Similarly to these studies, it appears that normalization of gastric emptying is not correlated with the improvement in symptoms. However, 13 (86%) of the 15 patients showed a significant increase in gastric emptying, and this mirrored their clinical outcome. Owyang and Hasler¹⁹ showed that antral distention may cause gastric slow-wave disruption and development of nausea. Although we did not specifically measure antral distention and gastric emptying was not normalized in this study, the observed improvements may have diminished antral distention

sufficiently to improve symptoms. Another possible explanation for the variable response in gastric emptying may be related to the prevalence of interstitial cells of Cajal in the muscularis propria. Although we did not specifically measure the prevalence of interstitial cells of Cajal, Forster et al³¹ have shown that some patients with gastroparesis have no intramuscular cells of Cajal, and GES with high frequency and low energy as used in this study would, therefore, not be able to influence gastric slow-wave activity or motility.³¹ In the future, the group of patients showing depleted interstitial cells of Cajal should possibly be stimulated with low frequency and high energy, which would entrain or pace the smooth muscle directly, independent of the cells of Cajal. A major limitation of this study is that gastric emptying studies were not performed in all of the patients postoperatively. Of the 14 patients who did not have their gastric emptying studied postoperatively, 3 died, 2 were lost to follow-up, 2 refused, and a postoperative study was denied for the remaining 7 patients by the patients' medical insurance companies (as it was deemed unnecessary).

The third category of patients who should be considered for GES includes those who have complications related to gastroparesis, such as the inability to control blood glucose levels and problems with line sepsis in those receiving total parenteral nutrition. Significant line sepsis was a problem in some of our patients preoperatively. Although we did not specifically monitor glucose level control, Lin et al²⁶ showed a significant reduction in the mean hemoglobin A_{1c} level after GES.

In summary, GES improves symptom control, restores eating behavior, decreases narcotic requirements, and improves gastric motor function, resulting in a better lifestyle and social reintegration. It is a simple and effective procedure with low morbidity and mortality and should be considered as an alternative to gastrectomy in patients with end-stage gastric dysfunction.

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Bruce E. Stabile, MD, Torrance, Calif: Dr Mason and his colleagues are to be congratulated on their initial results with gastric electrical stimulation for severe gastroparesis. Of 29 patients implanted with the neurostimulator device, 27 were followed for a median of 19.9 months or until their death. Almost one half of the patients had excellent clinical results, and another 22% had good results as assessed by a largely subjective scoring system. The operative complication rate was acceptable, and all patients were tolerating an oral diet and were without intravenous or enteral tube feedings at the time of their hospital discharge.

The median body mass index increased significantly over the period of follow-up. While all 29 patients had delayed gastric emptying preoperatively, only 15 were tested postoperatively. Of these 15, 7 (47%) of the postoperatively studied group had normalization of gastric emptying, and the median emptying rate doubled. These results are encouraging considering the failure of medical management and the lack of alternative therapies for this very challenging group of patients.

The overall reported experience to date with gastric electrical stimulation has yielded somewhat inconsistent symptomatic relief results. However, with the use of high-frequency, low-amplitude stimulation, symptoms of nausea, vomiting, pain, and bloating have improved in the majority of implanted patients. Somewhat unsettling is the fact that improvement of gastric emptying has infrequently been demonstrated, and there has been little or no correlation between symptomatic improvement and objective measurement of accelerated gastric emptying. Such results underscore our present state of relative ignorance with respect to the cause of the symptoms in gastroparesis and the mechanism by which gastric electrical stimulation provides palliation for those symptoms.

The series just reported differs from previous studies in that the stimulating current was titrated to control symptoms with a final median current level about 50% greater than that initially utilized. Perhaps refinements in electrical stimulation parameters and gastric electrode positioning can be expected to further improve clinical results. However, it should be noted that in the existing literature, the relationship between neural stimulation and symptom amelioration has not been very consistent over the long term. In fact, device deactivation after 6 months did not elicit recurrent nausea and vomiting in a number of previously reported patients, raising the possibility that symptom improvement may not be related to the electrical stimulus. This of course brings up the inevitable issue of placebo effect since the mechanism of action of electrical gastric stimulation remains largely unknown.

