



Original articles

## Gastric electrical stimulation for children with intractable nausea and gastroparesis

Saleem Islam<sup>a,\*</sup>, Laura R. Vick<sup>a</sup>, Matthew J. Runnels<sup>b</sup>,  
John R. Gosche<sup>a</sup>, Thomas Abell<sup>b</sup>

<sup>a</sup>*Division of Pediatric Surgery, Department of Surgery, University of Mississippi Medical Center, Jackson, MS 39216, USA*

<sup>b</sup>*Division of Gastroenterology, Department of Medicine, University of Mississippi Medical Center, Jackson, MS 39216, USA*

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Electrogastrograms;  
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stimulation;  
Interstitial cells of Cajal

### Abstract

**Purpose:** Gastric electrical stimulation (GES) has been performed in adults as a treatment of refractory nausea and vomiting in patients who have failed medical treatment, but has not been used in children.

**Methods:** Nine patients with chronic nausea and vomiting with a mean age of 14 years were evaluated for temporary GES. All 9 patients subsequently underwent placement of a temporary followed by permanent GES device. Symptoms were recorded at baseline, after temporary GES, and then after permanent GES using a Likert scale for gastroparesis. Statistical analysis was performed using a paired Student's *t* test.

**Results:** At baseline, all patients were symptomatic and most had delayed solid gastric emptying. As a group, there was a significant improvement in combined symptoms score ( $P = .04$ ), nausea ( $P = .039$ ), and vomiting ( $P = .0016$ ). Gastric emptying and electrogastrogram values did not change significantly. Follow-up ranged from 8 to 42 months, with 7 of the 9 patients reporting sustained improvement in symptoms and improved quality of life.

**Conclusions:** Gastric electrical stimulation can be successfully applied to adolescents with intractable nausea and gastroparesis symptoms who fail medical therapy. There is a significant improvement in symptoms over a prolonged period, and there are no adverse effects of the GES. Long-term efficacy of this therapy in children needs to be established.

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Gastroparesis (GP) is a disorder defined by symptoms of and evidence for gastric retention or disordered gastric emptying in the absence of mechanical obstruction [1,2]. The most common causes are diabetes mellitus, postviral illness, idiopathic, and postsurgical [3,4]. Most patients with GP are adults; and the symptoms include nausea, vomiting, early satiety, postprandial fullness, abdominal discomfort, and pain

[2]. The diagnosis of GP is not straightforward, especially in children, because the symptoms are often considered to be associated with other conditions and because of the lack of awareness among pediatric practitioners [5].

Gastroparesis is stratified into 3 groups by severity of symptoms (mild, compensated, or gastric failure) and is managed based on this classification [1]. Initial therapies include dietary modification, prokinetic and antiemetic therapy, and pain control. It is recommended that diabetic patients maintain strict glycemic control, which improves gastric emptying. Patients with more severe and uncontrolled symptoms may require long-term or even permanent

\* Corresponding author. Department of Surgery, Pediatric Surgery, University of Florida College of Medicine, PO Box 100286, Gainesville, FL 32610-0286, USA. Tel.: +1 352 392 3718; fax: +1 352 392 9081.

E-mail address: islamsa@surgery.ufl.edu (S. Islam).

enteral or parenteral nutritional support. There are few therapeutic alternatives for the patient with severe GP. Endoscopic injection of botulinum toxin in the pylorus has been attempted in uncontrolled series of patients with some degree of success; however, a randomized trial showed no efficacy [6-8]. Surgical options that have been attempted include pyloromyotomy, pyloroplasty (gastric emptying procedures), gastrostomy tubes for decompression, jejunal feeding tubes, and, in extreme cases, partial or total gastric resection [8-10]. A systematic review of the various surgical options for GP concluded that there were insufficient data to support the options of gastric and jejunal tubes for decompression and feeding, and they also did not favor other surgical options [8].

Over the past decade, gastric electrical stimulation (GES) has been performed in adults as a treatment of refractory nausea and vomiting associated with GP in patients who have failed medical treatment [1,4,11]. In 2000, the Food and Drug Administration granted humanitarian device exemption approval for the Enterra (Medtronic, Shoreview, MN) gastric electrical stimulator [12]. This system, initially approved only for refractory diabetic or idiopathic GP, consists of paired electrodes sutured to the anterior wall of the stomach through the seromuscular layer; and limited data in adults with GP show both relief of symptoms and reduced need for parenteral or enteral nutritional support [11,13]. To date, GES has not been systematically applied to individuals younger than 18 years with GP refractory to medical treatment. In this series, we report on 9 consecutive patients with GP who underwent temporary and/or permanent GES pacemaker placement.

## 1. Methods

As part of the overall institutional humanitarian device exemption Institutional Review Board approval, data were prospectively collected on all patients younger than 18 years with a diagnosis of GP who had implantation of a temporary and/or permanent gastric pacemaker. Nine patients, 8 female and 1 male, with chronic nausea and vomiting were evaluated with gastric emptying studies using scintigraphic tests and cutaneous electrogastrograms (EGGs) for temporary GES. All 9 patients went on to obtain temporary and permanent GES, either laparoscopically or via laparotomy. Intraoperative EGGs were performed on each patient. During permanent GES placement, seromuscular biopsies from the last 5 consecutive patients' stomach or jejunum were obtained for analysis of the interstitial cells of Cajal by histopathology.

### 1.1. Temporary stimulation

Each patient underwent temporary gastric GES before permanent placement. This was performed by mucosal

leads placed via endoscopy and using a transvenous cardiac pacing lead. The lead was brought out through the side of the mouth and connected to a stimulator that was kept in a pouch by the patient. This GES was left in place for 2 to 7 days; and symptoms, gastric emptying time (GET), and EGG were recorded.

### 1.2. Permanent placement

Laparoscopic placement involved 3 ports: two 5-mm ports (umbilicus, left mid abdomen) and one 10-mm port in the right upper abdomen. A distance of 9 to 12 cm from the pylorus was marked on the gastric antrum/body; and the leads were placed in that location, 1 cm apart. During the lead placement, we had endoscopic visualization to ensure that we did not perforate the mucosa. The leads were then attached to the stomach using small plastic devices and stitches, and the lead wires were brought out via the 10-mm port. The 10-mm port site was enlarged to a 3- to 4-cm incision, and a pocket was created for the stimulator. Before lead attachment, we measured the electrical impedance to ensure proper conduction. After connecting the leads, the stimulator was programmed and turned on. Initial settings usually involved low-energy, 0.1-second trains of pulses that are delivered by the generator at a frequency of 12 cycles per 60 seconds, with individual pulses oscillating at a frequency of 14 cycles per second.

### 1.3. Data collection and analysis

Symptoms of nausea, vomiting, abdominal bloating/distension, early satiety, and abdominal pain were recorded at baseline, after temporary stimulation, and after permanent pacing using a Likert scale. Patients graded their symptoms from 0 to 4 for severity on vomiting, nausea, anorexia, bloating, and pain. Individual symptom scores as well as the total symptom scores were compared using each patient as their own control with a paired *t* test. An investigator-derived independent outcome measure score (IDIOMS) was also calculated that evaluates the intensity of hospital service, severity of illness, and number of nongastrointestinal organ systems involved. These scores were also analyzed using a paired *t* test with each patient as his or her own control. In addition, we collected data on the GETs before and after stimulation as well as the EGG results, which were expressed as frequency of the intrinsic slow waves and the amplitude of the waves.

## 2. Results

Eight patients had either idiopathic (5) or postinfectious (3) GP, with one patient having postsurgical GP after multiple corrective operations for esophageal atresia with tracheoesophageal fistula (Table 1). Her last