In light of the unknown mechanism of action of gastric electrical stimulation, the lack of correlation between symptomatic relief and improvement in gastric emptying and the overall inconsistency of previously reported clinical results, I would like to pose a number of questions to the authors:

1. Can an uncontrolled and unblinded trial such as that presented be expected to convincingly demonstrate the therapeutic efficacy of this new device?
2. In your series, was there any direct correlation between symptomatic improvement and gastric emptying enhancement?
3. If there was such correlation, how do you explain that finding in the context of the existing literature in which there has been no such correlation shown?
4. What has been the experience in the patients having the device turned off or explanted?
5. What is the total cost of the device and its implantation, including the hospitalization time?

6. And, finally, can you enlighten us as to the most likely important mechanism or mechanisms of action of gastric electrical stimulation? Is it gastric emptying, receptive relaxation, GI [gastrointestinal] hormone release, autonomic or central nervous system activation, or what?

In closing, I applaud your fine efforts to address and elucidate this most vexing of clinical problems.

S. Eric Wilson, MD, Orange, Calif: Why are so many of your patients female? Is this a disorder that affects just females primarily?

Lee L. Swanstrom, MD, Portland, Ore: This is a great series, Dr Mason, and I applaud you for dealing with these patients. They are a very time-consuming and difficult group of patients. We have had a similar experience with the gastric stimulator, but we have not had very good luck with some of the other indications for the device, including postviral gastroparesis and, most importantly because I think there is a large group out there, postsurgical gastroparesis following resections, vagotomies, or inadvertent vagotomies. Maybe you can comment on your experience with these groups of patients.

Another thing that we have found is that the length of preoperative pathology, that is, how long these patients have had this problem, directly impacts their outcomes, and I wondered if you looked at that at all. I suspect that these patients get to a point where they are so addicted to narcotics, anxiolytics, and antiemetics that no treatment will work, and I wonder if you have found that same thing.

Finally, I have found that the gastric stimulator is best for nausea. Almost all patients have their nausea relieved, but it seems less successful for vomiting and even less so for pain and for loss of appetite. Could you comment on that?

Lygia Stewart, MD, San Francisco, Calif: Again, I want to also say that this is very exciting if these results are true. This is a major breakthrough for some very difficult patients. I have 2 questions. In your group that did better, did you look at narcotic usage overall, and was there any correlation with decreased narcotic usage and better outcomes? Maybe that would get at some other effects. Second, have you looked at this in patients who have had a vagotomy or a partial gastrectomy with delayed gastric emptying? Does this technique have any efficacy in these cases?

Nathalie M. Johnson, MD, Portland: I thought this was very interesting and a very clinically relevant paper. I have a question. Specifically in oncology, we have pancreatic cancer patients in which we do gastric bypass for palliation. This is a group in which gastroparesis or poor emptying is also an issue. Do you have any experience with this subgroup of patients and would this be helpful for them?

John K. MacFarlane, MD, Vancouver, British Columbia: I am sort of thinking outside of the box here and wondered whether there was any temptation to, before implanting this reasonably expensive device, perhaps trying to stimulate the gastric emptying with an external stimulator before implanting it, thereby reducing the cost somewhat. I found the paper very interesting. These are vexing problems.

Dr Mason: In answer to your question, as far as the mechanism of action, there is an ongoing trial which is double-blinded and it should hopefully answer some of the questions. The main problem is that we don't really know how this device works in gastroparetics, and this question was also addressed by some of the other discussants. As far as the correlation goes between symptoms and gastric emptying, we did look at that but we only really have 15 patients studied before and after the device, and with such small numbers it is very hard to get any correlation. I, therefore, wouldn't like to comment about any correlation at this stage. There has been some work done by Dr Forster's group looking at the numbers or

prevalence of the interstitial cells of Cajal in antral biopsies of patients with gastroparesis. It seems that some patients have depleted or absent interstitial cells of Cajal and other patients have normal amounts. The patients do poorly if they have depleted interstitial cells of Cajal, and in these patients, high-frequency stimulation like we used in this study wouldn't be expected to work. However, if they have depleted cells of Cajal, maybe the right thing to do would be to have low-frequency, high-energy stimulation, as this would then entrain the muscles of the stomach to improve emptying. Research in this area is currently being done. In the future, we may be able to determine which patients are going to respond and which patients are not, or what the optimal type of stimulation parameters should be used for individual patients based on the presence or absence of the interstitial cells of Cajal.

As far as whether the device has been turned off, well, I can tell you that sometimes the device gets turned off accidentally as when the patients go into the supermarket past a scanner or some other electromagnetic device that turns the device off. Just anecdotally, the patients are able to tell you that they do know when the device goes off and they feel it straightaway. The patient in our series that had the perforation of the leads into the stomach lumen knew straightaway when she lost the impedance and stimulating current. So based on their symptoms, some patients are able to tell you straightaway when there is a problem with the device.

Then as far as the total cost, the device costs about \$5000, but I think the total hospital charges are about \$35 000 or \$40 000. But, I am not sure on this figure.

As far as the mechanism of action goes, we still really don't know. It could be that it interferes with efferent nerves going to the brain or that it interferes with the slow waves and stops the gastric arrhythmia in these patients, but most people don't really know yet. As far as female patients go, there is a preponderance of female patients and it is well known that there is a hormonal influence on gastric emptying. As you know, many pregnant patients who are in their first trimester have severe gastroparesis with hyperemesis gravidarum. So, there definitely is a sex hormone relationship.

As far as postviral and surgical gastroparesis goes, we don't really have experience with any postviral patients. As far as surgical gastroparesis goes, none of these patients were postsurgical. However, we have done it in a few, but they are not reported in this series and I haven't gotten any follow-up on them.

They would be expected to do well with this device because their interstitial cells of Cajal will still be present. I think Dr McCallum's group has shown that it does work in postsurgical gastroparetic patients.

As far as the length of pathology and outcome, and the relationship to narcotics, we did not look at the length of pathology and outcome. It is true that these patients have severe epigastric pain and they really become addicted to narcotics, which I think is part of their problem. We have been very strict with the patients in our series, and we don't give them any narcotics whatsoever. The patients have to go through withdrawal and be weaned off the narcotics. As Dr Swanstrom stated, they are a difficult group of patients to deal with and they do become very dependent on hospitals, doctors, and narcotics. You have to be adamant that they are not going to get any narcotics and that they usually get better without them.

As far as nausea and vomiting, you are right. The procedure does seem to affect nausea better than vomiting, and maybe this is related to the findings in gastric emptying. We can see that about 56% of our patients still had delayed gastric emptying so vomiting still occurs, but the nausea definitely is better with this high-frequency stimulation, and this observation indicates stimulation working via some kind of efferent neural network going from the vagus to the brain.

Dr Johnson, as far as gastroparesis in patients who have other surgical problems, yes, you can pace the stomach if you use low frequency, high energy. The trouble is that the pacemaker only lasts for about 6 to 7 months because the battery gets depleted using such high energy. But if you are only thinking about doing this for a short term in this group of patients, yes, it is possible.

Finally, the last question dealt with doing some external stimulation instead of implanting this expensive device. The urologists, when they have patients with neurogenic bladders, do a similar thing. They initially implant the leads and have an external device. The same thing can be done with this gastric stimulator. You can implant the leads via a PEG [percutaneous endoscopic gastrostomy] gastrostomy tube and have the leads connected to an external device that is not implanted. In fact, an external stimulator was used in the first study that was done to get FDA [Food and Drug Administration] approval for the device. So, yes, the answer to the question is that it can be done externally and temporarily for a short period of time via a PEG gastrostomy tube.