**Table 1** Demographics, symptoms, pathology results, and complications in children with GES

Patient	Age/ Sex	Cause	Symptoms	Biopsy results	Other
1	8/F	Idiopathic	Pain, vomiting, weight gain	Large nerve bundles, few ganglion cells CD 117 <sup>a</sup> —few, faint; S-100 <sup>b</sup> —strong, positive	
2	13/F	Idiopathic	Pain, nausea, vomiting, bloating, weight loss	Abnormal number and distribution of ICC and ganglion cells, ganglion cell hyperplasia CD 117 <sup>a</sup> —none	J-tube Small bowel obstruction ×2
3	13/ M	Idiopathic/ Postviral	Nausea	—	
4	15/F	Idiopathic/ Postviral	Nausea	—	
5	15/F	Idiopathic	Vomiting	—	Irritable bowel syndrome
6	16/F	Idiopathic	Pain, nausea, vomiting	—	Constipation
7	16/F	Idiopathic	Nausea, vomiting	CD 117 <sup>a</sup> —plentiful S-100 <sup>b</sup> —focally large	Lupus, DM, ACE tube, constipation, hypothyroid
8	16/F	Idiopathic/ Postviral	Pain, nausea, vomiting, weight loss	S-100 <sup>b</sup> —intense staining C-Kit—no staining around nerve plexus Paucity of ICC	G-tube and J-tube Superior mesenteric artery syndrome
9	17/F	Postsurgical	Pain, nausea, bloating, weight loss	CD117 <sup>a</sup> —weak to absent staining 10-14 fibers/HPF in muscle layers S-100 <sup>b</sup> —weakly staining <10 fibers/HPF	Pacer removed because of pocket infection at 2 y Esophageal atresia with TE fistula, repaired with colonic interposition, redone at age 16 y with ileocolic interposition, scimitar syndrome, asthma, GERD

ICC indicates interstitial cells of Cajal; DM, diabetes mellitus; HPF, high-powered field; TE, tracheoesophageal; GERD, gastroesophageal reflux disease; ACE, antegrade colonic edema.

<sup>a</sup> CD 117 stains for interstitial cells of Cajal.

<sup>b</sup> S-100 stains for nerves.

operation was 1 year before presentation with a redo ileocolic anastomosis. Two of the patients who developed presumed postinfectious GP were brother and sister. One patient also had insulin-dependent diabetes mellitus and lupus as preexisting conditions. Before any treatment, all patients were symptomatic with a combination of symptoms from nausea, vomiting, weight loss, bloating, and pain.

The patients were symptomatic for a variable amount of time ranging from 6 months to 2 years. All patients had significant effects on their life, with all withdrawing from school and having multiple hospital admissions. The number of admissions varied as well, but was at least 3 to 4 times a year and, in half of the cases, more than 6 times a year. Four cases required total parenteral nutrition for variable lengths of time as well.

All had gastric emptying tests performed and were classified as delayed or “rapid” emptiers by the study. Cutaneous EGG was performed, as well as mucosal EGG when temporary stimulation was done. The patients were also divided into low- or high-frequency EGGs based on the tracings. There was no specific correlation between the GET and EGG with regard to the frequency and rate of emptying in this small series.

## 2.1. Temporary stimulation

There was a significant improvement in nausea symptoms from  $3.1 \pm 0.8$  to  $1.13 \pm 1.0$  ( $P = .006$ ) during temporary stimulation. Vomiting was also improved significantly ( $P = .03$ ). The total symptoms score decreased significantly from  $11.1 \pm 3.6$  to  $5.4 \pm 3.9$  ( $P = .006$ ) (Table 2).

## 2.2. Permanent stimulation

At the last evaluation, the mean score for nausea was  $1.6 \pm 1.5$  ( $P = .03$ ) and the total symptoms score was  $6.7 \pm 3.2$  ( $P = .045$ ), both of which remained improved. Vomiting

**Table 2** Symptom scores after GES (IDIOMS)

	Baseline	Temporary stimulation	Permanent stimulation
Vomiting	$1.9 \pm 1.7$	$0.13 \pm 0.35$ , $P = .03$	$0.44 \pm 1.01$ , $P = .016$
Nausea	$3.1 \pm 0.8$	$1.13 \pm 1.0$ , $P = .006$	$1.6 \pm 1.5$ , $P = .03$
Total score	$11.1 \pm 3.6$	$5.4 \pm 3.9$ , $P = .006$	$6.7 \pm 3.2$ , $P = .045$
IDIOMS	$15.7 \pm 2.6$	Not performed	$8.8 \pm 5.3$ , $P = .001$

scores dropped from  $1.9 \pm 1.7$  at baseline to  $0.44 \pm 1.01$  ( $P = .016$ ). Fig. 1 depicts the improvement graphically.

The base IDIOMS score was  $15.7 \pm 2.6$  and had significantly been reduced to  $8.8 \pm 5.3$  ( $P = .001$ ) at the last follow-up of the patients. This score measured health-related quality of life measures and showed improvement in most parameters (intensity of services, severity of illness, and other significant illnesses). Hospital use was also reduced in these patients overall with decreased numbers of admissions per year per patient.

### 2.3. GET and EGG

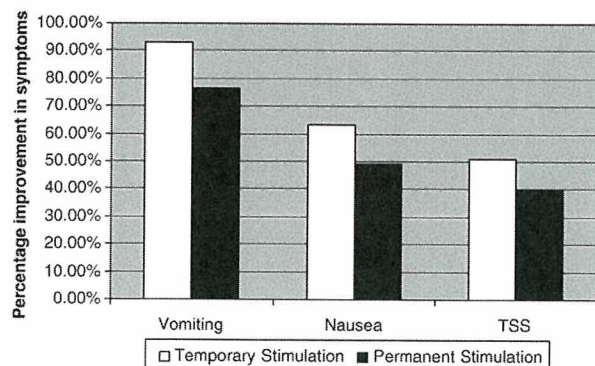
Gastric emptying values did not improve, as noted in Table 3. Normal values at our institution should be 50% or less at 1 hour, 25% or less at 2 hours, and less than 10% at 4 hours. Electrogastrogram results (Table 3) are also somewhat difficult to interpret; and by stratifying the patients into high and low frequency at baseline, we were unable to note any trends.

### 2.4. Pathology

Biopsy results of the stomach or jejunum were abnormal in 4 of 5 patients who had them performed, showing diminished and/or abnormal interstitial cells of Cajal. We found that the pathologic abnormality predicted a poorer response to the stimulation in the long term. We now routinely perform the seromuscular biopsies at the time of initial implantation for prognostic purposes.

### 2.5. Complications

We noted a few problems with the permanent stimulator, with one patient initially responding and then having the stimulator changed because of recurrent symptoms. She had gastrostomy and jejunostomy tubes placed for long-term feeding because biopsies revealed the absence of the interstitial cells of Cajal in the stomach and small bowel, at which point the stimulator was removed. She required 2



**Fig. 1** Percentage improvement in symptoms with temporary and permanent GES (1 = vomiting, 2 = nausea, 3 = total score).

**Table 3** Effects of GES on GETs and EGGs

Measure	Baseline	Temporary stimulation	Permanent stimulation
GET 1 h	59.5%	62%	61%
GET 4 h	12%	12.3%	18.3%
EGG frequency	4.4%	4.7%	4.7%
EGG amplitude	0.08	0.6	0.12
Frequency/Amplitude	0.39	2.61	0.49

The GET values represent percentage of meal remaining in stomach. Frequency/Amplitude is a derived number and not directly measured.

laparotomies for complications of the jejunal tube. Another patient required removal of the stimulator because of erosion of the skin over the pocket 2 years after implantation. She had trauma to the area, which caused the erosion. Her symptoms recurred after removal of the stimulator, and she is awaiting another implantation.

## 3. Discussion

Gastroparesis is a disabling condition with significant long-term consequences if symptoms cannot be improved [1]. It is perceived to be mostly an adult problem; however, there are some reports of GP in the pediatric age group, both diabetic associated and idiopathic or presumed postviral GP [5,14-17]. The treatment modalities that have been used in these children ranged from the conservative, with dietary modifications and medication, to the very aggressive, with subtotal gastrectomy [9,15]. There are also reports of using intrapyloric injection of botulinum toxin as well as decompressive gastrostomy and other gastric emptying procedures with varying degrees of success [8,10]. These reports, as ours, mostly involved small series of patients without any control group for comparison.

In our series of patients, there was significant disability at the time of evaluation for GES. All of the children had been withdrawn from formal schooling and were unable to lead a normal life. In most cases, the patients had lost weight; but 2 patients had actually gained weight because of the constant ingestion of complex carbohydrates. Two patients were on parenteral nutrition at the time of implantation. A total of 10 children had temporary mucosal stimulation performed at our center (one had a permanent GES placed elsewhere and was not included in the study); and the effects of GES were immediate, with all cases reporting improvement in vomiting, nausea, and total symptoms, as well as eating foods that they were unable to before. The long-term results of permanent stimulation were also impressive in this group of patients. Two of the 9 patients had initial good response, but failed within 2 to 4 months. In one of these cases, we found a complete absence of the Cajal cells in the stomach and small bowel, whereas in the other, there was progressive development of



multiple autoimmune diseases that complicated the GP. In the remaining 7 cases, the children were able to return to school and have a more normal life-style. The youngest patient (8 years old) developed similar problems with her urinary bladder and had subsequent implantation of a bladder pacer. She continues to do well, with no recurrence of the GP symptoms. In one patient in whom we had to remove the pacer because of infection, a recurrence of GP symptoms occurred; and she is currently being evaluated for reimplantation.

Adult series are larger and have longer-term follow-up than ours, and the data are quite convincing that GES is a promising therapy for a group of patients who have very limited options [11,13]. Lin et al noted that symptom improvement was maintained after 3 years and that there were no other deleterious effects [13]. Despite the clinical improvement, there was poor correlation between the patient's symptoms and gastric emptying test results [11,13]. Similar to that experience, we noted no significant "improvement" in the GET in our series, despite a significant improvement in total symptom scores. After temporary and permanent GES placement, the GETs were slightly increased in our patients, but not significantly. There is a lack of standardization of these tests between centers; and therefore, it is difficult to compare results. In addition, there is a growing understanding of the fact that there can be normal, rapid, and delayed gastric emptying based on GET in patients with classic symptoms of GP [1]. In our study, we noted 4 rapid and 5 delayed emptiers; but because of the small number of patients, we were not able to find a clinical difference between the groups.

Electrogastrography is another study used for evaluation of gastric dysfunction. Electrogastrography is a noninvasive technique using cutaneous electrodes on the abdomen to measure gastric myoelectrical activity, known as the *slow wave* [18]. Gastric dysrhythmias involve tachygastria, bradygastria, or decreased amplitude responses to meal ingestion. However, we note that in our series we could not reliably identify any pattern of change in the frequency or amplitude that correlated with clinical condition. Mucosal myoelectric activity had a better degree of correlation with symptoms in our series during temporary stimulation. Temporary stimulation was performed endoscopically or through a gastrostomy site and was a good predictor of response to permanent stimulation in our series as well as other adult experiences [19]. We performed temporary stimulation as a screening test and would not have implanted a permanent device if there was no response. Fortunately, all responded in this short series. The length of temporary stimulation was variable depending on whether it was done via a gastrostomy tube site (stronger electrodes, longer lasting) or transoral, which generally lasted a few days. In terms of the delay in permanent device placement, in all cases, it was because of the health insurance agencies that would not reimburse the hospital for the procedure or the device easily.

The mechanisms underlying the clinical benefits of GES have not been fully understood [4]. The low-energy, high-frequency stimulation programs that are used do not directly lead to contraction of the smooth muscle; nor does the gastric rhythm become entrained. It has been hypothesized that the mechanism may stem from a vagal and cerebral pathway [2]; however, the GES has been shown to work well in patients with vagotomy, as in one of our cases. More recent theories suggest a role for GES in fundic relaxation, the autonomic system, or gastrointestinal hormones; but these have not been confirmed [1]. As in our series, the benefit in symptoms for patients was not accompanied by objective measures of improvement in GET or EGG rhythms. There exists a possibility for a placebo effect of the implanted stimulator. However, in one study by Abell et al [11], patients were randomly and blindly assigned to have the stimulator on or off; and there was a significant improvement in the on group.

In summary, we believe that GES can be successfully used in children younger than 18 years with GP refractory to medical treatment. It offers hope for relief in a group of patients with few other alternatives. We plan on studying a larger patient population for a longer duration of time to assess the long-term efficacy and safety issues associated with GES in children.

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